Figure 4. Correlation between clarithromycin concentration and ΔQT_c after 500 mg bid administration for 1 day

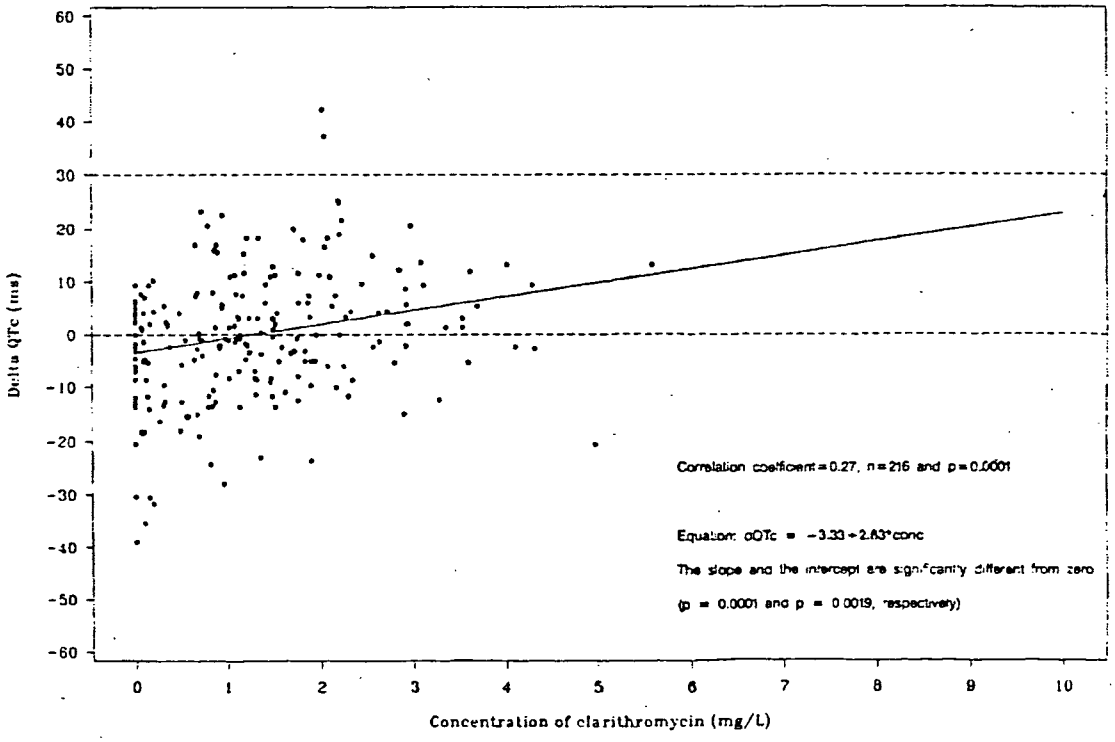


Figure 5. ΔQT_c vs. time after dosing

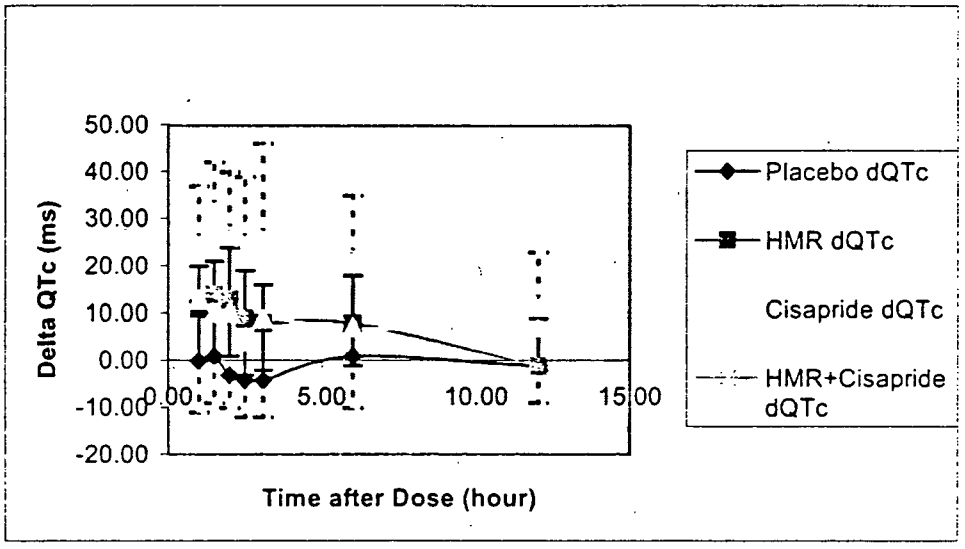
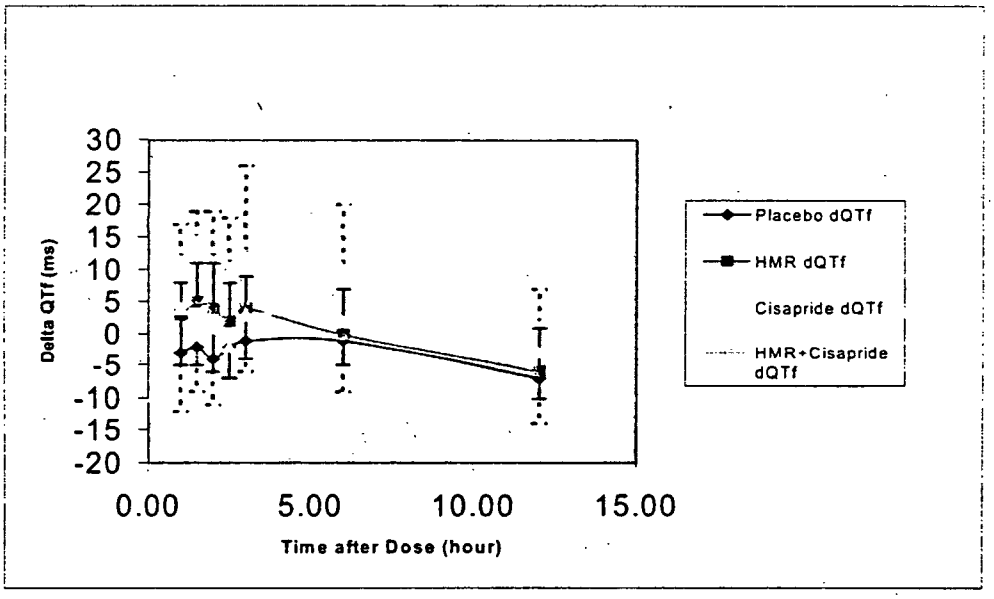


Figure 6. ΔQT_f vs. time after dosing



7. Phase III Studies: Cardiac Safety

a) Deaths and adverse events related to the cardiovascular system

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

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

A telithromycin-treated patient (Subject 0537/009 in Study 3010) with a baseline QT_c of 473 msec (measured using the longest lead) died on study day 2. The cause of death was stated to be a myocardial infarction that was assessed as having occurred on the day of study entry (prior to receiving study drug), on the basis of an entry EKG showing absent R waves in V2 and V3; however, serum concentrations of troponin I, creatinine phosphokinase, and the MB fraction of CPK were within normal limits.

A telithromycin-treated patient (Subject 0473/009 in Study 3010) who had a QT_c prolongation of 35 msec while on therapy died on day 5 of therapy. The stated cause of death in the case report form was acute aspiration. The patient had acute respiratory distress followed by an asystolic cardiac arrest. Of note, the patient had been receiving concomitant theophylline (a medication potentially interacting with telithromycin via the cytochrome P450 system) during the study period, and had complained of nausea and vomiting, which can be symptoms of theophylline toxicity.

A telithromycin-treated patient (Subject 1301/004 in Study 3001) with a history of coronary artery disease, atrial fibrillation, cerebrovascular disease, diabetes mellitus and liver disease died on study day 10 of heart failure. EKGs obtained on therapy showed nonspecific anterior, lateral and inferior ST-T wave abnormalities, atrial fibrillation, sinus tachycardia and irregular rhythm. No QT_c data were available due to the presence of atrial fibrillation.

A telithromycin-treated patient (Subject 0803/1520 in Study 3000) with a history of chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, and diabetes died 20 days after completion of therapy; Gram-negative septicemia was listed as the primary cause of death, with acute myocardial infarction and congestive heart failure as secondary causes of death. Of note, this patient developed a leukocytoclastic vasculitis involving the skin 2 days after completion of therapy.

A telithromycin-treated patient (Subject 1002/027 in Study 3001) with a history of coronary artery disease and chronic obstructive pulmonary disease died on study day 4 of circulatory failure, respiratory failure, and kidney failure. Sputum cultures grew *S. pneumoniae*, β-lactamase-producing *H. influenzae*, and telithromycin-resistant *S. aureus*. This patient was considered a therapeutic failure because of the need to change her therapy from telithromycin to intravenous ceftriaxone and gentamicin.

A telithromycin-treated patient (Subject 0369/108 in Study 3009) died 5 days after completion of therapy from respiratory failure, cardiomyopathy, liver failure, and immunosuppression due to HIV.

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

Medical Officer's Comment

In some of these cases, the cardiovascular event was most likely due to the patient's underlying disease (e.g., Subject 0369/108 in Study 3009), rather than to exposure to telithromycin. In others (e.g., Subject 0537/009 in Study 3010 and Subject 1301/004 in Study 3001), a relationship between telithromycin and cardiac dysfunction cannot be excluded.

b) Cardiovascular serious adverse events (SAEs)

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

c) Cardiovascular adverse events (AEs)

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

d) Electrocardiographic data

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

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

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

Medical Officer's Comment

Before discussing these data, the following general caveats regarding analysis of QT_c effects should be mentioned:

- *Because of the relative rarity of ventricular arrhythmias associated with QT prolongation, such as torsades de pointes, it would be unusual to detect such events even in a large NDA database. It is worth noting that no such events were detected at the time of approval for either terfenadine or cisapride, drugs now well known to be associated with torsade. This effect becomes even more important when specific high-risk subgroups are underrepresented in a database, further decreasing its power to detect a signal.*
- *Effects on QT_c prolongation may be diluted by normal inter-individual variability, obscuring clinically important effects. Such variability may be increased in a population containing ill patients rather than healthy volunteers. Again, this problem may be markedly exacerbated if there is underrepresentation of specific high-risk subgroups.*
- *Small changes in QT_c interval may become significant in the setting of concomitant factors that can contribute to QT_c prolongation, such as pharmacokinetic variability or co-administration of an interacting drug. For example, terfenadine causes a mean increase in QT_c interval of only 6 msec[4]; however, when administered with a inhibitor of CYP3A4 such as ketoconazole, terfenadine concentrations increase, leading to significantly lengthened QT intervals and increasing the risk of torsade.*
- *The increase in risk represented by a given increase in QT_c is difficult to determine. Conventionally, an increase of less than 30 msec is assumed to represent normal variability, an increase of 30 to 60 msec is thought to represent a possibly significant effect, and an increase of 60 msec or more is thought to represent a clearly significant effect. However, as just discussed, even a small increase in QT_c may be associated with an increased risk of torsade, as with terfenadine.*

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

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

[4] Pratt CM *et al.* Dose-response relation between terfenadine (Seldane) and the QTc interval on the scalar electrocardiogram: distinguishing a drug effect from spontaneous variability. Am Heart J 1996; **131**:472-80.

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

To minimize the effects of QT_c variability, the FDA analysis of telithromycin's effects on repolarization focused on patients from controlled trials. Data from telithromycin-treated patients were compared to data from patients drawn from the same randomized trials. The FDA analysis of EKG data focused on 3717 patients in controlled Phase 3 trials (2045 telithromycin and 1672 comparator). Of these, EKG data allowing analysis of on-therapy QT_c values were available for 2791 patients (1515 telithromycin and 1276 comparator).

In controlled trials, there were 17 patients (12 telithromycin (0.8%), 5 comparator (0.4%)) with a QTc of greater than 470 msec while on therapy. Of these, 8 telithromycin and 2 comparator patients had a baseline QTc of greater than 470 msec. None of these patients had torsades de pointes or other arrhythmias. Three of the telithromycin patients and two comparator-treated patients with prolonged on-therapy QTc intervals had a change from baseline of 30 msec or more.

Table ISS.21 shows mean changes in QT_c for telithromycin and comparators during therapy in controlled trials for representative groups. **Table ISS.22** shows mean changes in QT_c for telithromycin and clarithromycin during therapy for studies 3006 and 3008, the two controlled studies comparing these two agents. **Table ISS.23** shows mean changes in QTc for telithromycin in uncontrolled studies.

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Table ISS.21. Mean ± SD changes in QT_c (msec) in controlled telithromycin Phase 3 trials.

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

Table ISS.22. Mean ± SD changes in QT_c (msec) in pooled studies 3006 and 3008.

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

Table ISS.23. Mean ± SD changes in QT_c (msec) in uncontrolled Phase 3 studies.

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

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

Medical Officer's Comment

The Applicant has argued that Bazett's formula is inappropriate for this dataset, given that telithromycin tends to increase heart rate and Bazett's formula tends to overcorrect QT intervals in the presence of heart rate. To address this, a secondary analysis using Fridericia's formula was performed (Tables ISS.23A and ISS 23B). This analysis shows that although the changes in QT_f are similar to those for QT_c for the population as a whole, telithromycin causes greater changes in QT_f than do randomized comparator patients for subpopulations that are potentially at increased risk for increased exposure to telithromycin because of altered pharmacokinetics (e.g., It is important to note that these changes in QT_c and QT_f are small, and the degree of risk that they represent cannot be accurately quantified. However, it is also important to recognize that these are population averages that reflect the presence of outliers with more extreme changes in QT interval duration (see below). Thus, some patients with higher exposures to telithromycin may be at risk for greater changes in QT intervals than these small population changes.

It is important to recognize that despite its limitations, Bazett's formula is the correction method for which the most experience exists. There is some evidence that this formula, despite its heart rate dependence, may be more sensitive for predicting arrhythmias than other formulae[5].

Table ISS.23A. Mean ± SD changes in QT_f (msec) in controlled Phase 3 studies.

Group	Telithromycin	Comparator
All	3.3 ± 19.5 (n=1515)	3.2 ± 19.5 (n=1276)
F	3.5 ± 18.6 (n=805)	3.2 ± 18.2 (n=665)
M	3.0 ± 20.4 (n=710)	3.2 ± 20.1 (n=611)
Age 13-18	7.9 ± 16.7 (n=43)	4.5 ± 22.2 (n=55)
19-64	3.4 ± 19.7 (n=1251)	4.0 ± 19.2 (n=994)
≥65	1.5 ± 18.5 (n=221)	-0.5 ± 19.3 (n=227)

Table ISS.23B. Mean ± SD changes in QT_f (msec) in pooled studies 3006 and 3008.

Group	Telithromycin	Clarithromycin
All (Studies 3006 and 3008)	8.3 ± 19.3 (n=433)	8.4 ± 18.9 (n=431)
F	9.3 ± 18.3 (n=246)	7.6 ± 18.7 (n=239)
M	7.1 ± 20.6 (n=187)	9.4 ± 19.2 (n=192)
Age 13-18	9.6 ± 17.0 (n=27)	9.2 ± 19.4 (n=41)
19-64	8.1 ± 19.5 (n=377)	8.9 ± 18.9 (n=353)
≥65	9.9 ± 19.3 (n=29)	3.2 ± 18.2 (n=37)

Telithromycin patients receiving concomitant medications metabolized by CYP3A4 or CYP2D4 showed increases in QT_c relative to patients who did not receive such medications, as shown in **Tables ISS.24** and **ISS.25**.

