TEAEs was similar for telithromycin and comparator treated subjects. The proportion of patients discontinued from the non-comparative studies because of hepatic TEAEs was similar to what was observed in the comparative studies.

In the comparative studies, there were 2 serious hepatic AEs reported in telithromycin treated subjects and one serious hepatic AE reported in a comparator-treated patient. In the non-comparative studies, there was one additional serious hepatic AE in a telithromycin treated patient. There were reasonable alternative explanations for one of the serious hepatic AEs in the telithromycin treated patients and for the only comparator treated patient with a serious hepatic AE. It was quite plausible to consider that the two other telithromycin treated subjects with serious hepatic AEs were possibly related to telithromycin therapy. The first of these two events was a 76 year-old female with community-acquired pneumonia (CAP) and a history of hypercholesterolemia and hyperuricemia, maintained chronically on pravastatin 20 mg po qd and allopurinol 20 mg po qd. She experienced isolated asymptomatic elevations of alanine aminotransferase (ALT) (13x Upper Limit of Normal (ULN)) and aspartate aminotransferase (AST) (9x ULN) on Day 5 of therapy with telithromycin 800 mg po qd in the absence of an elevated total bilirubin (T. Bili.). Telithromycin was discontinued on Day 6 of therapy. Her transaminase abnormalities had nearly resolved by Day 12. The other serious hepatic AE that the MO considered as quite possibly associated with telithromycin is described in the following 2 paragraphs.

A 53 year-old male with CAP from a study center in — was enrolled in the Study 3000, a non-comparative CAP study. At baseline his ALT was slightly elevated [ALT=81 U/L (normal range (NR) <49)] and his peripheral eosinophil count was 774 cells/10^{-6}L (lab normal range not provided). He completed 10 days of telithromycin at 800 mg po qd. Four days after completing therapy, he developed a gastroenteritis-like illness similar to other members of his family, except that the subject's fever persisted. Ten days after completing therapy, he had laboratory studies drawn that demonstrated elevations of his ALT to 7x ULN and AST to 5x ULN with eosinophilia. His ALT increased to a peak of 31x ULN and his eosinophils peaked at 2856 cells/10^{-6}L. Serologic evaluations for hepatitis A, B, and C, were negative. Throughout the episode his T. Bili. was only mildly elevated (peak elevation 1.55x ULN). Other medications that the patient received around the time of this event included inhaled Atrovent, salbutamol, and fluticasone, Nasonex spray (mometasone furoate), six 500 mg acetaminophen tablets over a one-week time period. His ALT elevation almost completely resolved in the absence of specific therapy by 6-weeks after initial detection of the hepatic event (AST levels were only infrequently monitored). As part of the patient's evaluation of this episode of hepatitis a liver biopsy was performed. Review of the liver biopsy at the — found pathologic changes of centrilobular necrosis and eosinophilic infiltration, findings strongly suggestive of drug-induced liver disease.

Eight months later at a routine follow-up visit, the subject was noted to have an elevated ALT of 1331 U/L in the absence of eosinophilia. Prior to this second event there was no known antecedent exposure to a ketolide or macrolide class agent. Several weeks later he underwent a liver biopsy. Review of the patient's second liver biopsy at the —

/ found pathologic changes of chronic hepatitis with marked activity and extensive bridging fibrosis. These findings of chronic hepatitis probably autoimmune.

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

Laboratory abnormalities for ALT, AST, T. Bili., and Alkaline Phosphatase (Alk. Phos.) were analyzed in a number of analyses. The summary findings derived from the multiple analyses were as follows. For patients with normal ALT, AST, and T. Bili. at baseline, there was a greater proportion of telithromycin treated patients than comparator treated patients from the comparative CAP studies with low-level (between 1x and 3x ULN) elevations in AST. This difference was present for the On-Therapy and Post-Therapy visits and not demonstrated in the limited data from the Late Post-Therapy visit. For ALT, there was a slightly greater proportion of patients from the comparative CAP studies with low-level ALT elevations during On-Therapy and Post-Therapy. These differences were largely the result of a greater number of telithromycin treated patients with low level elevations (between 1x and 3x ULN). The proportion of excess elevations appears to be greater for AST rather than ALT. The number of patients experiencing elevations in the categories in excess of 3x ULN are small in both treatment groups. Similar analyses in subjects from the comparative Non-CAP studies found no significant differences in the proportion of subjects with elevations in AST, ALT, or T. Bili. in the two treatment groups. The finding of a greater proportion of elevations in the telithromycin treated subjects only in the comparative CAP studies could possibly be due to CAP patients being a more susceptible group (because of "other" host factors).

From the population of patients in the original NDA phase III studies and Study 3009OL with normal ALT & AST & T. Bili. at baseline, concomitant elevations in ALT and/or AST and T. Bili. in the range of >ULN and $\leq$ 2x ULN were infrequent and found only in telithromycin treated patients.

In summary, the findings from the preclinical studies demonstrate hepatotoxic effects for telithromycin in dogs, rats, and monkeys. Telithromycin is primarily metabolized by the liver by cytochrome P450 3A4 (CYP 3A4) and to a lesser extent by cytochrome P450 1A.

In the single dose phase I studies in humans there was a clustering of hepatic adverse events in elderly subjects at a dose of 2000 mg. However, hepatic adverse events were not reported from younger subjects receiving single doses of 2400 mg or from the multiple dose studies which used doses up to 1600 mg. One subject experienced a hepatic AE in the single dose studies of 3200 mg.