The analyses in Tables ISS.24 and ISS.25 should be regarded as exploratory and interpreted cautiously, since patients were not randomized on the basis of CYP3A4 or CYP2D6 substrate intake; therefore other variables not controlled for in this analysis could account for the observed differences.

Table ISS.24. Mean ± SD changes in QT_c (msec) in patients receiving medications metabolized by CYP3A4 and/or 2D6.

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

[5] Dabrowski A *et al.* Prolongation of QT interval corrected for heart rate by Bazett's equation and linear formula as predictor of arrhythmic events after myocardial infarction. Am J Cardiol 2000; **86**:469-72.

Table ISS.25. Mean ± SD changes in QT_c (msec) in patients receiving medications metabolized by CYP3A4 and/or 2D6 in studies 3006 and 3008.

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

Medical Officer's Comment

Although these analyses are post-hoc, *the consistency of the results is intriguing. An analysis of changes in QT_f in patients receiving 3A4 or 2D6 substrates gave similar results (see Tables ISS.25A and ISS.25B, below). It is certainly plausible that impaired clearance of telithromycin by competition from a 3A4 substrate (or by 3A4 inhibition by a mixed substrate/inhibitor) could lead to elevated concentrations, increasing QT_c. However, since telithromycin is not metabolized by 2D6, it is not clear why 2D6 substrates would have an effect on telithromycin. Possibly, this serves as a marker for drugs that show greater avidity for the 3A4 system.*

Table ISS.25A. Mean ± SD changes in QT_f (msec) in patients receiving medications metabolized by CYP3A4 and/or 2D6.

Group	Telithromycin	Comparators
No concomitant 3A4 substrate	2.4 ± 19.5 (n=972)	2.9 ± 19.6 (n=787)
Concomitant 3A4 substrate	4.8 ± 19.4 (n=543)	3.7 ± 19.1 (n=489)
No concomitant 2D6 substrate	2.8 ± 19.6 (n=1315)	3.0 ± 19.4 (n=1082)
Concomitant 2D6 substrate	6.8 ± 18.8 (n=200)	4.6 ± 19.5 (n=194)
Concomitant 3A4 and 2D6 substrates	7.9 ± 18.0 (n=110)	5.9 ± 18.5 (n=111)

Table ISS.25B. Mean ± SD changes in QT_f (msec) in patients receiving medications metabolized by CYP3A4 and/or 2D6 in studies 3006 and 3008.

Group	Telithromycin	Clarithromycin
No concomitant 3A4 substrate	8.1 ± 19.1 (n=276)	8.5 ± 19.4 (n=266)
Concomitant 3A4 substrate	8.7 ± 19.8 (n=157)	8.3 ± 18.2 (n=165)
No concomitant 2D6 substrate	7.6 ± 19.1 (n=378)	8.3 ± 18.8 (n=359)
Concomitant 2D6 substrate	13.6 ± 20.6 (n=55)	9.2 ± 19.6 (n=72)
Concomitant 3A4 and 2D6 substrates	15.8 ± 21.6 (n=31)	8.9 ± 18.5 (n=44)

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

Because of the inherent variability of QT_c intervals and the potential for measures of central tendency such as mean values to mask clinically important changes, outliers were also

examined. **Figure 7** shows the frequency distribution of QT_c changes for telithromycin and comparator-treated patients in controlled Phase 3 trials; **Figure 8** shows the corresponding distribution for studies comparing telithromycin to clarithromycin. There was a higher frequency of QT_c increases of more than 30 msec in telithromycin treated patients than in comparators, both for all controlled trials as well as for trials in which telithromycin was compared to clarithromycin; the difference was not statistically significant.

Because of the potential for Bazett's formula to overcorrect the QT interval, a similar analysis was performed using Fridericia's formula. There were 122 telithromycin-treated patients (8.0%) with an increase in QT_f of 30 msec or more than baseline, compared to 109 comparator-treated patients (8.5%); the difference was not statistically significant. In trials comparing telithromycin to clarithromycin, there were 59 telithromycin-treated patients (13.7%) with an increase in QT_f of 30 msec or more, compared to 50 clarithromycin-treated patients (11.6%); again, the difference was not statistically significant

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

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

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

Medical Officer Comments: Cardiac Safety

Phase I data from controlled studies in humans show that telithromycin causes QT_c prolongation in a dose- and concentration-dependent fashion; the magnitude of the effect is comparable to that of cisapride. The effect is enhanced by coadministration of a CYP3A4 inhibitor. Telithromycin shows considerable pharmacokinetic variability in populations such as the elderly and subjects with renal impairment. The concentration dependence of telithromycin-associated QT_c prolongation in combination with potential drug interactions and pharmacokinetic variability suggest that significant QTc prolongation may occur in at-risk patients receiving concomitant interacting medications.

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

Phase 3 data on QT_c changes in controlled studies must be interpreted cautiously because of limitations in the database; however, these data show a small but consistent increase in QT_c in telithromycin-treated patients, greater than changes in either comparator-treated patients or comparable clarithromycin-treated patients. This effect may be enhanced by coadministration of drugs metabolized by 3A4 or 2D6. An analysis using QT_f gave consistent results for at-risk subpopulations, particularly for analysis of changes in patients receiving concomitant 3A4 and/or 2D6 substrates.

Taken together, these findings suggest a potential for telithromycin to cause clinically significant effects on cardiac repolarization in individuals in whom telithromycin concentrations are elevated because of renal impairment, concomitant administration of drugs inhibiting clearance of telithromycin, or both.

Figure 7. Frequency of ΔQTc changes All controlled telithromycin trials

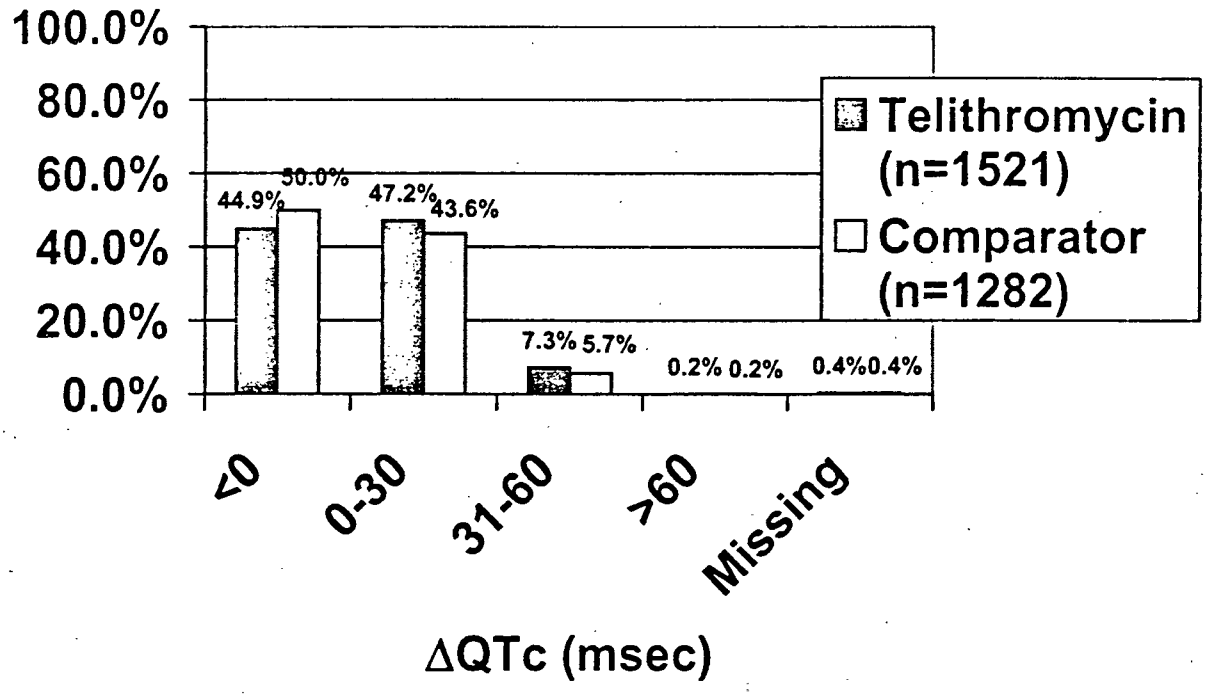
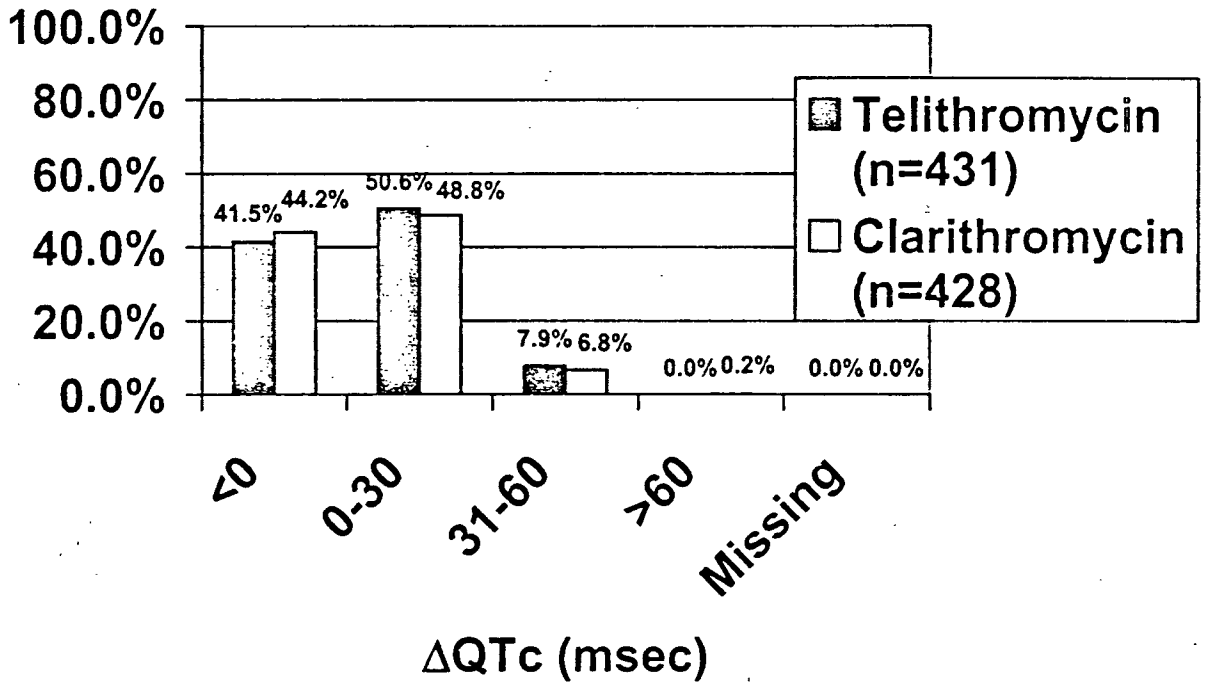


Figure 8. Frequency of ΔQTc changes Studies 3006 and 3008



Hepatic Safety

For a discussion of hepatic safety, please refer to the review by Dr. Edward Cox.

Central nervous system and special senses safety

The incidences of the most common nervous system and special sense TEAEs in controlled Phase 3 trials are shown in **Table ISS.26.**

Table ISS.26. Incidence of Nervous System and Special Sense TEAEs in Phase 3 controlled trials

	Telithromycin (n=2045)	Comparators (n=1672)
Headache	118 (5.8%)	118 (7.1%)
Dizziness	91 (4.4%)	48 (2.9%)
Taste perversion	36 (1.8%)	37 (2.2%)
Dry mouth	32 (1.6%)	27 (1.6%)
Somnolence	16 (0.8%)	14 (0.8%)
Insomnia	14 (0.7%)	11 (0.7%)
Blurred vision	14 (0.7%)	1 (0.1%)
Vertigo	4 (0.2%)	7 (0.4%)

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

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

As shown in **Table ISS.27**, blurred vision occurred in telithromycin-treated subjects on all dose regimens for telithromycin (5 days: 9; 7-10 days: 3; and 10 days: 3). Cases were reported for three indications (community-acquired pneumonia (4), sinusitis (4), and tonsillitis/pharyngitis (7). These events predominantly in females (females: 11, males 4). Subjects treated with telithromycin who experienced blurred vision had a mean age of 30 years (range: 19-45 years). There were no blurred vision adverse events among patients treated with clarithromycin. Of note, in at least one case, blurred vision persisted for several days.

Table ISS.27. Subjects with adverse event of blurred vision in phase III clinical trials.

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

[1]telithromycin 800 mg, [2]amoxicillin 500mg/clavulanate 125 mg

Medical Officer's Comment

The connection between telithromycin administration and blurred vision is unclear, but the frequency of this adverse event is concerning. From a practical viewpoint, the incidence raises concerns that individuals experiencing this adverse event might have difficulty with activities such as driving during a course of telithromycin therapy. From a broader perspective, the unexpected occurrence of decreased visual acuity in a drug that would not be expected to affect the nervous system is disturbing. The Applicant has suggested 'transient myopia' as the cause for the blurred vision, but there is no convincing physiologic mechanism that would be consistent with this explanation for this. Although blurry vision is a common adverse event with drugs that affect the central or autonomic nervous systems, it is a distinctly unusual adverse event in patients receiving antimicrobials. A search of the PDR showed that the only antimicrobials listed as having blurred vision as a reported adverse reaction are tetracyclines; blurred vision associated with tetracyclines is thought to be due at least in some cases to pseudotumor cerebri. In this regard, the frequent occurrence of headache and dizziness in telithromycin-treated patients is notable. Of the 15 telithromycin-treated patients who reported blurred vision, six also reported dizziness and two reported headache.

Laboratory abnormalities

Analysis of clinically noteworthy changes in renal and hematologic laboratory tests did not in general show significant differences between telithromycin and comparators. Patients receiving 7-10 d courses of telithromycin (as opposed to 5 d courses) did show a higher incidence relative to patients treated with 7-10 d of comparator of clinical noteworthy changes in the following: prothrombin time (4/343 (1.2%)v. 5/792(0.6%)), International Normalized Ratio (33/722 (4.6%) v. 48/1391 (3.5%)), leukocyte counts (13/781 (1.7%) v. 13/1663 (0.8%)), neutrophils (25/781 (3.2%) v. 42/1662 (2.5%)) and potassium level (21/781 (2.7%) v. 30/1662 (1.8%)). There was a relatively high incidence of decreases in creatinine clearance to <50 mL/min in patients receiving 7-10 d of telithromycin in uncontrolled studies: 83/1049 (7.9%).

For a detailed discussion of changes in liver function tests in telithromycin-treated patients, please refer to Dr. Cox's review.

Drug-drug interactions

As noted above under cardiovascular safety, telithromycin concentrations are increased by concomitant administration of a CYP 3A4 inhibitor. It is important to note that telithromycin can affect the metabolism of other drugs through its interactions with the 3A4 system or other clearance mechanisms, decreasing their rate of elimination and increasing exposure to these drugs. **Table ISS.28** shows increases in serum concentrations and AUCs of some drugs or metabolites of these drugs when they are given concomitantly with telithromycin. Of note, these are single dose studies; greater effects may occur with multiple dose studies.

Table ISS.28. Increases in C_{max} and AUC for drugs given concomitantly with telithromycin.

Drug	% increase C_{max}	% increase AUC
Simvastatin	433%	761%
Simvastatin acid	1400%	1100%
Digoxin	70%	37%
Midazolam	162%	511%

Medical Officer's Comment

These alterations in the pharmacokinetics of drugs metabolized by 3A4 are extremely concerning, since these increase the potential for toxicity of such drugs. Inhibition of the 3A4 system by macrolides is well described[6]; given the structural and metabolic similarities between macrolides and ketolides, it is not surprising that telithromycin would. Adverse events related to inhibition of 3A4 and decreased drug clearance include torsades de pointes (e.g., terfenadine, cisapride); rhabdomyolysis (simvastatin); severe hypotension (nifedipine, nicardipine); excessive sedation (midazolam); and ataxia (carbamazepine). While a number of currently marketed drugs have been implicated as inhibitors of 3A4 capable of altering clearance of concomitantly administered 3A4 substrates, and 3A4 inhibition is not per se ***a risk that would preclude marketing approval, it is important to note the regulatory experience with drugs such as terfenadine and mibrefadil, for which warnings in the package insert after establishment of prescribing patterns proved ineffective in alerting providers to the potential***

[6] Dresser GK *et al.* Pharmacokinetic-Pharmacodynamic consequences and clinical relevance of cytochrome P450 inhibition. Clin Pharmacokinet 2000; **38:** 41-57.

risks of drug-drug interactions causing decreased clearance of 3A4 substrates. Thus, the effects of telithromycin on medications that may be administered concomitantly represent another safety issue that needs to be weighed against the potential benefit of this agent.

Medical Officer Final Comments

The safety review of telithromycin revealed a number of significant concerns that must be weighed against its potential benefit.

With respect to cardiac safety, telithromycin elicited delayed repolarization in in vitro *models of cardiac repolarization, and in vivo in animals. In Phase I studies, telithromycin consistently caused concentration-dependent increases in the QT_c interval. In Phase III studies, telithromycin caused a consistent effect on mean QT_c duration in humans, with evidence that interactions with drugs metabolized by CYP 3A4 may further prolong QT_c duration. Although this analysis is confounded somewhat by the increase in heart rate induced by telithromycin, analyses using a correction formula more independent of heart rate (QT_f) gave similar results for Phase 1 studies and for Phase 3 subpopulations potentially at risk for increased exposure to telithromycin. In addition, a clinical pharmacology study (Study 1049) was performed in which no heart rate increase was observed in telithromycin-exposed subjects.*

Telithromycin's effect on QT_c is concentration-dependent. Telithromycin concentrations in human plasma are highly variable (i — , after a single dose in phase I, up to — after multiple doses in phase III), with a significant increase in C_{max} in elderly subject and those with impairment. Telithromycin is a CYP 3A4 substrate, and is primarily metabolized and eliminated by the liver and via first-pass metabolism. Co-administration of a 3A4 inhibitor significantly increases telithromycin concentrations.

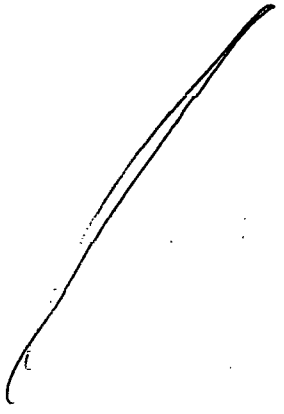
These results suggest that while the overall effect of telithromycin on cardiac repolarization is quite modest, in certain individuals, particularly those with renal (or renal and hepatic) impairment and/or those receiving concomitant agents that might impede clearance of telithromycin, telithromycin exposures may be significantly higher than for the average patient, with a consequently greater effect on cardiac repolarization. Such individuals may be at increased risk for occurrence of torsades de pointes if they have other risk factors that could amplify the effect of telithromycin (e.g., bradycardia, severe hypokalemia). Estimation of the risk is not possible with any accuracy because of lack of data about the significance of given changes in QT_c and the severe limitations in the Phase 3 dataset.

Other safety concerns include the potential for hepatotoxicity, as outlined by Dr. Cox, and the potential for effects on other 3A4 substrates. The Applicant has attempted to show that the risk profile of telithromycin is no worse than that of clarithromycin; however, the preclinical toxicology data argues against this; in addition, direct comparison of the two agents in the Phase 3 EKG database found small but consistent differences between their effects on QT_c, with telithromycin-treated patients showing a greater increase in QTc.

Given these concerns, and the lack of added benefit relative to other, currently marketed antimicrobials (e.g., in terms of efficacy against resistant pathogens), approval cannot be recommended at this time. Given that the drug is intended for several indications which are not life-threatening (e.g., acute exacerbation of chronic bronchitis) and may carry life-threatening risks, the risk-benefit calculus does not favor its approval. Although telithromycin has demonstrated efficacy overall in the treatment of community-acquired

pneumonia, it does not have any advantages for this indication relative to macrolides or fluoroquinolones, given the paucity of data supporting its use against penicillin- or macrolide-resistant Streptococcus pneumoniae.

For approval to be granted, additional efficacy and safety data would be required. These should include the following:



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/s/

David Ross
11/21/02 02:25:30 PM
MEDICAL OFFICER

Revised Ketek safety reivew - original NDA

Janice Soreth
11/21/02 03:19:08 PM
MEDICAL OFFICER

MEDICAL OFFICER SAFETY REVIEW OF NDA 21-144: TELITHROMYCIN (KETEK)

General Information

Date Submitted:	July 24, 2002
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Date Action Taken:	January 24, 2003
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Date to Supervisor	September 25, 2003
Medical Officer	Charles Cooper, M.D.

Applicant: Aventis Pharmaceuticals Inc.
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Bridgewater, NJ 08807-0890

Contact Person: Steve Caffé
Head, U.S. Regulatory Affairs
(908) 231-5863

Drug: Proprietary Name: Ketek
Generic Name: Telithromycin

Drug Class: Ketolide antibiotic

Formulation: 400 mg tablet

Route of administration: Oral

Table Of Contents

Executive Summary of Safety

Introduction

After review of the initial submission for telithromycin (NDA 021-144), several specific safety concerns were raised, including potential for QT prolongation, hepatic toxicity, and visual toxicity. To address these concerns, the applicant submitted additional data at the time of NDA re-submission on July 24, 2002. These included results from eight new Phase 1 studies, four new Phase 3 efficacy/safety studies, and post-marketing data from approximately 1 million prescriptions for telithromycin in countries where this drug has been approved. This report focuses on the safety review of the three additional efficacy studies, and the post-marketing data. Review of the large Phase 3 safety study (Study 3014) was conducted by Dr. George Rochester. Individual review of the results of the additional Phase 1 studies was conducted by Dr. Chuck Bonapace.

Table **ES.1** summarizes all new safety data covered in this review.

ES.1. New Safety Data in Telithromycin Re-submission (excluding Study 3014)			
Study Type	**Study Number**	**Number of Patients**	**Study Description**
Phase 1	1060, 1062	71	To assess pharmacokinetics in patients with renal (Study 1062) and hepatic impairment (Study 1060)
Phase 1	1063	12	Effect of cytochrome P450 3A4 inhibition by ketoconazole on telithromycin PK in elderly subjects with renal failure
Phase 1	1059, 1064	54	Visual adverse event studies
Phase 1	1058, 1061	24	Drug interaction study (metoprolol and rifampicin)
Phase 1	1050	6	Intestinal permeability study
Phase 3	3012	550	Open label, non-comparative CAP study
Phase 3	4003	575	Double-blinded, randomized, active-controlled CAP study
Phase 3	3013	549	Blinded, randomized, active-controlled AECB study
Post-Marketing	N/A	1 million prescriptions	Passive AE surveillance German post-marketing survey (28,000 patients)

Deaths / Serious Adverse Events / Adverse Events in New Phase 3 Clinical Trials

The number of deaths on treatment and post-treatment for telithromycin and comparators were 10/1207 (0.83%) and 5/467 (1.1%) respectively. There were no deaths in telithromycin-treated or the comparator-treated patients which were attributed by the applicant to study drug. This was confirmed by a detailed Medical Officer review of all case report forms for those patients who died. Serious adverse events occurred with equal frequencies in the telithromycin-reated patients and comparator-treated patients. The majority of these serious adverse events were related to underlying co-morbidities or the infection for which the patient was being treated. Demographic factors and concomitant medications did not affect the rates of serious adverse events for telithromycin-treated and comparator-treated patients.

In all controlled Phase 3 trials, telithromycin-treated patients had higher rates of diarrhea (10.8% vs. 8.6%), nausea (7.9% vs. 4.6%) and vomiting (2.9% vs. 2.2%) than those receiving comparator drugs. Telithromycin-treated patients also had higher rates of dizziness (3.7% vs. 2.7%) than those receiving comparator drugs. These adverse events occurred in a higher proportion of telithromycin-

treated females than males. The incidences of these adverse events in telithromycin-treated females compared to males were: diarrhea, 12.2% vs. 9.3% ; nausea, 10.4% vs. 5.2% ; vomiting, 4.1% vs. 1.7% ; and dizziness, 4.4% vs. 2.9%.

There were also higher rates of adverse events in those telithromycin-treated patients who received a concomitant CYP3A4 inhibitor. The rates of these adverse events for patients receiving a concomitant CYP3A4 inhibitor vs. patients who did not receive a CYP3A4 inhibitor were: diarrhea, 12.4% vs. 10.5% ; nausea, 9.3% vs. 7.6% ; dyspepsia, 2.5% vs. 1.5%; gastritis, 1.2% vs. 0.3%; blurred vision, 1.9% vs. 0.4%.

The rates of discontinuation of study medication were slightly higher for telithromycin-treated patients than comparator-treated patients for certain gastrointestinal adverse events. The rates of discontinuation due to specific adverse events for telithromycin-treated patients vs. comparator-treated patients were: diarrhea 0.9% vs. 0.6% ; vomiting 0.8% vs. 0.5% ; nausea 0.7% vs. 0.5%.

Cardiac Toxicity/ QT Prolongation in New Phase 3 Clinical Trials

Additional ECG data was only available from one of the new Phase 3 efficacy studies (Study 3013). When the additional QTc data from Study 3013 was integrated with the data from the initial NDA submission, there were no significant differences between the initial and new datasets. Telithromycin treatment was associated with a mean on-therapy increase of QTc (Bazett's formula) of 1.5 ms and a mean on-therapy increase of QTc (Fridericia's formula) of 3.8 ms. The proportion of outliers for absolute QTc values for patients on-therapy with telithromycin was similar to that for patients pre-therapy. The number of patients pre-therapy with a QTc of $\geq$ 500 ms was 8/3098 (0.3%) vs. 4/2451 (0.2%) for patients on-therapy.

The incidence of serious and non-serious treatment emergent cardiac adverse events was low and similar between telithromycin-treated patients and comparator-treated patients.

Hepatic Toxicity in Phase 3 Clinical Trials

In all Phase 3 studies, the rates of hepatic adverse events and of treatment discontinuation because of a hepatic adverse event were similar between telithromycin- and comparator-treated patients. In the comparative studies there were two serious hepatic AEs in telithromycin-treated patients and one serious hepatic AE in comparator-treated patients. There was one additional serious hepatic AE from the non-comparative telithromycin studies. One of these serious adverse events in the telithromycin-treated group was a patient with a liver biopsy showing recent centrilobular necrosis and eosinophilic infiltration, strongly suggestive of drug-induced liver disease. The patient's baseline labs included an alanine aminotransferase (ALT) of 81 U/L , Normal Range (NR) <49 U/L) and an eosinophil count of 774 cells/10^{-6} L (NR) not available. (Note: Erythromycin estolate, ethylsuccinate, and propionate have been associated with cholestatic hepatitis, sometimes accompanied by fever and eosinophilia. The pathologic changes for some of the cases of trovafloxacin-associated hepatitis were described as centrilobular necrosis and eosinophilic infiltration on liver biopsy). Several months later this patient went on to have an episode of asymptomatic ALT and AST elevation and a repeat liver biopsy showed changes consistent with chronic hepatitis, probably autoimmune.

Analysis of liver function tests from the comparative Phase 3 CAP studies in patients who were normal at baseline showed a greater proportion of telithromycin-treated patients with low level elevations of AST and ALT (<5 x Upper Limit of Normal) relative to comparator. The AST and ALT elevations from patients in the CAP studies is present during the On-Therapy and Post-Therapy visits. This pattern was unchanged after the addition of the new Phase 3 data.

Visual Toxicity in Phase 3 Clinical Trials

There was a higher rate of visual adverse events in telithromycin-treated patients than in comparator-treated patients. The overall rate of visual adverse events in all controlled Phase 3 studies for telithromycin-treated patients was 1.0% vs. 0.2% for comparator-treated patients. Visual adverse events were more common in women than men (1.4% vs. 0.5%) in controlled studies and were more common in younger patients (mean age: 35.6 y, median age: 32 y). Visual adverse events in telithromycin-treated patients most commonly began on treatment day 2, however the onset ranged from treatment day 1 to 13. The duration of visual adverse events in telithromycin-treated patients was most commonly 1-2 days with a range of 1-2 days . Of telithromycin-treated patients with visual adverse events, 13/30 (43.3%) experienced the event for > 3days. Approximately 39% of telithromycin-treated patients with visual adverse events in controlled clinical trials had a reported severity of moderate to severe. There was no standardized grading system to allow consistent categorization of severity of the visual adverse events. One telithromycin-treated patient was significantly disabled and discontinued treatment because of a serious adverse event of "accommodation disorder."

Post-Marketing Safety Data

Post-marketing safety data from approximately 1 million telithromycin prescriptions written in several European and South/Central American countries was submitted for review. The majority of prescriptions were written in Germany ( ), Italy ( ), and Spain ( ). This data includes adverse events from 377 patients.

The most common reported post-marketing adverse events were related to vision, which were reported in 124 of 377 patients (33%). Many of these events were severe and disabling and lasted many hours. One patient did not have a complete resolution of her visual adverse event. However, no follow-up report had been submitted at the time of this review.

There were 18 post-marketing reports of hepatic adverse events, all from Germany. Six of these events represented symptomatic transaminase elevation and five involved hospitalization. Of these five, three required liver biopsy and four had ALT> 3 x Upper Limit of Normal (ULN) and Total Bilirubin (Tbili) > 1.5 x ULN. One of these patients also received amoxicillin/clavulanate. All 10 patients with hepatic adverse events with outcome information were reported as having recovered.

There were also five cases of exacerbation of myasthenia gravis with close temporal relationships to telithromycin administration. This included one case of death due to respiratory failure (200211064EU).