The proportion of patients in phase III studies experiencing hepatic adverse events or treatment discontinuation because of a hepatic adverse event were similar between telithromycin and comparator treatment groups. In the comparative studies there were 2 serious hepatic AEs in the telithromycin treated patients and one serious hepatic AE in comparator treated patients. There was one additional serious hepatic AE from the noncomparative telithromycin studies. One of these serious adverse events in the telithromycin treated group was a patient with a liver biopsy showing centrilobular necrosis and eosinophilic infiltration, likely representing drug-induced liver disease (Note: Erythromycin estolate, ethylsuccinate, and proprionate have been associated with cholestatic hepatitis, sometimes accompanied by fever and eosinophilia.[1,2,3] The pathologic changes for some of the cases of trovafloxacin-associated hepatitis were described as centrilobular necrosis and eosinophilic infiltration on liver biopsy.[4,5]) Several months later this patient went on to have an episode of asymptomatic elevations in his ALT and AST and a liver biopsy showing changes consistent with chronic hepatitis, probably autoimmune.

The presence of the following constellation of findings raises significant concerns regarding the hepatotoxic potential of telithromycin:

- hepatotoxicity in the three animal species tested in preclinical studies
- an excess of low level AST, ALT, or T. Bili. elevations in telithromycin treated patients from the comparative phase III CAP studies
- a few patients, only in the telithromycin treated group, with low level concomitant transaminase & T. Bili. elevations
- two serious hepatic events that are plausibly attributed to drug with one of the events involving marked hepatitis with a biopsy showing centrilobular necrosis and eosinophilic infiltration strongly suggestive of drug-induced liver disease and a subsequent biopsy in this same patient 9-months later showing chronic hepatitis, probably autoimmune
- the phase I studies where there was a clustering of hepatic adverse events in elderly patients receiving single 2000 mg doses of telithromycin suggesting a possible drug-induced effect.

Typically in an NDA database of this size, one would only be looking for evidence of a "signal" of hepatotoxic potential. In this NDA safety database of 3265 telithromycin treated subjects, the case involving hepatitis with biopsy evidence of centrilobular necrosis with eosinophilic infiltration, appears to represent an "event" of a significant

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[1] Steigbigel NH. Macrolides and Clindamycin. In Principles and Practices of Infectious Diseases, 5th Ed. Mandell GL, Bennett JE, and Dolin R. Churchill Livingstone. Philadelphia. 2000. p. 366-382

[2] Pessayre D, Larrey D. Acute and chronic drug induced hepatitis. Bailliere's Clinical Gastroenterology. 1988:(2):385-422.

[3] Diehl AM, et al. Cholestatic hepatitis from erythromycin ethylsuccinate: report of two cases. Am J Med. 1984:(76); 931-4.

[4] Chen HJL, Bloch KJ, Maclean JA. Acute eosinophilic hepatitis from trovafloxacin. NEJM 2000, 342 (5):359.

[5] Lucena MI, Andrade, RJ, Rodrigo L, Salmeron J, et. al. Trovafloxacin-induced acute hepatitis. Clin Infect Dis. 2000. 30(2):400-1.

drug-induced hepatitis that quite possibly is associated with telithromycin. To observe even one serious adverse liver event of this nature thought to be associated with telithromycin in a safety population of this size is remarkable.

The evidence supporting the potential hepatic toxicity of telithromycin should be carefully considered in the overall risk-benefit assessment of telithromycin.

Pre-Clinical

The noteworthy hepatic findings from the pre-clinical studies are summarized in Table 1. These findings are summarized from Dr. Peters' Pharmacology/Toxicology reviews. For detailed discussions of the findings from these studies, the reader is referred to Dr. Peters' Pharmacology/Toxicology reviews.

Table 1. Liver-Related Findings for Telithromycin from the Preclinical Studies

Study	NOEL	HED*	Liver-Related Findings
4 Week Rat Oral	50 mg/kg/d	8 mg/kg AUC/Cmax increased but not proportional to dose but widely variable results	-increased ALT -increased AST (2-15xULN) -increased leucine aminopeptidase -histopathologic findings of moderate to severe hepatic necrosis at doses of 150 & 300 mg/kg/d -phospholipidosis
4 Week Dog Oral	50 mg/kg/d	27 mg/kg AUC/Cmax marked increases between Days 1-30 that are not proportional to dose	-increased ALT -increased AST- up to 6xULN -one premature decedent with liver and renal failure
4 Week Rat IV	10 mg/kg/d	1.62 mg/kg	-no treatment-related hepatic findings
13 Week Rat Oral	50 mg/kg/d (NOAEL)	8 mg/kg	-increased ALT -increased AST (up to 3.6xULN) -histopathologic findings of increased inflammatory cell foci in liver at doses of 150 mg/kg/d -phospholipidosis
6 Month Rat Oral	20 mg/kg/d	3.2 mg/kg	-increased ALT (2-3x ULN) -increased AST -increased Alk. Phos. -increased liver weights -histopathologic findings of bile duct epithelial vacuolation
4 Week Dog IV	30 mg/kg/d	16.2 mg/kg	-histopathologic findings of hepatocyte hypertrophy
13 Week Dog Oral	50 mg/kg/d	27 mg/kg	-increased ALT -increased AST (up to 4.7xULN) -histopathologic findings of hepatocyte hypertrophy
4 Week Monkey	60 mg/kg/d	19 mg/kg	-increased ALT -increased AST (up to 4xULN) -increased total bilirubin -no histopathologic lesions
*Note a dose of 800 mg of Ketek per day in a 70 kg human is 11.4 mg/kg/day			

From the preclinical studies it is apparent that telithromycin is capable of producing hepatic toxicity in animals. The Applicant notes that for telithromycin *the liver is the main site for organ toxicity* (8:v251:p184).

The Applicant also performed in vitro studies to evaluate the propensity of isolated hepatocytes of different species to take up telithromycin. The study found the following relative intracellular concentrations of telithromycin by species: mouse≥human>monkey>rat≥dog. (8:v251:p181). Hence based upon the results from this in vitro study, one could hypothesize that human hepatocytes in vivo may internalize greater concentrations of telithromycin than that of monkeys, rats, and dogs at similar levels of systemic exposure.

> **MO Comment:** If in fact human hepatocytes have a greater propensity to uptake or retain telithromycin than that of monkey, rat, or dog hepatocytes, the extrapolation of expected levels for development of toxicity from these pre-clinical models may to some degree underestimate the levels at which human hepatic toxicity might occur.

Studies of the metabolism of telithromycin have found that it is primarily metabolized in the liver by cytochrome P450 3A4 (CYP3A4) and to a lesser extent by cytochrome P450 1A (CYP1A). Telithromycin displays competitive inhibition of CYP3A4 and CYP2D6. In vitro studies of telithromycin and cytochrome P450 using hepatic microsomal suspensions from male rats did not demonstrate the formation of nitrosoalkane complexes. Analysis of microsomal suspensions from male rats treated with telithromycin did not demonstrate findings suggesting that telithromycin forms complexes with hepatic cytochrome P450.

Phase I Studies

In the single oral dose phase I studies of telithromycin alone in humans there were a total of 653 single-dose dosing periods that contributed to the safety population. There were 98 placebo dosing periods. The number and type of adverse events per dosing period are tabulated below (Table 2).

Table 2. Frequency of Hepatic AEs per Dosing* Period for Telithromycin– Phase I Single Dose Studies

Coded Term for Hepatic AE	Telithromycin Periods = 653 n/N	Placebo Periods = 98 n/N
Liver Damage[a]	2/653	1/98†
Increased AST	3/653	0/98
Increased ALT	2/653††	0/98
Liver Function Test Abnormal	2/653	0/98
Increased Alk. Phos.	1/653	0/98

*Note: the unit of analysis is the dosing period not per subject. A subject may have been involved with multiple dosing periods.
†This subject's (subject 12 from Study 1030) AE of liver damage is attributed to placebo because his liver AE was first detected Day 7 after placebo which is also Day 14 after his 2000 mg dose of telithromycin. His case is further described in Appendix A.1.
†† One of these subjects (subject 5 from Study 1030) had 2 hepatic TEAEs "Increased AST" and "Increased ALT". She is recorded under both categories in the table above (i.e., her event is one of the 3 events under the category of "Increased AST" and she is the 1 subject with an event under the category of "Increased ALT".) She is the only subject represented in more than one hepatic AE category within this table.
[a] "Liver damage" refers to asymptomatic increases in ALT and AST

> **MO Comment:** Important to note is that some of these patients were enrolled in studies with a crossover design (i.e., patients may receive different doses of study medication or placebo in various different sequences). Findings from crossover design studies may provide inadequate attribution for AEs with onset periods that exceed the washout period. If an effect caused by prior dosing isn't manifest or recognized until a later dosing period, attribution may be incorrect.

In addition to the subjects from the single oral dose phase I studies, there were 323 additional dosing periods (281 telithromycin + 42 placebo) in the multiple oral dose studies of telithromycin alone. (Some subjects were involved in multiple dosing periods.) There was one hepatic AE in the multiple dose studies of telithromycin alone. Brief summaries of the patients from the phase I studies with hepatic AEs and selected patients with LFT abnormalities are provided in Appendix A.1.

Hepatic TEAEs in single and multiple oral dose phase I studies by dose level per period are tabulated (Table 3). The table shows a greater frequency of events in the subjects in the 2000 mg telithromycin dose group compared to the other single dose groups. Two of the three hepatic AEs at 2000 mg occurred in elderly patients. There was one additional elderly patient that experienced a hepatic adverse event 7-days after placebo, which is also 14-days after a 2000 mg dose of telithromycin. (This reflects the study's crossover design.) The dose of 2000 mg was the highest dose studied in elderly patients. The highest telithromycin dose studied in the multiple dose studies was 1600 mg daily.

Table 3. Frequency of Hepatic TEAEs in Single and Multiple Oral Dose Phase I Studies of Telithromycin by Dose Level

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

"-" signifies no patients exposed to this dose
† In this table Subject 005 from Study 1030 AEs of "AST increased" and "ALT increases" are counted as one event
†† This subject's AE of liver damage (subject 12 from Study 1030) is attributed to placebo because his liver AE was first detected 7 days after placebo which is also 14 days after his 2000 mg dose of telithromycin. His case is further described in Appendix A.1.
Adapted from the Applicant's Table ISS-ISE/s09/0000612t.1[a] 22 March 2001

In addition to the phase I studies of oral administration of telithromycin tablets, there were 64 subjects in single dose intravenous studies of telithromycin. In these studies subjects received single intravenous doses ranging from to 120 to 480 mg. The Applicant reports that there were no hepatic adverse events reported in these studies.

Summary of Findings from Phase I

During the phase I studies several subjects experienced hepatic abnormalities. Some of the hepatic AEs appeared to be clustered in the group of elderly patients that received telithromycin at 2000 mg orally as a single dose. While there were no events attributed to the 2400 mg dose of telithromycin, the population receiving the 2400 mg single dose was not elderly subjects. While there was one hepatic adverse event among the patients receiving 3200 mg, this study did not enroll older patients. The design of the phase I studies limited the conclusions that could be drawn regarding the association of telithromycin with the observed hepatic AEs.