There was one case of possible torsade de pointes. This patient had multiple confounding medical conditions and ECG data was incomplete. It is not possible to make a determination as to the potential role that telithromycin may have played in this patient's cardiac adverse event. There were no other post-marketing cardiac adverse events that were consistent with a mechanism of prolonged QT interval.

Summary

The most common adverse events related to telithromycin in Phase 3 studies were gastrointestinal (in controlled studies: diarrhea NOS 10.8%; and nausea 7.9%). There were no deaths reported by the sponsor as having been related to telithromycin treatment and the rates of possibly related serious adverse events was the same between telithromycin-treated patients and comparator-treated patients (0.3%). The types of possibly related serious adverse events that occurred in telithromycin-treated patients were similar to those of comparator-treated patients and were consistent with well described antibiotic-related adverse events such as pseudomembranous colitis.

From the available Phase 3 safety data, it can be concluded that telithromycin does cause an increase in the rate of visual adverse events, many of which are moderate to severe and can be disabling. This increase is highest in females, young patients, and possibly in patients taking concomitant CYP3A4 inhibitors.

Based on the current available data, the cardiac adverse event profile and the degree of QT prolongation exhibited in telithromycin-treated patients appear to be similar to approved macrolides, such as clarithromycin.

Pre-clinical data suggests that telithromycin may be a significant hepatotoxin in humans. However, the available data from Phase 3 trials and post-marketing adverse event reporting are not sufficient to assess the risk of telithromycin-associated serious hepatic adverse events such as idiosyncratic liver reactions. The finding that transaminases were elevated in telithromycin-treated CAP patients and that there were several patients in the post-marketing database with symptomatic transaminase elevation, some even requiring biopsy, indicates that telitromycin may be a significant hepatotoxin. Telithromycin-treated patients in study 3014 also had a higher rate of transaminase elevation than did control-treated patients (see review by Dr. George Rochester). However, overall, these findings are not conclusive. As more post-marketing safety data becomes available, a better understanding of telithromycin's potential for hepatotoxicity will emerge.

Post-marketing data suggest that telithromycin may cause severe exacerbations of myasthenia gravis with at least one case of death resulting from such an exacerbation. Thus, such patients should not receive this drug.

Integrated Review of Safety –NDA 21-144 – Telithromycin (Ketek)

On June 1, 2001, the FDA issued an approvable letter to the applicant for NDA 21-144. The letter outlined several specific safety concerns that were identified during the first review cycle. These included questions about the cardiac, visual, and hepatic toxicity profiles of telithromycin.
In response to the approvable letter, the applicant has attempted to address these issues in this re-submission which includes three new Phase 3 clinical trials and eight new Phase 1 clinical trials. The new Phase 3 studies include Studies 3012, 3013, and 4003. The review of additional safety data accrued from the conduct of these trials will be integrated into prior data and presented as the All Integrated population. Data from the initial review cycle will be presented as the Previous Studies Population. An additional study, 3014, enrolled approximately 24,000 patients. This study was conducted for the purposes of providing further safety data in a usual care setting; for details, see reviews by Drs. George Rochester, Janice Pohlman, and Tom Smith, and the TL memo by Dr. David Ross.

Patient Accounting, Demographics, and Extent of Exposure

Phase 1
There were eight additional Phase 1 studies completed in response to FDA's approvable letter, which requested, among other things:

- A study investigating the pharmacokinetics of telithromycin in patients with mild, moderate or severe renal impairment, with an assessment of changes in QT interval duration.
- A study investigating the effect of ketoconazole on pharmacokinetics of telithromycin in elderly patients with mild to moderate renal impairment, to characterize drug exposure in subjects at potentially greater risk due to multiple perturbations of drug elimination pathways.
- Additional studies addressing the potential mechanisms for the visual blurring reported in previous clinical studies.

Table ISS.1 shows the total number of patients exposed to telithromycin in Phase 1 studies for the entire NDA, including data submitted in the initial NDA.

Table ISS.1. Telithromycin exposure in all Phase 1 studies.

Regimen	No. of Subjects	Dose Range (mg)	Age Range	No. of Doses
Single PO	397	50-2400	18-76	1
Multiple PO	636	100-2000	18-84	1-21
Single IV	45	120-2000	18-76	1

***Medical Officer Comment**: Several of the new studies involved co-administration of a second agent. Studies 1058, 1061, and 1063 involved the co-administration of rifampicin, metoprolol, and ketoconazole, respectively. Six patients from study 1050 received single 800 mg doses of telithromycin via oro-jejunal tube. In addition, Study 1060 specifically enrolled patients with varying*

degrees of hepatic dysfunction and Study 1062 specifically enrolled patients with varying degrees of renal insufficiency.

Phase 2
As with the original submission, there were no traditional Phase 2 dose-finding studies or proof-of concept studies. Therefore, the safety review focuses only on Phase 1 and 3 studies.

Phase 3
The extent of exposure (number of subjects exposed, duration of exposure, and dose) to active study drugs is described in this section for the 16 integrated Phase 3 studies. For the Phase 3 studies, extent of exposure is given for the 5-day, 7-day and 7- to 10-day telithromycin treatment regimens and for the 7 to 10 day pooled comparator regimens, as well as by indication: CAP, AECB, AS, and tonsillitis/pharyngitis.

The safety database comprised all subjects who received at least one dose of study treatment and had at least one safety assessment following randomization and included data from three studies completed after the submission of the NDA.

Table ISS.2 shows that 6611 subjects were evaluable for safety analyses in 16 Phase 3 studies (excluding Study 3014). This total included 4472 subjects who received telithromycin and 2139 subjects who received comparator drugs. This represents a 37.0% increase in the number of safety evaluable telithromycin-treated patients and a 27.9% increase in the number of safety evaluable comparator-treated patients, relative to the original submission.

Table ISS.2. Safety evaluable population

	Telithromycin			**Comparators**
	Controlled Studies	Uncontrolled Studies	All Studies	Controlled Studies
Initial NDA	2045	1,220	3265	1672
New Studies	657	550	1207	467
Total	2702	1,770	4472	2139

Of the 4,472 telithromycin-treated safety evaluable subjects in controlled and uncontrolled Phase 3 studies, 1,891 subjects participated in 5-day studies; 1,175 in 7-day studies; and 1,406 subjects in 7- to 10-day studies. A 5-day dosing regimen of telithromycin was administered to 193 subjects in community acquired pneumonia (CAP) studies, 609 subjects in acute exacerbations of chronic

Extent of exposure by indication and by dosage regimen is shown in **Tables ISS.4** and **ISS.5.**

Table ISS.4. Extent of exposure to telithromycin 800 mg by indication in all integrated Phase 3 studies

	CAP [a]		AECB [a]	AS		TONS/PHAR
	TEL 5 days (N=193)	TEL 7-10 days[b] (N=2160)	TEL 5 days (N=609)	TEL 5 days (N=662)	TEL 10 days (N=421)	TEL 5 days (N=427)
Duration						
N [c]	192	2144	607	659	419	424
Mean (days)	4.9	8.3	4.9	4.9	10.0	4.9
SD	0.6	2.1	0.4	0.6	1.8	0.6
Median	5.0	7.0	5.0	5.0	10.0	5.0
No. of days						
N [c]	191	2144	607	661	419	424
Mean (days)	4.9	7.9	4.9	4.8	9.5	4.9
SD	0.6	1.9	0.5	0.6	1.6	0.6
Median	5.0	7.0	5.0	5.0	10.0	5.0
No. of doses						
N [c]	191	2144	607	661	419	424
Mean (days)	4.9	7.9	4.9	4.8	9.5	4.9
SD	0.6	1.9	0.5	0.8	1.6	0.6
Median	5.0	7.0	5.0	5.0	10.0	5.0

[a] The only difference between the data examined in the first review cycle and current All Integrated Studies data is the change in data for CAP (5 days and 7-10 days) and AECB (5 days) studies.
[b] 7-day, 7 to 10-day and 10-day regimens were pooled.
[c] Data exclude missing values.
TEL=telithromycin
(Source page 7, Applicant's ISS)

Table ISS.5. Extent of exposure to telithromycin 800 mg by dosage regimen: Comparison between previous studies and all integrated studies

Dosage Regimen	Previous Studies[a]		All Integrated Studies[b]	
	N	Mean duration (days)	N[c]	Mean duration (days)
Telithromycin 5 d	1422	4.9	1882	4.9
Telithromycin 7 d	430	6.7	1168	7.3
Telithromycin 7-10 d	1395	9.6	1395	9.6

[a] Includes all studies submitted in initial review cycle.
[b] Previous Studies plus 3 new studies.
[c] Based on subjects with data.
N=number of subjects, excluding missing values.
(Source: page 8, Applicant's ISS)

Medical Officer Comment: *The extent of exposure of patients to telithromycin 800 mg in terms of duration of treatment, number of days, and number of doses was consistent with the proposed dosing*

recommendations in the product labeling for each indication. Safety data collected at the test of cure visit for these Phase 3 studies should allow for some assessment of potential safety problems which might arise after cessation of therapy as the result of telithromycin's long terminal half-life.

Demographics for all Phase 3 studies are shown in **Table ISS.6.**

Table ISS. 6. Demographic characteristics for safety population in Phase 3 studies: Comparison between previous studies and all integrated studies

	Number (%) of subjects/characteristics					
Demographic Variable	**Previous Studies[a]**			**All Integrated Studies[b]**		
	TEL 5 d N=1429	**TEL 7-10 d[c] N=1836**	**Comparator 7-10 d N=1672**	**TEL 5 d N=1891**	**TEL 7-10 d[c] N=2581**	**Comparator 7-10 d N=2139**
Sex						
Male	648 (45.3)	983 (53.5)	785 (46.9)	913 (48.3)	1383 (53.6)	1031 (48.2)
Female	781 (54.7)	853 (46.5)	887 (53.1)	978 (51.7)	1198 (46.4)	1108 (51.8)
Race						
White	1282 (89.7)	1409 (76.7)	1438 (86.0)	1678 (88.7)	1858 (72.0)	1830 (85.6)
Black	85 (5.9)	313 (17.0)	163 (9.7)	128 (6.8)	535 (20.7)	220 (10.3)
Asian/Oriental	28 (2.0)	32 (1.7)	26 (1.6)	34 (1.8)	37 (1.4)	30 (1.4)
Other[d]	34 (2.4)	82 (4.5)	45 (2.7)	51 (2.7)	150 (5.8)	58 (2.7)
Age (years)						
13 to 18	57 (4.0)	38 (2.1)	69 (4.1)	58 (3.1)	55 (2.1)	73 (3.4)
>18 to <65	1219 (85.3)	1579 (86.0)	1343 (80.3)	1539 (81.4)	2196 (85.1)	1650 (77.1)
≥65	153 (10.7)	219 (11.9)	260 (15.6)	294 (15.5)	330 (12.8)	416 (19.4)
N	1429	1836	1672	1891	2581	2139
Mean SD	41.2 ± 16.1	43.8 ± 16.0	43.7 ± 17.6	44.3 ±17.1	44.1 ±16.2	46.0 ± 18.1
Median	38.0	42.0	41.0	42.0	42.0	44.0
Range	13-86	13-99	13-97	13-92	13-99	13-97
***Weight* (kg)**						
□50						
N	59	133	82	93	219	118
Mean □ SD	47.2 ± 3.0	46.1 ± 3.2	46.1 ± 3.9	46.8 ± 3.3	45.8 ± 3.4	46.1 ± 3.5
Median	48.0	46.3	47.1	47.7	46.0	47.0
Range	37-50	33-50	36-50	37-50	33-50	36-50
>50 to <90						
N	1059	1335	1238	1383	1878	1584
Mean □ SD	70.2 ± 10.1	69.1 ± 10.1	69.9 ± 10.3	70.1 ± 10.2	68.8 ± 10.1	69.8 ± 10.4
Median	70.0	69.0	70.0	70.0	68.0	70.0
Range	50.3-89.8	50.8-89.8	50.3-89.8	50.1-89.8	50.3-89.8	50.3-89.8
≥90						
N	311	365	351	415	480	433
Mean □ SD	104 ± 14.2	104 ± 14.4	106 ± 15.8	104.1 ± 14.4	104.6 ± 14.5	105.8 ± 15.8
Median	99.8	99.8	99.8	99.8	100.0	100.0
Range	90-175.7	90-186	90-172.3	90-175.7	90-190	90-172.3

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

(Source: Applicant's ISS page 10)

Medical Officer Comment: *The demographic characteristics of the safety population are not significantly changed when taking into account the additional Phase 3 studies. There is a moderate increase in the percentage of patients over the age of 65 years. The most significant increase in telithromycin exposure amongst patients > 65 years old occurred in those patients who received a 5*

day course of antibiotics (not the 7-10 day course). Therefore, these studies do not greatly enhance the understanding of the safety of this drug in patients > 65 years old who received longer durations of therapy (i.e., >5 days). When the demographics of telithromycin and comparators are compared for controlled studies only, they remain well matched.

Table ISS.7 shows the numbers of patients with co-existing medical conditions who may have been at higher risk for telithromycin-associated toxicity. **Table ISS.8** shows the numbers of patients receiving selected concomitant medications with the potential to interact with telithromycin.

Table ISS.7. Pretreatment disease profile of subjects in Phase 3 trials, All Integrated population

Pretreatment Disease	Telithromycin			Comparator
	No. in controlled trials (%) (N=2702)	No. in uncontrolled trials (%) (N=1770)	Total (%) (N=3265)	No. of Subjects (%) (N=1672)
Chronic respiratory disease	1149 (42.5)	1068 (60.3)	2217 (49.5)	967 (45.2)
Cardiovascular disease	595 (22.0)	389 (22.0)	984 (22.0)	506 (23.7)
Ischemic heart disease	134 (5.0)	85 (4.8)	219 (4.9)	122 (5.7)
CrCl<30 mL/min	19 (0.7)	36 (2.0)	55 (1.7)	17 (1.0)
CrCl <50 mL/min	241 (8.9)	228 (12.9)	469 (14.4)	205 (12.3)
CrCl <80 mL/min	869 (32.2)	757 (42.8)	1626 (49.8)	757 (45.3)
Diabetes mellitus	126 (4.7)	89 (5.0)	215 (4.8)	108 (5.0)
Liver Disease	48 (1.8)	23 (1.3)	71 (1.6)	39 (1.8)
Risk factors for torsade de pointes	1096 (40.6)	746 (42.1)	1842 (41.2)	903 (42.2)
Abnormal baseline ECG	670 (24.8)	721 (40.7)	1391 (31.1)	645 (30.2)
Increased baseline QTc	133 (4.9)	129 (7.3)	262 (5.9)	143 (6.7)

***Medical Officer Comment:** For the most part, the addition of the new Phase 3 data (Studies 3012, 3013, 4003) did not change the overall percentages of patients with various co-morbid conditions. There were, however, increases in the overall numbers of patients treated with telithromycin within each of the different co-morbidity categories. This increase should provide additional useful safety data in populations where telithromycin toxicity is expected to be enhanced. The Applicant defined "Risk Factors for torsade de pointes" as one or more of the following: an increased QTc interval at baseline, underlying cardiovascular disease, concomitant drugs that increase the QTc interval, heart*

rate < 60, and potassium below the lower bound of the normal range. It is not clear what potassium lab value was used. Fluoxetine was included in the list of concomitant drugs causing increased risk for QTc prolongation. However, fluoxetine by itself, does not cause QTc prolongation. Additionally, there is no evidence to support a cytochrome P450 interaction leading to an increased risk of QT prolongation since fluoxetine is a 2D6 substrate and telithromycin, a 3A4 substrate, does not appear to be affected by 2D6. Given that fluoxetine is a very commonly prescribed drug, there may be a large number of patients included in the category of having increased risk of QTc prolongation, but who actually do not have this risk. It would have been more accurate to include in this category those patients taking fluoxetine concomitantly with thioridazine. It is difficult to quantify the level of risk for QTc prolongation for patients categorized by the applicant as having a risk factor for torsades de pointes, thus limiting the usefulness of this categorization.