Phase III

Phase III Hepatic TEAEs

The number of hepatic TEAEs reported in the completed phase III controlled studies of telithromycin are summarized in Table 4. Hepatic TEAEs are tabulated as "all TEAEs" and then as the subset of TEAEs judged to be "possibly related" to study drug by the investigator. For the TEAEs of all causality and possibly related TEAEs, the proportion of patients for which each of the particular hepatic TEAEs were reported were similar for telithromycin and its comparators. Three of the hepatic TEAEs from the controlled phase III studies were classified as serious adverse events (2 for telithromycin and 1 for comparators). These three patients experiencing serious AEs are discussed in further detail in the serious hepatic AE section that follows. The other hepatic AEs were all considered of mild or moderate severity by the investigator. The proportion of patients experiencing one or more hepatic TEAEs in the controlled studies is similar between telithromycin and comparators.

Table 4. Hepatic TEAEs (coded terms) in all Completed Controlled Phase III studies

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

[a] A subject may have had more than one hepatic TEAE.
Adapted from Applicant's Table from NDA 21-144 8:v251:p188, Table 8-276, 8:v253:p043, Table 170 from the Study 3011 Study Report p. 0532, and the Applicant's SAS.txp files for NDA 21-144

MO Comment: Tabulation of hepatic AEs by Study for telithromycin vs. its comparators are provided for each of the individual controlled phase III studies in Appendix A.2.

The hepatic TEAEs from the completed uncontrolled phase III studies of telithromycin are summarized in Table 5. The number of patients in the analysis population is smaller than the controlled studies, the proportion of patients experiencing hepatic TEAEs is somewhat higher than what was observed in the controlled studies. Most of the TEAEs were judged by the investigator to be possibly related to study medication (with the exception of alkaline phosphatase increased and cholelithiasis). One of the TEAEs was classified as a serious TEAE ("hepatitis with abnormal liver function tests", subject 502/1069 from study 3000 who is further discussed in the serious hepatic AEs section). The tabulations of hepatic AEs are also provided for each of the studies in Appendix A.2.

Table 5. Hepatic TEAEs in all Completed Uncontrolled Phase III Studies

Coded Term	Number (%) of Subjects			
	All TEAEs		Possibly Related TEAEs	
	Telithromycin N=1220		Telithromycin N=1220	
	n	(%)	n	(%)
Liver Function Test Abnormal	37	(3.0)	35	(2.9)
SGPT/ALT Increased	8	(0.7)	7	(0.6)
SGOT/AST Increased	4	(0.3)	3	(0.2)
Alkaline Phosphatase Increased	4	(0.3)	0	(0.0)
Liver Damage	2	(0.2)	2	(0.2)
Cholelithiasis	2	(0.2)	0	(0.0)
Hepatitis	1	(0.1)	1	(0.1)
Hepatomegaly	1	(0.1)	0	(0.0)
Total Number of Hepatic Events *	59		48	
Total Number of Patients with One or More Hepatic Events *	57	(4.7)	47	(3.9)

*A subject may have had more than one hepatic TEAE
Adapted from Applicant's Table from 8:v251:p190 and the Applicant's SAS.txp files for NDA 21-144

Examination of the hepatic TEAEs reported for each of the uncontrolled phase III studies reveals that most of the reports of "liver function test abnormal" were from study 3000 (Table 6). Comparison of the frequency of reporting for "SGPT/ALT increased" finds the reporting rates to be higher in the 5-day treatment arm of study 3002 than the 10-day treatment arm, although comparisons are limited by the small number of events. The total number of hepatic TEAEs reported in study 3002 for the 5- and 10-day treatment arms are similar. The proportion of patients with hepatic TEAEs is approximately 3.5 times higher in the uncontrolled CAP study compared to the acute sinusitis study. The

proportion of CAP patients with hepatic TEAEs in Study 3000 (uncontrolled CAP) also exceeds what was observed in the other CAP studies.

Table 6. All Hepatic TEAEs (Coded Term) in Completed Uncontrolled Phase III Studies by Indication

Coded Term	Number (%) of Subjects									
	CAP Study 3000		Acute Sinusitis Study 3002				CAP Study 3009OL		CAP Study 3010	
	7 to 10 days N=239		5 days N=166		10 days N=167		7 to 10 days N=218		7 days N=430	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Liver function test abnormal	28	(11.7)	2	(1.2)	1	(0.6)	5	(2.3)	1	(0.2)
SGPT/ALT increased	2	(0.8)	4	(2.4)	1	(0.6)	0	(0.0)	1	(0.2)
Alkaline phosphatase increased	2	(0.8)	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Liver damage	1	(0.4)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)
SGOT/AST increased	1	(0.4)	0	(0.0)	3	(1.8)	0	(0.0)	0	(0.0)
Hepatitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cholelithiasis	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)
Hepatomegaly	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Total No. of Hepatic Events*	35		8		7		5		4	
Total No. of Patients with One or More Hepatic Events *	34	(14.2)	7	(4.8)	7	(4.2)	5	(2.3)	4	(0.9)

*A subject may have had more than one hepatic TEAE.
Adapted from Applicant's Table from 8:v251:p190 and the SAS.txp files for NDA 21-144

Phase III – Treatment Discontinuations

The number of patients discontinuing study medication due to a hepatic TEAE in the completed controlled phase III studies is summarized in Table 7. The proportion of telithromycin and comparator-treated patients that are discontinued due to hepatic TEAEs of all causality were similar between treatment arms [telithromycin 10/2045 (0.5%) vs. comparator 8/1672 (0.5%)]. The reasons that patients were discontinued for hepatic TEAEs of all causality were similar between treatment arms. The proportion of patients discontinuing treatment with possibly related hepatic TEAEs was similar between treatment arms.