Table ISS.8. Frequency of concomitant use of drugs with potential for causing drug interactions with telithromycin: All integrated Phase 3 studies

Concomitant medication	Telithromycin			Comparator
	No. in controlled trials (%) (N=2702)	No. in uncontrolled trials (%) (N=1770)	Total (%) (N= 4472)	No. of Subjects (%) (N=2139)
Theophylline	74 (2.7)	52 (2.9)	126 (2.8)	74 (3.5)
Anticoagulants	235 (8.7)	186 (10.5)	421 (9.4)	214 (10)
Warfarin	25 (0.9)	19 (1.1)	44 (9.8)	18 (0.8)
Cardiac glycosides	32 (1.2)	25 (1.4)	57 (1.3)	24 (1.1)
Antiarrhythmics	11 (0.4)	8 (0.5)	19 (0.4)	9 (0.4)
CYP 3A4 substrates	1172 (43.4)	733 (41.4)	1905 (42.6)	941 (44.0)
CYP 2D6 substrates	474 (17.5)	296 (16.7)	770 (17.2)	378 (17.7)
CYP 3A4 inhibitors	484 (17.9)	202 (11.4)	686 (15.3)	241 (11.3)
High potential to prolong QTc	171 (6.3)	29 (1.6)	200 (4.8)	108 (5.0)
CNS-active drugs	373 (13.8)	184 (10.4)	557 (12.5)	317 (14.8)
Statins	68 (2.5)	48 (2.7)	116 (2.6)	62 (2.9)

Medical Officer Comment: *The numbers of some of these at-risk populations in the safety database have increased as a result of the additional clinical trials. However, there are still very limited numbers of patients receiving some potentially interacting medications. For example, since there were only 219 patients treated with telithromycin who had a history of ischemic heart disease, it would be expected that a specific adverse event caused by an interaction between telithromycin and*

pre-existing ischemic heart disease would likely be observed in the safety database only if the rate of the adverse event were at least 1.4% (or 1,370 events per 100,000).

Two of the new studies did not specifically exclude patients in all at-risk populations, while the third (4003) did actually exclude most of them, including patients with renal insufficiency, hepatic insufficiency, and cardiac disease. All excluded patients with certain risk factors for torsades (severe hypokalemia, known prolonged QTc syndrome, personal or family history of syncope). Although there was a substantial increase in the number and percentage of patients who took telithromycin while also taking a CYP3A4 inhibitor, the exclusion criteria of two of the new studies excluded patients who received many potentially interacting drugs, such as macrolide antibiotics. In the general population, telithromycin might be used in patients who failed therapy with a macrolide. Enrollment of such patients would have provided useful safety data, since concomitant macrolide use may result in significant drug interactions via the CYP3A4 system.

Deaths

In the three new studies (studies 3012, 3013, 4003) there were 15 deaths, 10/1,207 (0.83%) in the telithromycin arm and 5/467 (1.1%) in the comparator arm. Of the 10 new deaths in the telithromycin arm, 5 were in the open label, non-comparative CAP study, 3012, and the other 5 were from the two double-blinded, active controlled studies, 4003 (CAP), and 3013 (AECB).

The following is a detailed review of each death occurring in a telithromycin-treated patient in the three new studies (3012, 3013, 4003). Medical Officer review of each death included review of summaries and case report forms. For a detailed review of deaths which occurred in prior Phase 3 studies, please see the ISS for the original submission.

Study 3012 (Open-label CAP Study):

2004/004: This patient was an 84-year-old female who was admitted into the study after hospitalization. She developed acute sepsis shortly after enrollment into the trial (within several hours of receiving first dose of telithromycin). She was withdrawn from the study, and sent to the ICU where she died within one day. During hospitalization, she developed leukopenia, hypotension, atrial fibrillation, and acidosis. ECG at time of decompensation did not show QT prolongation. Her antibiotic was changed to ceftriaxone/clarithromycin. Blood cultures were negative and a culture of a tracheal aspirate grew normal flora. An autopsy was not performed. The investigator reported the death as not related to study medication.

Medical Officer Comment: *This elderly patient decompensated soon after enrollment into the study. The time between enrollment and deterioration was too rapid to attribute lack of therapeutic effect as a contributing factor. In addition, the patient's deterioration did not appear to be related to toxicity from the study drug.*

4002/022: This patient was a 70-year-old female with a history of chronic obstructive pulmonary disease (COPD) who experienced worsening of her congestive heart failure two days after the start of study medication. Symptoms included dyspnea, nausea, and nervousness. The initial

electrocardiogram (ECG) revealed premature ventricular contractions, right atrial-enlargement, low T-waves, and sinus tachycardia. Baseline QT intervals were normal, but repeat QT intervals were not measured. Although the patient was treated with furosemide on the day of study entry, she did not respond and subsequently died two days later of worsening heart failure. *H. influenzae* was isolated from a sputum culture. Concomitant medications include theophylline, prednisone, salbutamol, ipratropium, Phenergan, berotec, amitriptiline, and cimetidine.

Medical Officer Comment: *After a request to the applicant for all ECG's for this patient, the sponsor indicated that there were no repeat or follow-up ECG's done. It is difficult to understand how this patient did not have a repeat ECG done, since the patient experienced a cardiac deterioration as an inpatient. Certainly, it would be expected that any inpatient who experienced a serious cardiac complication would have had a repeat ECG. Because there is no repeat ECG reported, the potential for QT prolongation cannot be excluded as a contributing factor. It is concerning from the perspective of clinical trial conduct, that a patient enrolled in a clinical trial who had a serious cardiac adverse event did not have the necessary evaluation to allow for assessment of the potential contribution of the study drug.*

4003/013: This patient was a 46-year-old HIV-positive patient who was enrolled with typical baseline symptoms of pneumonia but with a chest radiograph which indicated "multisegmental patchy consolidation in both lung fields favoring post primary bronchopulmonary TB." *Morganella morganii* was isolated from a sputum specimen and was not susceptible to telithromycin. A blood culture was negative. The patient was felt better after two days of treatment, and fevers had decreased on acetaminophen, but then he was found to have persisting symptoms on study day 5. The patient subsequently died on study day 8, one day after completing treatment with telithromycin. This patient's CD4 count was listed on the CRF as 38, but no CD4 count was listed in the laboratory SAS transport file.

Medical Officer Comment: *A CD4 count of 38 should have resulted in exclusion from the study, however, the patient was enrolled in the study before it was known that he had HIV infection or AIDS. Because of this state of severe immunodeficiency as well a lack of post-mortem data, it is difficult to accurately assign a cause of death. This patient should have been discontinued or excluded from the study once it was learned that his CD4 count met exclusion criteria.*

4003/022: This patient was a 53-year-old [redacted] male with HIV infection (CD4 =44) who was hospitalized and treated with a full 7 day course of telithromycin for CAP due to *S. pneumoniae,* which was isolated from sputum culture. Baseline symptoms included fever, chills, cough, dyspnea, sputum production, chest pain, rales, dullness on percussion, rhonchi, and tachypnea. The patient's symptoms were improved after therapy, however, on study day 11, the patient requested to withdraw from the study on the advice of his "witch doctor" who had advised him that the study medication was considered "poison." The patient was readmitted on [redacted] with recurrence/worsening of CAP symptoms and died two days later. Treatment with ciprofloxacin and TB medications was ordered on [redacted] but the patient died prior to receiving the medications.

Medical Officer Comment: *This patient was also enrolled in the study before it was known that he had advanced HIV disease. Because of this state of severe immunodeficiency as well a lack of post-mortem data, it is difficult to accurately assign a cause of death. This patient also should have been*

discontinued or excluded from the study. The fact that he was treated with TB medications and ciprofloxacin indicates that the exact cause of his deterioration was unclear.

4003/040: This patient was a 56-year-old male who had a history of COPD, pneumoconiosis, and HIV, (with a CD4 count of 380). A causative pathogen was not isolated at baseline visit and the applicant reports that the baseline chest radiograph was not consistent with a diagnosis of pneumonia. The chest radiograph revealed a right upper lobe fluid-filled cavity, patchy consolidation in both upper lobes, a small pleural effusion in the right side, and underlying pneumoconiosis. A subsequent reading by a radiologist indicated that there was no evidence of pneumonia on the chest radiograph. The patient was treated with 7 days of telithromycin; however, on visit two, several signs/symptoms persisted, including elevated WBC, mild cough, dyspnea, and sputum production as well as severe bronchial breath sounds. *S. pneumoniae* was isolated from a sputum culture obtained at this visit; however, a repeat culture at the end of therapy (day 8) did not yield a positive culture for *S. pneumoniae.* Five days after completion of antibiotics, the patient presented with fever, elevated WBC, mild cough, dyspnea, rales, and sputum production, and moderate bronchial breath sounds. At this time, he was diagnosed as having worsening bilateral upper lobe pneumonia (no organism isolated) and he died the same day. No autopsy was performed and the cause of death was reported as pneumonia followed by the subject's immunocompromised state.

Medical Officer Comment: *This patient does potentially reflect a death resulting from insufficient treatment effect. The cause of death appears to have been bilateral upper-lobe pneumonia. It is possible that HIV infection played a role in his death. Note: study exclusion criteria regarding HIV were as follows: subjects with Human Immunodeficiency Virus (HIV) infection who had either an acquired immune deficiency syndrome (AIDS)-defining condition (e.g., Kaposi's sarcoma, Pneumocystis carinii pneumonia, or a CD4 + T-lymphocyte count of $<200/mm^3$. Subjects who were HIV positive without an AIDS defining condition and CD4 + T-lymphocyte count $>200/mm^3$ were allowed to participate in this study. So, this patient was appropriately enrolled into the study.*

Study 3013 (Randomized Active Controlled AECB Study)

1203/004: This patient was a 79-year-old woman who died of a presumed myocardial infarction after presenting with severe precordial chest pain 117 days after study medication was completed.

1403/004: This patient was an 81-year-old woman who died of an acute myocardial infarction 116 days after study medication was completed.

Medical Officer Comment: *Neither of the these patients is likely to have died as a result of telithromycin administration because of the lack of a temporal relationship between the study drug exposure and the death. In this study, there were three patients in the control arm (clarithromycin) who died; none of these deaths appears to have been related to study medication. The causes of these deaths included neoplasm (48 days post-treatment), severe COPD exacerbation (54 days post-treatment), and cardiopulmonary arrest (82 days post-treatment).*

Study 4003 (Randomized Active Controlled CAP Study)

3657/025: This patient was a 41-year-old male with a history of alcohol dependency and hemoptysis who was enrolled as an inpatient in the telithromycin 5-day treatment group. On the day of enrollment, the patient had fevers, chills, severe dyspnea, severe tachypnea, and severe pleuritic chest pain as well as delerium. On day three, sputum and blood cultures were obtained and grew *Klebsiella pneumoniae* resistant to telithromycin and clarithromycin. On the same day, the patient developed septicemia and therapy was changed to IV cefuroxime and IV gentamicin. The patient died that day of septicemia.

Medical Officer Comment: *It is possible that lack of treatment effect contributed significantly to this patient's death. The isolated etiologic organism was found to be resistant to telithromycin and clarithromycin, however, the mechanism of resistance is not clear. Presumably, because of the absence of prior telithromycin exposure, the decreased susceptibility of this isolate to telithromycin reflects cross resistance to other agents (such as clarithromycin). The patient did have at least moderately severe pneumonia at the time of enrollment. Although vital signs were not recorded in the case report form, review of signs and symptoms from the time of enrollment indicate that I.V. antibiotics may have been a more appropriate treatment choice for this patient. In addition, the history of ongoing alcohol abuse and delirium are both exclusion criteria, and on this basis, the patient should have been excluded.*

3410/004: This patient was a 78-year-old female with a history of congestive heart failure, left ventricular hypertrophy, and ventricular arrhythmia (unspecified) for which she was treated with amiodarone and lisinopril. The patient had a Fine Score of IV and was hospitalized for treatment. Entry sputum cultures grew telithromycin-susceptible *S. pneumoniae* and entry ECG revealed first degree AV block (PR = 0.22 sec) and a QTc interval within normal limits (440 msec). On the morning of study day 3, the patient was pronounced dead after being found with no pulse and no respiration.

Medical Officer Comment: *Although it is not possible based on the available information to exclude telithromycin toxicity as a contributor to this death, the patient had other clear potential causes of death such as a Fine Score indicative of severe disease and history of ventricular arrhythmia requiring treatment with amiodarone.*

3652/003: This patient was a 30-year-old male who was brought to the hospital the morning of study day 8 (one day after completing 7 day course of telithromycin). The prior evening, he had developed headache, emesis, and convulsions. He was treated with diazepam, cefazolin, gentamicin, and IV fluids. Later that day, the patient died. No LP was performed and the family refused autopsy. The investigator attributed the death to acute meningitis based on clinical diagnosis.

Medical Officer Comment: *This patient did not have a history of epilepsy. The only reported medical history included a prior episode of pneumonia. At the time of the On-therapy visit (on study day 3), the patient had experienced improvement in almost all of the baseline CAP symptoms. The data available are not sufficient to definitively determine the cause of death (i.e., status epilepticus vs. bacterial meningitis vs. subarachnoid hemorrhage).*

Table ISS.9 shows a summary of all deaths in new Phase 3 studies, including 3012, 3013, and 4003.

Table ISS.9. Summary of deaths in new Phase 3 studies (3012, 3013, 4003)

Study	Study Drug	Number	Causes (Age in years, Gender)	Related to study Medication*
3012 No control	Telithromycin	5	Septicemia (84 F), pneumonia x 2 (46 M, 56 M); heart failure (70 F); immune mechanism (AIDS) (43 M)	None
3013	Telithromycin	2	Myocardial Infarction x 2 (79 F, 81 F)	None
	Clarithromycin	3	Neoplasm (90 F); cardiac dysrrhythmia (79 F); cardiac arrest (88 F)	None
4003	Telithromycin	3	Gram-negative septicemia (41 M) ; cardiac arrest (78 F); convulsions (30 M)	None
	Clarithromycin	2	Myocardial infarction (83 F); lung cancer (57 M)	None

* Relation to study medication as determined by the investigator.

Medical Officer Comment: *There is no evidence of an increased rate of serious adverse events resulting in death for telithromycin-treated patients compared to control-treated patients based on review of CRF's, case summaries, and SAS transport files for the reported deaths in studies 3012, 3013, and 4003. There also does not appear to be any difference in the rate of deaths for telithromycin-treated patients and comparator-treated patients by indication.*

Deaths in All Integrated Phase 3 clinical studies

Table ISS.10 provides a comparison between AE's resulting in death for the initial NDA submission and the integrated NDA re-submission. Table ISS.11 shows deaths in the original submission. The integrated analysis contains the new information described above from studies 3012, 3013, and 4003, but does not include data from study 3014. For a detailed review of deaths which were submitted as part of the initial NDA submission, please see Dr. David Ross's ISS review for that submission.

Table ISS.10. Deaths (on-treatment and post-treatment) in all integrated Phase 3 studies: Comparison with previous studies

	n/N (%) subjects			
	Previous Studies[a]		All Integrated Studies[b]	
Indication	**Telithromycin**	**Comparator**	**Telithromycin**	**Comparator**
Subjects who died	7/3265 (0.2)	4/1672 (0.2)	17/4472 (0.4)	9/2139 (0.4)
Controlled Studies	2/2045 (0.1)	4/1672 (0.2)	7/2702 (0.3)	9/2139 (0.4)
CAP	2/528 (0.4)	3/536 (0.6)	5/916 (0.5)	5/723 (0.7)
AECB	0/340 (0.0)	0/346 (0.0)	2/609 (0.3)	3/626 (0.5)
Tonsillitis/Pharyngitis	0/427 (0.0)	1/424 (0.2)	0/427 (0.0)	1/424 (0.2)
Uncontrolled Studies	5/1220 (0.4)	NA	10/1770 (0.6)	NA
CAP	5/887 (0.6)	NA	10/1437 (0.7)	NA

[a] Includes all studies submitted in the initial review cycle.
[b] Previous Studies plus 3 new studies.
(page 38, Applicant's ISS)

Medical Officer Comment: *The rates of death on treatment and post-treatment for telithromycin and comparators are similar. There were no deaths in the telithromycin group or the comparator group which were attributed to study drug by the sponsor. This was confirmed by the reviewing Medical Officer by detailed review of all case report forms for those patients who died.*

Table.ISS.11. Summary of deaths in previous Phase 3 studies

Study	Study Drug	Number of Patients	Cause
3000	Telithromycin	2	Leptospirosis, Gram-negative septicemia
3001	Telithromycin	2	Multi-organ failure, Heart Failure
	Amoxicillin	1	Asthma
3004	Telithromycin	0	
	Penicillin	1	Acute Lymphoid Leukemia
3006	Telithromycin	0	
	Clarithromycin	2	Pneumonia, lung cancer
3009	Telithromycin	1	Pneumonia
3010	Telithromycin	2	Foreign body in larynx, Acute MI

Nonfatal Serious Adverse Events (SAE's)

Phase 1
In the eight additional submitted Phase 1 studies (167 patients) there were a total of 2 SAE's. Both were from Study 1062 and neither was thought to be related to study medication. One was an episode of congestive heart failure occurring two days after the last dose of telithromycin. The other SAE was an episode of stroke.

Medical Officer Comment: *Medical Officer review of these cases is in agreement with this assessment.*

Phase 3
In all controlled Phase 3 trials, there were a total of 59 (2.2%) serious treatment-emergent adverse events in the telithromycin arm as compared to 61 (2.9%) in the comparator arm. There was no significant change in the rates or types of serious adverse events before and after integration of the new Phase 3 studies, as shown in Table ISS.12.

Table ISS.12. All and possibly related non-fatal serious TEAEs in controlled Phase 3 studies: Comparison between previous studies and all integrated studies

Serious adverse event preferred term	Number (%) of subjects			
	Previous Studies[a]		All Integrated Studies[b]	
	Telithromycin (N=2045)	Comparator (N=1672)	Telithromycin (N=2702)	Comparator (N=2139)
Subjects with all serious TEAEs[c]	**40 (2.0)**	**41 (2.5)**	**59 (2.2)**	**61 (2.9)**
AECB NOS	2 (0.1)	2 (0.1)	3 (0.1)	3 (0.1)
Pleural effusion	2 (0.1)	1 (0.1)	3 (0.1)	1 (0.0)
Pneumonia aggravated	1 (0.0)	7 (0.4)	2 (0.1)	11 (0.5)
Lung abscess NOS	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
Bronchospasm NOS	1 (0.0)	0 (0.0)	2 (0.1)	1 (0.0)
Empyema NOS	1 (0.0)	0 (0.0)	2 (0.1)	1 (0.0)
Hypersensitivity NOS	1 (0.0)	1 (0.1)	2 (0.1)	1 (0.0)
COPD	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Hepatocellular damage[e]	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Subjects with possibly related serious TEAEs[d]	**8 (0.4)**	**4 (0.2)**	**9 (0.3)**	**6 (0.3)**
Hepatocellular damage[e]	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Colitis pseudomembranous	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.0)
Hypersensitivity NOS	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.0)
AECB NOS	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Drug hypersensitivity	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Erythema multiforme	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Gastroenteritis NOS	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Vomiting NOS	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Dyspnea NOS	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Gastrointestinal disorder NOS	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Mania	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Overdose NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

[a] Includes all controlled studies submitted in first review cycle.
[b] Previous Studies plus CAP Study 4003 and AECB Study 3013.
[c] Based on a minimum of 2 subjects with all serious TEAE in telithromycin group in controlled studies.
[d] All possibly related serious TEAEs in controlled studies are shown.
[e] asymptomatic transaminase elevation
NOS = not otherwise specified
(page 54 ISS)

Medical Officer Comment: *In Table ISS.12, the section of the table which includes all TEAE's, regardless of whether they were thought by the investigator to be possibly related, contains those TEAE's with a minimum of 2 subjects. In the new controlled studies, there was one patient in the telithromycin arm with a non-fatal serious TEAE identified by the investigator as possibly related.*

This patient was a 51-year-old woman who was enrolled in study in AECB study 3013 and who had worsening of her acute exacerbation of chronic bronchitis as the serious adverse event. This occurred 10 days after completion of study medication and was thought by the investigator to possibly be related to study medication due to lack of treatment effect. Medical officer review of the new serious adverse events which were not thought to be possibly related to study drug revealed that most were related to underlying co-morbidities or the infection for which the patient was being treated. It is also important to note that there was one patient in the telithromycin group with a serious AE of "accommodation disorder" that was initially categorized by the investigator as possibly related to study medication. However, five months later, this was changed to "not related" to study medication and no basis was given for this change. This patient's AE was considered "significantly disabling" and she required a visit to the ophthalmologist. Medical Officer review of this case concludes that it is consistent with visual toxicity known to occur with telithromycin exposure.

Table ISS.13 shows a comparison between previous studies and all integrated uncontrolled studies with regard to treatment-emergent serious adverse events.

Table ISS.13. All and possibly related non-fatal serious TEAEs in uncontrolled Phase 3 studies: Comparison between previous studies and all integrated studies

	Number (%) of subjects	
	Previous Studies[a]	All Integrated Studies[b]
Serious adverse event preferred term	**Telithromycin (N=1220)**	**Telithromycin (N=1770)**
Subjects with all serious TEAEs [c]	**40 (3.3)**	**58 (3.3)**
Pneumonia aggravated	7 (0.6)	10 (0.6)
Pleural effusion	4 (0.3)	5 (0.3)
Chronic obstructive airways disease	1 (0.1)	2 (0.1)
Renal impairment NOS	1 (0.1)	2 (0.1)
Pleuritic pain	2 (0.2)	2 (0.1)
Pneumonia NOS	1 (0.1)	2 (0.1)
Respiratory failure	2 (0.2)	2 (0.1)
Sepsis NOS	1 (0.1)	2 (0.1)
Chest pain aggravated	0 (0.0)	2 (0.1)
Subjects with possibly related serious TEAEs [d]	**4 (0.3)**	**5 (0.3)**
Pleural effusion	0 (0.0)	1 (0.1)
Gastroenteritis NOS	1 (0.1)	1 (0.1)
Hepatitis NOS [e]	1 (0.1)	1 (0.1)
Neutropenia	1 (0.1)	1 (0.1)
Skin vasculitis NOS	1 (0.1)	1 (0.1)

[a] Includes all uncontrolled studies submitted in first review cycle.
[b] Previous Studies plus CAP Study 3012.
[c] Based on a minimum of 2 subjects with all serious TEAE in telithromycin group in uncontrolled Phase 3 studies.
[d] All possibly related serious TEAEs in uncontrolled studies are shown.
NOS = not otherwise specified
[e] subject 502/1069 in study 3000

(page 57, Applicant's ISS)

Medical Officer Comment: *In Table ISS.13, the section of the table which includes all TEAE's, regardless of whether they were thought by the investigator to be possibly related, contains those TEAE's with a minimum of 2 subjects. In the new uncontrolled study, there was one additional possibly related non-fatal serious TEAE. This patient was a 24-year-old with community acquired pneumonia who experienced a worsening pleural effusion requiring hospitalization for aspiration of the effusion. This patient had a positive sputum culture which was positive for* H. influenzae. *As with the controlled studies, medical officer review of the new serious adverse events which were not thought to be possibly related to study drug revealed that most were related to underlying co-morbidities or the infection for which the patient was being treated.*

Adverse Events

Definitions and methods used to describe adverse events in the new clinical studies are the same as those used in the initial NDA.

All on-treatment adverse events were classified as treatment-emergent adverse events (TEAE's) or non-treatment-emergent. The following definitions were used:

- TEAEs include any on-treatment adverse event that was not present before treatment or was present before treatment and became more intense (increased in severity) or more frequent during the treatment period, as determined by the investigators. The treatment period encompassed the period from the first day of study medication to 7 days (or three days for clinical pharmacology trials) after the last day of study medication. In addition, any on-treatment adverse event considered possibly related to study medication by the investigators that led to permanent discontinuation of study medication, or resulted in death, was considered treatment-emergent. This group of adverse events was of primary interest.
- Possibly related treatment-emergent adverse events are those treatment-emergent adverse events the investigators reported as "possibly related" to study medication and those on-treatment adverse events with missing causality.

Medical Officer Comment: *There was no change in the methods and definitions used to characterize adverse events in the new studies or in the All Integrated analyses. It should be noted, that, at the request of the FDA, MedDRA 4.0 was used to code adverse events for studies 3012, 3013, and 4003. Since prior studies used HARTS coding, this data had to be converted to MEDRA to allow for integration and comparison with the new studies. For the conversion of HARTS to MedDRA, verbatim terms (adverse events and signs and symptoms data) were loaded in a separate database with an identifier (subject identifier, study identifier, etc) and terms were autocoded using the MedDRA dictionary. Terms that could not be autocoded were coded manually and reviewed by a Global Coding Officer. If an "as reported" term could not be coded in MedDRA, the HARTS decode was used in place of the "as reported" term in the coding process. Once recoding was complete, a SAS dataset was created from this separate database containing the MedDRA terms. Although HARTS AE terms were autocoded using the MedDRA dictionary, there were terms that could not be autocoded, and thus were coded manually. The manual coding was not reported by the sponsor as having been done in a blinded fashion, and the sponsor did not indicate what portion of the conversions were done manually.*

Table ISS.14 shows the most common TEAE's in controlled Phase 3 studies. Rates of the most common TEAE's did not change significantly when the new studies were integrated with the previous studies.

Table.ISS.14. All and possibly related TEAEs by decreasing frequency in controlled Phase 3 Studies: Comparison between previous studies and all integrated studies

Preferred term	Number (%) of subjects			
	Previous Studies[a]		All Integrated Studies[b]	
	Telithromycin N=2045	Comparator N=1672	Telithromycin N=2702	Comparator N=2139
All TEAEs*				
Diarrhea NOS	246 (12.0)	142 (8.5)	292 (10.8)	184 (8.6)
Nausea	184 (9.0)	72 (4.3)	213 (7.9)	99 (4.6)
Headache NOS	112 (5.5)	110 (6.6)	148 (5.5)	125 (5.8)
Dizziness (excl vertigo)	91 (4.4)	47 (2.8)	99 (3.7)	57 (2.7)
Vomiting NOS	67 (3.3)	40 (2.4)	79 (2.9)	48 (2.2)
Loose stools	55 (2.7)	27 (1.6)	63 (2.3)	33 (1.5)
Dyspepsia	44 (2.2)	25 (1.5)	46 (1.7)	31 (1.4)
Dysgeusia	34 (1.7)	36 (2.2)	43 (1.6)	77 (3.6)
Possibly related TEAEs	1056 (51.6)	806 (48.2)	861 (31.9)	606 (28.3
Diarrhea NOS	227 (11.1)	134 (8.0)	270 (10.0)	171 (8.0)
Nausea	166 (8.1)	63 (3.8)	190 (7.0)	87 (4.1)
Headache NOS	44 (2.2)	48 (2.9)	54 (2.0)	53 (2.5)
Dizziness (excl vertigo)	73 (3.6)	26 (1.6)	75 (2.8)	33 (1.5)
Vomiting NOS	57 (2.8)	24 (1.4)	64 (2.4)	30 (1.4)
Loose stools	51 (2.5)	24 (1.4)	58 (2.1)	30 (1.4)
Dyspepsia	35 (1.7)	16 (1.0)	36 (1.3)	21 (1.0)
Dysgeusia	32 (1.6)	35 (2.1)	40 (1.5)	76 (3.6)

[a] Includes all controlled studies submitted in first review cycle.
[b] Previous Studies plus CAP Study 4003 and AECB Study 3013.
*Based on a frequency of all TEAEs of ≥2.0% in telithromycin or comparator treatment groups in previous or all integrated studies.
NOS = not otherwise specified
Source: p. 21; Applicant's ISS

Medical Officer Comment: *After integration of the new controlled data, there continues to be a trend towards an increased rate of TEAE's in telithromycin-treated patients vs. comparator-treated patients for the common AE's of diarrhea, nausea, dizziness, vomiting, looses stools, and dyspepsia.*

Table ISS.15. shows all TEAE's and possibly related TEAE's in Phase 3 uncontrolled studies. This table contains all previous uncontrolled data in addition to one new uncontrolled CAP study (3012) which increased the number of safety evaluable telithromycin-treated subjects in the uncontrolled studies by 550 from 1220 to a total of 1770 subjects, an increase of 45.1%. There were no new uncontrolled studies in any other indications in this resubmission.