> **MO Comment:** All of the comparative studies that provide data for Table 7 below were double-blind studies

Table 7. Patients Discontinuing Study Medication Due to Hepatic TEAEs in Completed Controlled Phase III Studies

TEAE – Coded Term	Number (%) of Subjects*			
	All Causality		Possibly Related	
	Telithromycin N=2045	Comparators N=1672	Telithromycin N=2045	Comparators N=1672
	n (%)	n (%)	n (%)	n (%)
Liver Function Test Abnormal	5 (0.2)	5 (0.3)	3 (0.1)	3 (0.2)
Alkaline Phosphatase Increased	1 (0.05)	0 (0.0)	0 (0.0)	0 (0.0)
SGOT & SGPT Increased	1 (0.05)	0 (0.0)	1 (0.05)	0 (0.0)
SGPT Increased	0 (0.0)	2 (0.1)	0 (0.0)	1 (0.1)
SGOT/AST Increased	1 (0.05)	0 (0.0)	1 (0.05)	0 (0.0)
Liver Damage	1 (0.05)	0 (0.0)	1 (0.05)	0 (0.0)
Cholestatic Jaundice	1 (0.05)	0 (0.0)	1 (0.05)	0 (0.0)
Hepatitis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Total No. of Subjects Discontinuing Study Medication due to a Hepatic TEAE	10 (0.5)	8 (0.5)	7 (0.4)	5 (0.3)

*Unit of Analysis is the patient
Source: NDA 21-144 N-000 original submission 8:v251:p193-5 and data Table SS-116 from 1:v116:p350, February 28, 2001

In the uncontrolled phase III studies, there were 3 patients discontinued from study medication because of hepatic TEAEs of all causality (Table 8). The proportion of patients discontinued from the uncontrolled studies was similar to what was observed in the controlled phase III studies.

Table 8. Patients Discontinuing Study Medication Due to Hepatic TEAEs in Completed Uncontrolled Phase III Studies

TEAE – Coded Term	Number (%) of Subjects*	
	All Causality	Possibly Related
	Telithromycin N=1220	Telithromycin N=1220
	n (%)	n (%)
Liver Function Test Abnormal	2 (0.2)	2 (0.2)
Alkaline Phosphatase Increased	1 (0.1)	0 (0.0)
Cholelithiasis	1 (0.1)	0 (0.0)
Total No. of Patients Discontinuing Study Medication due to a Hepatic TEAE	4 (0.3)	2 (0.2)

*Unit of Analysis is the patient
Source: NDA 21-144 N-000 original submission 8:v251:p193-5 and data Table SS-116 from 1:v116:p350, February 28, 2001

Patients with Serious Hepatic TEAEs

The number of patients experiencing serious hepatic TEAEs in the phase III clinical studies are summarized in Table 9. In the controlled phase III studies there were 2 telithromycin treated patients and one comparator-treated patient that experienced a serious hepatic TEAE. In the uncontrolled phase III studies one telithromycin-treated patient experienced a serious hepatic TEAE. All three of the serious hepatic TEAEs in telithromycin treated patients were considered possibly-related by the study investigator, whereas the one serious hepatic TEAE in a comparator-treated patient was not considered by the investigator to be possibly related to study therapy.

Table 9. Patients with Serious Hepatic TEAEs in all Completed Phase III Studies

Serious Hepatic TEAEs	**Number (%) of Subjects***			
	All Causality		**Possibly Related**	
	Telithromycin	**Comparators**	**Telithromycin**	**Comparators**
Controlled Studies	**N=2045** **n (%)**	**N=1672** **n (%)**	**N=2045** **n (%)**	**N=1672** **n (%)**
Liver Damage	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Jaundice	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Total No. of Subjects with Serious Hepatic TEAEs Controlled Studies	2 (0.1)	1 (0.1)	2 (0.1)	0 (0.0)
Uncontrolled Studies	**N=1220** **n (%)**	-	**N=1220** **n (%)**	
Hepatitis	1 (0.1)	-	1 (0.1)	-
Total No. of Telithromycin treated Subjects with Serious Hepatic TEAEs Uncontrolled Studies	1 (0.1)	-	1 (0.1)	-
Total Controlled and Uncontrolled Studies	**N=3265** **n (%)**	-	**N=3265** **n (%)**	-
Total No. of Telithromycin-treated Subjects with Serious Hepatic TEAEs Controlled and Uncontrolled Studies	3 (0.1)	-	3 (0.1)	-

*Unit of Analysis is the patient

The 4 patients experiencing serious hepatic TEAEs are identified in Table 10. Narratives for the 4 patients experiencing serious TEAEs are provided in the sections that follow.

Table 10. Serious Non-Fatal Hepatic TEAEs for Subjects in Phase III Clinical Studies

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

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

MO Comment: There was an additional telithromycin treated patient from Study 3010 (0473/001) with a serious adverse event involving the hepatobiliary system. This patient's adverse event was cholelithiasis (along with the AEs of pancreatitis, pancreatic mass, gallstones, biliary tract occlusion, and small cell carcinoma of the lung). He was a 54-year-old male admitted to study with RUQ pain and a productive cough. CXR showed patchy infiltrates in the right middle and right lower lobes and his amylase was elevated. He was started on telithromycin 800 mg po QD. On Day 3 he had an ultrasound and a CT scan which showed a gallstone and a probable mass in the head of the pancreas. He completed therapy on Day 7 and his pneumonia was clinically improved. Eight days after completing therapy he returned jaundiced with an amylase of 4174 and lipase of 35,600 (no units provided). Repeat CT scan confirmed a gallstone and dilated common bile duct and intrahepatic ducts. An ERCP showed probable extrinsic compression of the common bile duct and pancreatic duct. A stent was placed and his hyperbilirunemia resolved. A biopsy of a mass in the area of the left hilum revealed small cell carcinoma. Twenty-six days after completing therapy with telithromycin, a laparoscopic cholecysectomy was performed followed by Porta-Cath placement for chemotherapy.

Narratives for Patients with Serious Hepatic TEAEs

Subject 0060/039 from Study 3006 (CAP telithromycin): A 76-year-old female with a history of cigarette smoking, hypercholesterolemia since 1992, hyperuricemia since 1997, s/p amygdalectomy (1928), was enrolled in Study 3006 and started telithromycin 800 mg po qd on 11 Feb 1999 for treatment of pneumonia. Sputum culture at pretherapy/entry yielded Group A Streptococcus. During study she was also maintained on her other chronically used medications, pravachol (pravastatin sodium) 20 mg po qd for hyperlipidemia since 1997 and allopurinol 200 mg po qd for hyperuricemia since 1997. On [redacted] asymptomatic elevation of her liver associated enzymes was discovered. This led to discontinuation of the study medication on 16 Feb 1999, and withdrawal from the study on 17 Feb 1999. Therapy was changed to Ceftin (cefuroxime axetil) 500 mg twice daily on 16 Feb 1999. Selected laboratory test results are presented in Table 11.

Table 11. Selected Lab Values for Patient 0060/039 from Study 3006

Laboratory analyte		[redacted]		
AST/SGOT (NR 9-34 U/L)	37	295	66	24
ALT/SGPT (NR 6-32 U/L)	24	418	200	64
Alk phos (NR 35-115 U/L)	79	146	131	–
Bilirubin (NR 3-21 mmol/L)	17	22	10	–

NR= normal range

Both the investigator and the Sponsor assessed the patient's hepatic AE ["liver injury" (verbatim term) coded as "liver damage"] as possibly related to the study medication. At the time of the elevated transaminases ([redacted] the patient reported mild diarrhea and associated abdominal pain. The Sponsor notes that the patient's transaminases were lower on [redacted] espite continued telithromycin therapy from 15 Feb 1999 to 16 Feb 1999. The event resolved without sequelae.

> **MO Comment:** A drug-induced elevation of the subject's transaminases seems to be a very plausible explanation for the event. In addition to telithromycin, subject 0060/039 was also taking concurrent pravastatin and allopurinol (both reportedly since [redacted] 1997). Both pravastatin[6] and allopurinol[7] have been associated with increases in transaminases. The timing of this event increases the likelihood that telithromycin was a causal or contributing factor. While it is possible that the culprit medication could be acting independently, another possibility is an interaction between telithromycin and one of her other medications causing the event, either directly or by increasing the level of an interacting medication. Regarding drug interaction, telithromycin has been shown to markedly increase the levels of simvastatin and its metabolites by inhibiting the metabolism of simvastatin by cytochrome P450 3A4. However, based on in vivo and in vitro data *pravastatin is not metabolized by cytochrome P450 to a clinically significant extent.*[8] The patient is also elderly and is noted to have renal insufficiency (creatinine at baseline 124 (NR 31-101 umol/L)). Hence, her exposure to telithromycin may be greater than the average patient. This possible higher level of exposure to telithromycin could predispose her to a direct toxic effect of telithromycin and the observed elevations in transaminases.

Subject 0259/005 from Study 3008 (Tonsillopharyngitis telithromycin): A 19-year-old white male with no significant past medical history experienced liver damage (verbatim term "drug-induced hepatic toxicity") characterized by increased AST (SGOT), ALT (SGPT), and lactate dehydrogenase (LDH) on [redacted] after treatment with telithromycin for tonsillitis. The patient was diagnosed with tonsillopharyngitis (with a throat culture subsequently yielding Group A beta-hemolytic Streptococci) and was enrolled in study 3008. He began his course of telithromycin 800 mg po qd on 29 March 1999. [redacted] days after study entry at the End of therapy visit, subject 0259/005 was noted to have elevations in his transaminases (AST = 273 U/L and ALT 124 U/L). The subject had no associated signs or symptoms, but stated that he had ingested an excessive amount of alcohol during the previous evening. He received telithromycin from 29 Mar 1999 to 2 Apr 1999. Study medication (telithromycin for 5 days followed by 5 days of placebo) was completed as planned on 7 Apr 1999, [redacted] prior to the laboratory draw, which

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[6] Excerpted from the Pravachol product labeling: *In the largest long-term placebo-controlled clinical trial with pravastatin (Pravastatin Primary Prevention Study; see* ***Clinical Pharmacology****). the overall incidence of AST and/or ALT elevations to greater than three times the upper limit of normal was 1.05% in the pravastatin group as compared to 0.75% in the placebo group. One (0.03%) pravastatin-treated patient and 2 (0.06%) placebo-treated patients were discontinued because of transaminase elevations. Of the patients with normal liver function at week 12, three of 2875 treated with pravastatin (0.10%) and one of the 2919 placebo patients (0.03%) had elevations of AST greater than three times the upper limit of normal on two consecutive measurements and/or discontinued due to elevations in transaminase levels during the 4.8 years (median treatment) of the study.* Source, product labeling for Pravachol (pravastatin) May 1999 version. http://www.pdrel.com/pdr/static.htm?path=pdrel/pdr/10455500.htm

[7] Zyloprim (allopurinol) product labeling. PDR Edition 52, 1998. p. 1144.

[8] Pravachol (pravastatin) product labeling, May 1999 version from http://www.pdrel.com/pdr/static.htm?path=pdrel/pdr/10455500.htm

showed elevated SGOT, SGPT, and LDH. There was no counteractive treatment given. By the SGOT, SGPT, and LDH had decreased to near baseline values and by nad returned to baseline values. Selected laboratory values for subject 0259/005 are presented in Table 12.