Table ISS.15. All and possibly related TEAE's in all uncontrolled integrated Phase 3 studies

Preferred Term	All TEAE's N=1770 n (%)	Possibly Related TEAE's N= 1770 n (%)
Diarrhea (NOS)	104 (5.9)	94 (5.3)
Nausea	74 (4.2)	60 (3.4)
Headache (NOS)	45 (2.5)	14 (0.8)
Vomiting	35 (2.0)	24 (1.4)
Liver Function Tests NOS abnormal	25 (1.4)	22 (1.2)
Abdominal pain	20 (1.1)	17 (1.0)
Herpes simplex	19 (1.1)	0 (0)
Insomnia	18 (1.0)	4 (0.2)
Dizziness (excl. vertigo)	17 (1.0)	12 (0.7)
Loose stools	15 (0.8)	14 (0.8)
Rash NOS	15 (0.8)	5 (0.3)
Constipation	14 (0.8)	3 (0.2)
Gastritis NOS	13 (0.7)	11 (0.6)
Dysgeusia	12 (0.7)	12 (0.7)
Vaginal Candidiasis	12 (0.7)	12 (0.7)
Pneumonia aggravated	12 (0.7)	0 (0.0)
Dry Mouth	11 (0.6)	9 (0.5)
Thrombocythemia	10 (0.6)	6 (0.3)
Dyspepsia	11 (0.6)	5 9 (0.3)
UTI	9 (0.5)	0 (0.0)
Transaminase NOS increased	9 (0.5)	9 (0.5)
Fatigue	8 (0.5)	4 (0.2)
Alanine aminotransferase increased	8 (0.5)	7 (0.4)
Somnolence	8 (0.5)	6 (0.3)
Bronchospasm	8 (0.5)	0 (0.0)
Pleural effusion	8 (0.5)	1 (0.1)

Medical Officer Comment: *In general, the rates of most of the adverse events in all uncontrolled studies are unchanged from the original submission.*

Drug Demographic Interactions

Table ISS.16 shows the incidence of the most common TEAE's in all integrated controlled studies by sex.

Table ISS.16. Incidence of TEAEs by sex in all integrated controlled Phase 3 trials

	Men		Women	
Preferred Term	Telithromycin (n=1317)	Comparators (n=1031)	Telithromycin (n=1385)	Comparators (n=1108)
Diarrhea NOS	123 (9.3%)	84 (8.1%)	169 (12.2%)	100 (9.0%)
Nausea	69 (5.2%)	38 (3.7%)	144 (10.4%)	61 (5.5%)
Headache NOS	68 (5.2%)	54 (5.2%)	80 (5.8%)	71 (6.4%)
Dizziness	38 (2.9%)	26 (2.5%)	61 (4.4%)	31 (2.8%)
Vomiting NOS	22 (1.7%)	22 (2.1%)	57 (4.1%)	26 (2.3%)
Dyspepsia	13 (1.0%)	16 (1.6%)	33 (2.4%)	15 (1.4%)
Vaginal moniliasis	0 (0.0%)	0 (0.0%)	30 (2.2%)	33 (3.0%)
Taste perversion	14 (1.1%)	34 (3.3%)	29 (2.1%)	43 (3.9%)
Abdominal pain NOS	23 (1.7%)	5 (0.5%)	24 (1.7%)	17 (1.5%)
Abdominal pain upper	11 (0.8%)	7 (0.7%)	16 (1.2%)	12 (1.1%)
Dry mouth	12 (0.9%)	9 (0.8%)	16 (1.2%)	15 (1.4%)
ALT increased	14 (1.1%)	10 (1.0%))	7 (0.5%)	7 (0.6%)
Fatigue	10 (0.8%)	13 (1.3%)	25 (1.8%)	10 (0.9%)
Rash NOS	6 (0.5%)	3 (0.3%)	13 (0.9%)	17 (1.5%)
Vision Blurred	5 (0.4%)	0 (0.0%)	12 (0.9%)	3 (0.3%)
Glossitis	1 (0.1%)	1 (0.1%)	7 (0.5%)	1 (0.1%)

(Data from table SS-145, Applicant's ISS)
Columns are not additive since a patient may have had more than one adverse event.

Medical Officer Comment: *As was found in the original submission, the rates of diarrhea, nausea, vomiting, and dizziness were increased in women treated with telithromycin relative to comparator. Other adverse events which were increased in women included dyspepsia and blurred vision.*

Table ISS.17 shows the incidence of common TEAE's in all integrated controlled studies by age.

Table ISS.17. Frequency of all TEAE's by age: All integrated studies

	Number (%) of subjects					
	13 to 18 years		>18 to <65 years		≥65 years	
	TEL	Comp	TEL	Comp	TEL	Comp
Preferred term	(N=113)	(N=73)	(N=3735)	(N=1650)	(N=624)	(N=416)
Subjects with TEAEs	35 (31.0)	33 (45.2)	1663 (44.5)	817 (49.5)	272 (43.6)	185 (44.5)
Diarrhea NOS	8 (7.1)	5 (6.8)	335 (9.0)	135 (8.2)	53 (8.5)	44 (10.6)
Nausea	7 (6.2)	2 (2.7)	242 (6.5)	88 (5.3)	38 (6.1)	9 (2.2)
Vomiting NOS	3 (2.7)	1 (1.4)	101 (2.7)	41 (2.5)	10 (1.6)	6 (1.4)
Headache NOS	3 (2.7)	7 (9.6)	174 (4.7)	107 (6.5)	16 (2.6)	11 (2.6)
Dizziness (excl vertigo)	2 (1.8)	1 (1.4)	102 (2.7)	44 (2.7)	12 (1.9)	12 (2.9)
Dysgeusia	1 (0.9)	0 (0.0)	49 (1.3)	53 (3.2)	5 (0.8)	24 (5.8)
Dry mouth	1 (0.9)	2 (2.7)	35 (0.9)	18 (1.1)	3 (0.5)	4 (1.0)
Pharyngolaryngeal pain	1 (0.9)	2 (2.7)	35 (0.9)	14 (0.8)	4 (0.6)	4 (1.0)
Cough	0 (0.0)	2 (2.7)	14 (0.4)	16 (1.0)	1 (0.2)	2 (0.5)

Source: Page 89 Applicant's ISS

Medical Officer Comment: *Review of this data indicates that increased age does not correlate with a higher rate of adverse events. The table above combines data from controlled and uncontrolled studies. Medical officer review assessing the frequency of AE's by age in only the controlled studies yielded the same lack of correlation. The sponsor did not provide an analysis of adverse events according to race. Medical officer review of submitted data indicates that there were similar rates of AE's and SAE's amongst different racial groups in telithromycin-treated patients and comparator-treated patients. However, it should be noted that minorities represented less than 10% of the total safety population, thus, strong conclusions regarding a possible interaction of race and safety cannot be determined based on this data.*

Frequency of TEAE's by Intensity

The majority of TEAEs in Phase 3 controlled studies were of mild or moderate intensity for both telithromycin- and comparator-treated subjects.

Table ISS.18 shows the frequency of all and possibly related TEAE's by intensity in all integrated controlled Phase 3 studies.

Table ISS.18. Frequency of all and possibly related TEAEs by intensity in controlled Phase 3 studies: Comparison between previous studies and all integrated studies

	Number (%) of subjects			
	Previous Studies[a]		All Integrated Studies[b]	
Intensity	Telithromycin N=2045	Comparator N=1672	Telithromycin N=2702	Comparator N=2139
All TEAEs				
Mild	763 (37.3)	573 (34.3)	979 (36.2)	758 (35.4)
Moderate	473 (23.1)	366 (21.9)	589 (21.8)	465 (21.7)
Severe	117 (5.7)	83 (5.0)	134 (5.0)	106 (5.0)
Possibly related TEAEs				
Mild	510 (24.9)	329 (19.7)	623 (23.1)	435 (20.3)
Moderate	254 (12.4)	180 (10.8)	296 (11.0)	230 (10.8)
Severe	66 (3.2)	34 (2.0)	70 (2.6)	40 (1.9)

[a] Includes all controlled studies submitted in first review cycle.
[b] Previous Studies plus CAP Study 4003 and AECB Study 3013.
Source: Table SS-22, Table SS-21
(Applicant's ISS page 31)

Medical Officer Comment: *Review of various specific TEAE's by severity did not reveal significant differences between telithromycin-treated patients and comparator-treated patients.*

Drug-Drug Interactions

CYP3A4 Inhibitors

It should be stressed that the following analysis is exploratory and should be interpreted with caution. Patients were not randomized at baseline by exposure to CYP3A4 inhibitors.

Table ISS.19 shows the frequency of TEAE's by the presence of CYP 3A4 inhibitors in Phase 3 all integrated controlled studies.

Table.ISS.19. Frequency of TEAE's in all integrated controlled Phase 3 studies by the presence of CYP3A4 inhibitors

	Received CYP 3A4 Inhibitor		Did not Receive CYP 3A4 Inhibitor	
Preferred Term	**Telithromycin N=484**	**Comparators N=424**	**Telithromycin N=2218**	**Comparators N=1715**
Diarrhea NOS	60 (12.4%)	33 (7.8%)	232 (10.5%)	151 (8.8%)
Nausea	45 (9.3%)	18 (4.2%)	168 (7.6%)	81 (4.7%)
Dyspepsia	12 (2.5%)	3 (0.7%)	34 (1.5%)	28 (1.6%)
Gastritis NOS	6 (1.2%)	2 (0.5%)	6 (0.3%)	9 (0.5%)
Vision Blurred	9 (1.9%)	0 (0.0%)	8 (0.4%)	3 (0.2%)
Liver Function Abnormality*	14 (2.9%)	7 (1.7%)	57 (2.6%)	48 (2.8%)
Headache	23 (4.8%)	22 (5.2%)	125 (5.6%)	103 (6.0%)
Dizziness (excl. vertigo)	19 (3.9%)	13 (3.1%)	80 (3.6%)	44 (2.6%)
Cardiac Disorders	7 (1.4%)	6 (1.4%)	16 (0.7%)	26 (1.5%)

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

Medical Officer Comment: *There does appear to be a trend towards increased rates of diarrhea, nausea, dyspepsia, gastritis, and blurred vision in patients who received telithromycin and a CYP3A4 inhibitor in comparison to patients who received telithromycin without a CYP3A4 inhibitor. However, because of small overall numbers, and the post-hoc nature of this analysis, it is difficult to draw a firm conclusion regarding this potential increase. Medical officer review of each individual category of liver function abnormality did not reveal differences in rates between those telithromycin-treated patients who received a CYP3A4 inhibitor and those who did not. A similar analysis assessing adverse event rates when HMG-CoA reductase inhibitors were co-administered with telithromycin was performed by the sponsor and did not show any differences. However, because only 68 patients treated with telithromycin in controlled studies actually received an HMG-CoA reductase inhibitor, it is not possible to draw any definitive safety conclusions. Furthermore, many of these patients received HMG-CoA reductase inhibitors such as pravastatin or atorvastatin that are less likely to cause CYP3A4 interactions. A much smaller proportion of patients received HMG-CoA reductase inhibitors likely to cause a drug interaction (e.g., simvastatin, lovastatin). Therefore, the risk profile of telithromycin when concomitantly administered with HMG-CoA reductase inhibitors cannot be determined based on the data provided. However, because it is known that the co-administration of telithromycin and simvastatin results in a 700% increase in simvastatin levels, it can be presumed that this and similar interactions with other HMG-CoA reductase inhibitors have the potential to result in an increased rate of potentially serious adverse events.*

Table ISS.20 shows frequency of TEAEs by strength of co-administered CYP3A4 inhibitor in all integrated controlled Phase 3 trials.

Table ISS.20. Frequency of all TEAEs* by strength of concomitant CYP3A4 inhibitors: All integrated studies

	Number (%) of subjects					
	Mild CYP3A4 inhibitor		Moderate CYP3A4 inhibitor		Strong CYP3A4 inhibitor	
Preferred term	TEL (N = 406)	Comp (N = 220)	TEL (N = 224)	Comp (N = 164)	TEL (N = 45)	Comp (N = 38)
Subjects with TEAEs	209 (51.5)	111 (50.5)	126 (56.3)	97 (59.1)	30 (66.7)	33 (86.8)
Diarrhea NOS	37 (9.1)	19 (8.6)	26 (11.6)	12 (7.3)	8 (17.8)	2 (5.3)
Nausea	37 (9.1)	8 (3.6)	17 (7.6)	10 (6.1)	1 (2.2)	0 (0.0)
Headache NOS	22 (5.4)	9 (4.1)	8 (3.6)	11 (6.7)	1 (2.2)	2 (5.3)
Dizziness (excl vertigo)	16 (3.9)	7 (3.2)	4 (1.8)	6 (3.7)	1 (2.2)	0 (0.0)
Vomiting NOS	15 (3.7)	6 (2.7)	11 (4.9)	5 (3.0)	2 (4.4)	2 (5.3)
Dyspepsia	7 (1.7)	2 (0.9)	5 (2.2)	1 (0.6)	2 (4.4)	0 (0.0)
Gastritis NOS	7 (1.7)	1 (0.5)	2 (0.9)	1 (0.6)	2 (4.4)	0 (0.0)
Loose stools	6 (1.5)	1 (0.5)	4 (1.8)	2 (1.2)	2 (4.4)	3 (7.9)
Vaginosis fungal NOS	4 (1.0)	2 (0.9)	4 (1.8)	3 (1.8)	5 (11.1)	9 (23.7)
Vaginal candidiasis	1 (0.2)	2 (0.9)	1 (0.4)	3 (1.8)	5 (11.1)	5 (13.2)
Vaginitis	1 (0.2)	1 (0.5)	1 (0.4)	1 (0.6)	4 (8.9)	1 (2.6)

TEL = telithromycin. Comp = comparator
* TEAEs reported in ≥3% of subjects in telithromycin group with any strength of CYP3A4 inhibitor
NOS = not otherwise specified

Medical Officer Comment: *The analysis in Table ISS.20 reveals an increasing overall TEAE rate in telithromycin-treated patients as well as comparator-treated patients with increasing strength of concomitant CYP3A4 inhibitors. This pattern was only seen in the telithromycin arm for the most common TEAE's (Diarrhea NOS and Nausea). This analysis combined both controlled and uncontrolled studies. When frequency of all TEAE's and possibly related TEAE's in only controlled Phase 3 trials (excluding Study 3014) is analyzed according to strength of concomitant CYP3A4 inhibitor, there did also appear to be an increase in the incidence of diarrhea in telithromycin-treated patients with strength of 3A4 inhibitor. However, no other gastrointestinal AE's or AE's of other system organ classes showed this same pattern. Therefore, it may be that the response seen with diarrhea is a spurious finding. It should be noted that the numbers of patients who received telithromycin and CYP3A4 inhibitors was limited, particularly for the strong inhibitor and moderate inhibitor categories. Among 2702 patients who received telithromycin in controlled Phase 3 studies, there were 270 who received a concomitant weak CYP3A4 inhibitor, 175 who received a concomitant moderate CYP3A4 inhibitor, and 33 who received a concomitant strong CYP3A4 inhibitor. Such limited data prevents a more accurate assessment of the effect of these inhibitors on the frequency of adverse events.*

There were not enough patients who received telithromycin with concomitant anti-arrhythmic drugs (n= 11 in controlled Phase 3 studies) to detect a potential interaction with such drugs. The same is true for cardiac glycosides (n=32 in controlled studies) or for warfarin (n=25 in controlled studies).

No increase in adverse events was noted in patients who took both telithromycin and CNS drugs or both telithromycin and drugs metabolized by CYP2D6.

As telithromycin is metabolized by CYP3A4, plasma concentrations of telithromycin can theoretically be increased when co-administered with drugs metabolized by the same pathway, but with a higher affinity for the enzyme. Similarly, telithromycin may increase plasma concentrations of drugs metabolized by CYP3A4 that have a lower affinity for the enzyme.

Table ISS.21 shows the most frequently reported TEAEs in subjects with and without concomitant receipt of drugs metabolized by CYP3A4.