Table 12. Selected Lab Values for Patient 0259/005 from Study 3008

Laboratory Analyte	Pretherapy /entry	On-therapy	End of therapy	TOC	LPT
AST/SGOT (NR=11-36 U/L)	23	ND	273	29	19
ALT/SGPT (NR=6-43 U/L)	27	ND	124	44	28
SGGT(NR= 10-61 U/L)	31	ND	37	39	35
LDH (NR= 53-234 U/L)	192	ND	592	133	108
Bilirubin NR= 3-21 umol/L	21	ND	14	22	15

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

The investigator considered the observed transaminase elevation as possibly related to study medication but suspected the patient's reported excessive alcohol intake as the most probable cause of the patient's elevated AST, ALT, and LDH. The Applicant commented that the history of excessive alcohol intake, and the AST/ALT ratio of 2:1 was compatible with an alcohol-related etiology. The Applicant also noted that it is not known if the subject has early alcoholic liver disease or a history of chronic alcohol abuse.

> **MO Comment:** The history of excessive alcohol intake the evening before raises the likelihood that the observed increase in transaminases (AST>ALT) and LDH is secondary to excessive alcohol consumption. Review of his concomitant medications reveals that the patient took a single dose of Zinc-echinacea (amount of dose unknown) and a single dose of Vitamin C (amount of dose unknown) on 28 March 1999. A role for telithromycin in the patient's hepatic AE, either causal or contributory, cannot be excluded. Unfortunately laboratory studies were not performed at the on-therapy visit.

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

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

> **MO Comment:** The presence of anatomic findings demonstrated on CT scan and ultrasound consistent with a disseminated neoplasm raises the likelihood that the observed jaundice and obstructive pattern for liver function tests are secondary to the patient's suspected malignancy. Results of a tissue diagnosis (i.e., a biopsy result) for the suspected malignancy are not provided.

Subject 502/1069 from Study 3000 (CAP telithromycin): A 53-year-old white male with a history of asthma (since 1975) and diabetes mellitus (since 1982) was enrolled in Study 3000 at center 502 in — on 02 Feb 1999 with CAP. He received telithromycin from 3 Feb 1999 through 12 Feb 1999, with an outcome of cure. The investigator noted that the patient was feeling "quite well" after completing therapy for CAP. — days after the last dose (— he reported exposure to family members suffering from a gastroenteritis-like illness. Jaundice was not noted in the affected family members. Four days after his last dose of telithromycin (—) he developed an acute illness with symptoms of fever, vomiting, and diarrhea. The vomiting and diarrhea resolved, but at visit 4 (—) he still complained of fever (Temp 38.1°C tympanic, reportedly the patient had temps to 39°C). At Visit 4 he had an elevated ALT of 354 U/L, measured at a local laboratory. Of note is that the patient's ALT at baseline was elevated (81 IU/L [NR 0-49]) when tested at the local laboratory and when tested at the central laboratory (69 IU/L [NR 6-43 IU/L]). On — three days after Visit 4, his ALT was significantly elevated (1529 U/L). The subject was hospitalized with a diagnosis of hepatitis. Serologic testing for Hepatitis A, B, and C were negative. EBV- and CMV-serologies were positive for IgG, consistent with past infection. A percutaneous liver biopsy was performed on — and the results were reported by the pathologist in Finland as acute hepatitis with predominantly centrilobular liver necrosis, granulomata-like structures, and eosinophilic infiltration. An abdominal ultrasound examination suggested fatty liver. The subject was discharged from the hospital on — The patient's liver-associated enzymes from the both the central and local laboratory are provided in Table 13.

Table 13. Selected Lab Values for Patient 502/1069 from Study 3000

Lab Laboratory Analyte	Date*																	
Local Laboratory																		
AST (NR<49 U/L)	38	-	-	-	-	170	-	-	-	-	-	-	-	-	-	-	-	-
ALT (NR<49 U/L)	**81**	-	-	**354**	**1529**	**947**	**694**	**550**	**454**	**456**	**463**	**519**	**518**	**362**	**130**	-	**53**	**53**
Alk Phos (NR 60-275 U/L)	-	-	-	-	169	164	194	260	242	259	-	-	261	251	-	-	169	28
T. Bilirubin (NR 2-20 umol/L)	9	-	-	-	**29**	**31**	**26**	**24**	18	18	-	-	15	13	-	-	16	16
Central Laboratory																		
AST (NR 11-36 U/L)	36	29	35	**167**	-	-	-	-	-	-	-	-	**193**	-	-	-	-	-
ALT (NR 6-43 U/L)	**69**	**69**	**69**	**280**	-	-	-	-	-	-	-	-	**463**	-	-	-	-	-
Alk Phos (NR 31-110 U/L)	78	73	74	60	-	-	-	-	-	-	-	-	104	-	-	-	-	-
T. Bilirubin (NR 3-21 umol/L)	7	6	9	10	-	-	-	-	-	-	-	-	10	-	-	-	-	-
Other Lab Values from the Local Laboratory																		
INR for PT (NR <1.20)	0.97	0.95	0.90	-	-	-	-	-	-	-	-	-	1.04	-	-	-	-	-
Absolute Eosinophils (cells/uL)†	**774**	-	-	**960**	**1062**	-	-	-	-	-	-	**1729**	**2856**	-	-	-	-	-
Hemoglobin (NR13.0-18.0 g/dL)	14.4	-	-	14.9	**12.5**	**12.0**	**11.9**	**11.2**	**11.4**	**11.4**	**10.6**	-	-	-	-	**12.9**	-	-
ESR (NR 0-20)	**87**	**92**	17	-	-	-	-	-	-	-	-	-	**69**	-	-	-	-	-
C-Reactive Protein (mg/L)	-	-	-	**68**	**170**	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Lab Values from the Central Laboratory																		
Albumin (NR 33-49)	**31**	33	36	36	-	-	-	-	-	-	-	-	**31**	-	-	-	-	-
Total Protein (NR 61-84)	67	74	71	70	-	-	-	-	-	-	-	-	74	-	-	-	-	-
Absolute Eosinophils (NR 0.00-0.57 GI/L)	-	**0.65**	0.00	**0.78**	-	-	-	-	-	-	-	-	**2.54**	-	-	-	-	-
C-Reactive Protein (NR 0-8mg/L)	**120**	77	5	**66**	-	-	-	-	-	-	-	-	8	-	-	-	-	-