Table ISS.21. Frequency of all TEAEs* by presence of concomitant drugs metabolized by CYP3A4: All integrated studies

	Number (%) of subjects			
	With concomitant drug metabolized by CYP3A4		Without concomitant drug metabolized by CYP3A4	
Preferred term	Telithromycin (N = 1905)	Comparator (N = 941)	Telithromycin (N = 2567)	Comparator (N = 1198)
Subjects with TEAEs	928 (48.7)	526 (55.9)	1042 (40.6)	509 (42.5)
Diarrhea NOS	171 (9.0)	87 (9.2)	225 (8.8)	97 (8.1)
Nausea	131 (6.9)	48 (5.1)	156 (6.1)	51 (4.3)
Headache NOS	113 (5.9)	71 (7.5)	80 (3.1)	54 (4.5)
Dizziness (excl vertigo)	50 (2.6)	31 (3.3)	66 (2.6)	26 (2.2)
Loose stools	28 (2.4)	17 (1.8)	35 (1.3)	16 (1.3)
Dysgeusia	18 (0.9)	47 (5.0)	37 (1.4)	30 (2.5)

*TEAEs reported in ≥3% of subjects in either treatment group subjects with or without concomitant drug metabolized by CYP3A4. NOS = not otherwise specified

(Source: Applicant's ISS, page 82)

Medical Officer Comment: *With the possible exception of AE's affecting vision, the presence of a concomitant CYP3A4 substrate did not result in an increase in the rates of AE's in telithromycin-treated patients compared to comparator-treated patients. This finding was true for controlled studies alone and also for less frequent AE's as well (<3%). The possible effect of the concomitant administration of CYP3A4 substrates and telithromycin on the rates of visual AE's is discussed later in the review in the Visual Adverse Events section.*

Drug-Disease Interactions

The frequency of TEAEs associated with telithromycin therapy in Phase 3 studies was evaluated for subjects with and without renal insufficiency, liver disease, diabetes mellitus, cardiovascular diseases, ischemic heart disease, chronic respiratory disease, or an abnormal pretherapy/entry

electrocardiogram (ECG). In addition, subjects with and without risk conditions such as increased QTc interval at pretherapy/entry and risk factors for torsades de pointes were also evaluated.

Table ISS.22 shows the frequency of all TEAE's (controlled and uncontrolled combined) by the presence of underlying disease or risk factor.

Table ISS.22. Frequency of all TEAEs by presence of underlying disease or risk conditions: All integrated studies

Disease state or risk condition	With disease/risk conditions n/N (%)		Without disease/risk conditions n/N (%)	
	Telithromycin	Comparators	Telithromycin	Comparators
Diabetes mellitus	94/215 (43.7)	51/108 (47.2)	1876/4257 (44.1)	984/2031 (48.4)
Cardiovascular disease	460/984 (46.7)	271/506 (53.6)	1510/3488 (43.3)	764/1633 (46.8)
Ischemic heart disease	94/219 (42.9)	65/122 (53.3)	1876/4253 (44.1)	970/2017 (48.1)
Chronic respiratory disease	871/2217 (39.3)	464/967 (48.0)	1099/2255 (48.7)	571/1172 (48.7)
Abnormal ECG at pretherapy/entry	615/1391 (44.2)	315/645 (48.8)	1355/3081 (44.0)	720/1494 (48.2)
Increased QTc at pretherapy/entry	118/262 (45.0)	66/143 (46.2)	1852/4210 (44.0)	969/1996 (48.5)
Risk factors for torsade de pointes	857/1842 (46.5)	464/903 (51.4)	1113/2630 (42.3)	571/1236 (46.2)
Renal insufficiency:				
CrCl <30 mL/min	23/55 (41.8)	9/17 (52.9)	1947/4417 (44.1)	1026/2122 (48.4)
CrCl <50 mL/min	189/469 (40.3)	91/205 (44.4)	1781/4003 (44.5)	944/1934 (48.8)
CrCl <80 mL/min	614/1626 (37.8)	293/679 (43.2)	1356/2846 (47.6)	742/1460 (50.8)
Liver disease	31/71 (43.7)	27/39 (69.2)	1939/4401 (44.1)	1008/2100 (48.0)

n = number of subjects with underlying disease or risk condition who have TEAEs;
N = total number of subjects with underlying disease or risk condition.
CrCl = creatinine clearance
Source: Page 94, Applicant's ISS

Medical Officer Comment: *The rates of adverse events by preferred term and system organ class were assessed according to underlying disease. The following diseases were examined: diabetes mellitus, ischemic heart disease, chronic respiratory disease, abnormal baseline ECG, risk factors for torsade de pointes, renal insufficiency (creatinine clearance of <30 and <50 cc/min, and liver disease. Rates of all TEAE's and rates of possibly related TEAE's for controlled studies alone and also uncontrolled studies were examined for possible interactions between telithromycin administration and existence of these diseases. There were no definite differences in the rates of adverse events or possibly related adverse events between patients taking telithromycin with or without these underlying disease processes. This is true for all TEAE's, specific TEAE's, and TEAE's by system organ class. Several of the disease/risk factor categories had very few patients in them (see Table ISS.7), making it difficult to draw definitive conclusions regarding some of the*

potential drug-disease interactions. Also, it is unclear what the criteria were for the category of "risk factors for torsade de pointes." The percentage of patients who were reported by the sponsor to be in this category could not be confirmed by the reviewing Medical Officer and appears to be quite high. Therefore, the reviewing medical officer was unable to draw conclusions with regard to patients with risk factors for torsade de pointes. In addition, the raw data used to calculate the number of patients with "increased QTc at pretherapy/entry" was not available for review. The number of patients that the sponsor reported as being in this category also appears to be unusually high. Therefore, the reviewing Medical Officer was unable to draw conclusions with regard to this data.

Discontinuations

In Phase 3 controlled trials, discontinuations due to adverse events occurred in 119/2702 (4.4%) of telithromycin-treated patients and 92/2139 (4.3%) of comparator-treated patients. **Table ISS.23** shows the most common reasons for discontinuation in controlled Phase 3 trials.

Table ISS.23. All and possibly related TEAEs resulting in discontinuation of study medication in controlled Phase 3 telithromycin studies

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

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

Medical Officer Comment: *There was a slightly higher rate of discontinuation in telithromycin-treated patients than in comparator-treated patients resulting from certain gastrointestinal disorders including Diarrhea NOS, Vomiting NOS, and Nausea.*

Adverse Events Of Special Interest

During the first review cycle, FDA identified specific possible safety concerns for telithromycin which include the following: cardiac toxicity (specifically, the potential for QT prolongation), visual toxicity, hepatic toxicity, and vasculitis. For the purposes of the second NDA submission, adverse events which fall into these categories have been described as "adverse events of special interest (AESI)." The following contains the Medical Officer Review for each category of AESI. Vasculitis is not presented because there were only a few cases in the entire database, and none of these were felt to be causally related to study drug exposure.

Cardiac

Electrocardiac QT Interval Findings

In this Amendment, ECG data from Study 3013 has been added to the existing integrated Phase 3 ECG data reported in the first review cycle. ECG data from studies 4003 and 3012 were not integrated because ECGs were only recorded in selected subjects in these studies.

QT interval data are shown in the following sections for telithromycin-treated subjects and for studies where clarithromycin was the comparator. QTc represents the QT interval corrected by Bazett's formula. (Bazett's formula normalizes the QT interval according to heart rate and is calculated by dividing the QT interval in seconds by the square root of the R-R interval).

Table ISS.24 shows a summary of the integrated ECG data obtained for telithromycin-treated subjects in the 12 Phase 3 studies (controlled and uncontrolled) is provided in the following table.

Table ISS.24. QT interval data for telithromycin-treated subjects in Phase 3 studies*

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

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

† Because of electrophysiologic differences in cardiac repolarization, the QTc interval is longer for females than males.

Source: Table SS-189 through Table SS-192

Medical Officer Comment: *When the additional QTc data from Study 3013 was integrated with the data from the initial NDA submission, there are no significant differences between telithromycin-treated patients and comparator-treated patients. Table* ***Table ISS.24*** *shows that telithromycin treatment resulted in a mean on-therapy increase of QTc (Bazett's formula) of 1.5 ms and a mean on-therapy increase of QTc (Fridericia) of 3.8 ms for all controlled and uncontrolled studies combined. The Fridericia formula was used in addition to Bazett's formula because telithromycin is associated with increases in heart rate, and the Fridericia formula may be more accurate in situations where there is an increased heart rate. However, it is not clear whether it is appropriate to use the Fridericia formula in this situation for three reasons. First, the increase in heart rate associated with telithromycin may not be large enough to justify the use of this formula. Second, the comparator drugs do not result in increases in heart rate, and it is not clear what affect the use of the Fridericia formula would have when applied to comparator QT data. Third, there is more experience with Bazett's formula than Fridericia's formula with regard to risk assessment, which allows for more meaningful comparisons with previous drugs.*
*The proportion of outliers for patients on- therapy with telithromycin was similar to that for patients pre-therapy. Telithromycin did not produce a greater on-therapy or post-therapy prolongation of the QT interval when compared to clarithromycin in the one new study, 3013, with ECG data. The sponsor did not provide separate analyses assessing QT prolongation for controlled vs. uncontrolled data. The following table (****Table ISS.25****) includes data generated by a Medical Officer analysis summarizing mean and standard deviation for QTC according to visit number only for controlled studies.*

Table ISS.25. Mean QTC and standard deviation for Ketek and comparator-treated patient from controlled clinical trials (Bazett's formula)

Visit	Ketek Mean QTC	Ketek Standard Deviation†	Comparator Mean QTC	Comparator Standard Deviation†	Change from previous visit	
					Ketek	Comp
Visit 1	421.423	20.381	422.346	20.335	N/A	N/A
Visit 2	424.281	19.471	424.685	19.747	2.86	2.34
Visit 3	421.043	20.013	422.710	20.282	-0.38	0.37
Visit4	420.883	21.230	422.949	20.595	-0.54	0.60

Visit 1= enrollment; Visit 2= on therapy; Visit 3= test of cure visit; Visit 4= post-therapy
† Standard Deviation around the mean.

Table ISS.26 shows the proportions of telithromcyin-treated subjects with significant prolongation of QTc (Bazett's formula) at enrollment, on-therapy, and post-therapy.

Table ISS.26. Frequency of telithromycin-treated subjects with significant prolongation of QTc (Bazett's formula) interval at pretherapy/entry and on therapy and post-therapy: Phase 3 studies (controlled and uncontrolled)

Variable	Entry n/N (%)	On Therapy n/N (%)	Post-Treatment n/N (%)
QTc Increase			
≥30 and ≤60 ms	n/a	212/2411 (8.8)	142/2116 (6.7)
≥60 ms	n/a	22/2241 (0.9)	11/2116 (0.5)
QTc value			
≥450 msec, male	62/1571 (3.9)	51/1236 (4.1)	21/1067 (2.0)
≥470 msec, female	14/1527 (0.9)	17/1215 (1.4)	9/1087 (0.8)
≥500 msec male or female	8/3098 (0.3)	4/2451 (0.2)	2/2154 (0.1)
Both QTc increase ≥ 60 msec and:			
≥450 msec, male	n/a	5/1210 (0.4)	1/1043 (0.1)
≥470 msec, female	n/a	2/1201 (0.2)	1/1073 (0.1)
≥500 msec male or female	n/a	1/2451 (0.6)	0/2116 (0)

Medical Officer Comment: *Medical Officer review of the twelve telithromycin-treated patients who had a QTC value of ≥500 msec, revealed that most had underlying cardiovascular disease or were on medications which could have contributed to the prolongation of the QTc. These include baseline bundle branch block and amiodarone therapy. Of these 12 patients, nine did not have a sequential pattern of QTc increases consistent with telithromycin exposure as the etiology. Of the other three, two had bundle branch block and one was on therapy with amiodarone. There were no adverse events in this group of 12 patients which could be potentially explained by telithromycin's potential to prolong the QT interval. Other categories of QTc prolongation less than 500 msec were examined and were not found to be associated with an increase in adverse events or adverse events of possible cardiac origin.*

In the three new Phase 3 studies, 3 telithromycin-treated subjects (all in uncontrolled Study 3012) and 1 comparator-treated subject (in Study 3013) had a QTc ≥500 ms. All 4 of these subjects had this prolongation at the baseline (pretherapy) visit. None of the subjects had an on-therapy QTc value ≥500 ms.

There were three Phase 3 controlled blinded clinical trials in which QT data were collected and clarithromycin was used as the comparator agent. The QTC data from these trials were pooled and the effect of telithromycin on the QTC interval was compared to the effect that clarithromycin had on the QTC interval. **Table ISS.27** summarizes the findings of this comparison.

Table ISS. 27. QT interval data for telithromycin vs. clarithromycin (controlled studies 3006, 3008 and 3013)

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

Data are mean ± SD TEL = telithromycin; CLA = clarithromycin
[a] Represents number of subjects with both a pretherapy and on-therapy ECG
[b] Represents number of subjects from the on-therapy group who also had a post-therapy ECG
[c] ΔQTc interval on-therapy minus QTc interval pretherapy
[d] ΔQTc represents QTc interval post-therapy minus QTc interval pretherapy
Source: Table SS-197 through Table SS-200

Medical Officer Comment: *Telithromycin and clarithromycin were similar with respect to their effect on QTc interval changes in these three trials. The frequency of subjects with a QTc increase of ≥60 ms at on-therapy was low and similar between treatment groups, as was the frequency of subjects with QTc outliers. No subject in either treatment group of these three studies had a QTc value ≥500 ms at pre-therapy, on-therapy or post-therapy.*
The sponsor did not present data assessing QTc changes for comparator treated patients, except for the three studies (3006, 3008, 3013) in which clarithromycin was used as the comparator. Although a comparison between all comparator-treated patients and telithromycin-treated patients would have been appropriate, it is reasonable for the sponsor to have focused on comparisons between clarithromycin and telithromycin.

Cardiac Adverse Events

Table ISS.28 summarizes all and possibly related TEAE's of the cardiac system organ class. The most frequent cardiac TEAE was palpitations. None of the cases of palpitations was characterized as serious and ECG data for these patients was not collected.

Table ISS.28. All and possibly related TEAEs* of cardiac disorders system organ class by decreasing frequency in all integrated Phase 3 studies

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

* Based on all TEAE frequency of ≥0.1% in telithromycin or comparator treatment group.
NOS = not otherwise specified
Source: Table SS-299
(ISS, page 117)

Additional cardiac TEAEs of interest were reported at very low rates (<0.1%) in the All Integrated Phase 3 study population. Atrial fibrillation occurred in 2/4472 (0.05%) telithromycin-treated subjects and 1/2139 (0.05%) comparator-treated subjects. Cardiac Arrest occurred in 1/4472 (0.02%) telithromycin-treated subject (see patient 4003/3410/004 in **Deaths**) and no comparator-treated subjects. Syncope occurred in 1/4472 (0.02%) telithromycin-treated subjects and 2/2139 (0.09%) comparator-treated subjects

The incidence of serious TEAEs of the cardiac disorders SOC was similar in telithromycin- (8/4472, 0.2%) and comparator-treated subjects (8/2139, 0.4%). None of the serious cardiac events were considered possibly related to study medication.

Hepatic Adverse Events

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