NR = normal range

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

Subject 1069 also had urinalyses performed on [redacted], and [redacted], that were negative for proteinuria, glycosuria, blood, and WBCs. There are no results for subsequent urinalyses (from the time period when subject 1069's transaminases were known to be elevated).

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

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

- Fluticasone 2 puffs (1000 mcg) inhaled bid for asthma which he had been taking since 1995
- Salbutamol inhaler used prn for asthma since 1979
- Atrovent 1 mL inhaled 5x a day from [redacted] 1999 to [redacted] 1999
- Nasonex aerosol 200 mcg nasal inhalation "x1" started on [redacted] 1999
- Calcichew one 500 mg tablet "x1" started on [redacted] 1999 for hypocalcemia
- Acetaminophen 500 mg tablets orally, frequency unknown started on [redacted] 1999 to an unknown subsequent date in [redacted] 1999. The investigator notes in the previous and concomitant medication case report form "all together 6 tablets in one week." In the Serious adverse event Case Report Form

(CRF), the investigator notes — Has also taken paracetamol 6 tbl's for treatment of fever (500mg/tabl.)."

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

MO Comment: Regarding the patient's intake of acetaminophen: The MedWatch report form for the event contains the following statement "On —— , fever; paracetamol 6x500mg tblts given." Reviewing the case report forms, there is no entry that confirms that the patient actually received 3 grams of acetaminophen on —— . It is possible that this statement represents an interpretation/misinterpretation of the statements from the CRFs quoted above. Presumably the data from the CRFs should be the more primary information.

Although not mentioned in the "Previous/Concomitant Medication" Case Report Forms for Subject 502/1069 or in the MedWatch forms (submitted August 11, 2000 to IND 55,283 N-144) summarizing the serious adverse event, the case narrative provided in the NDA submission describes the following previous and concomitant medications:

Concomitant medication:
cardiol carvedilol (25 mg x 2) p.o., for hypertension. from —— 1996; cozaar losartan potassium (75 mg x 1) p.o., for hypertension, from —— 1997; diurex hydrochlorothiazide (50 mg, infrequently) p.o., for hypertension, from —— 1996; kefurion (1.5 g x 3) i.v.. for pneumonia, from —— 1999; para-tabs (500 mg x 1) p.o., for fever, from —— , 1999; atrovent (1 mL x 5) by inhalation, for asthma, from —— 1999; calcichew (500 mg x 1) p.o., for hypocalcemia, from —— 1999; fluticasone (1 mg 2 x 2) by inhalation, for asthma, from an unknown date; nasonex nasal aerosol (0.2 mg x 1) nasal application, for chronic rhinitis, from an unknown date; paracetamol (500 mg x ?) p.o., for fever, from —— 1999; salbutamol (dose unknown, p.r.n.) by inhalation, for asthma.

Source: NDA 21-114, 8:v215:p256-7

MO Comment: A query was faxed to the Applicant on January 12, 2001 requesting clarification of the apparent inconsistencies regarding the concomitant medications for subject 502/1069. The Applicant's response submitted January 31, 2001 provided the following clarifications. Subject 502/1069 did not receive Cardiol (caverdilol), Cozaar (losartan potassium), Diurex (hydrochlorothiazide), Kefurion (cefuroxime for injection), or para-tabs as noted above. The Applicant notes that the subject received only the following concomitant medications:

In fact the subject received only the following concomitant medication: atrovent (1mL x 5) by inhalation, for asthma, from — , 1999; calcichew (500 mg x 1) p.o., for hypocalcemia, from —— 1999; fluticasone (1mg 2 x 2) by inhalation, for asthma from an unknown date; nasonex nasal aerosol (0.2 mg x 1) nasal application, for chronic rhinitis, from an unknown date; nasonex nasal aerosol (0.2 mg x 1) nasal application for chronic rhinitis, from an unknown date in — 1999; paracetamol (500 mg x ?) p.o., for fever, from —— , 1999; salbutamol (dose unknown, p.r.n.) by inhalation, for asthma.

From Section D of the Applicant's submission dated January 31, 2001

MO Comment: The Applicant notes that the medications that Subject 502/1069 did not receive that are listed in the case narrative for subject 502/1069 (8:v215:p256-7) were actually medications that either subject 502/1067 or 502/1068 received that were inadvertently attributed to subject 502/1069.

Additional evaluation included serologic studies that were negative for HIV, Toxoplasma, "F-para-O", Tularemia (x2), Legionella, Brucella, Mycoplasma, Coxiella burnetii, Fasciola hepatica, and Toxocara canis. Serologic testing for EBV, CMV, and HSV was "low positive" with a negative IgM class antibody consistent with previous infection. He also had serologic testing for Ebola virus which returned with

results of "low-positive", the significance of which is unclear. Stool examination for parasites was negative. The patient also had the following additional results from testing performed on — CH50=68 U/mL; IgA=3.1g/L, IgG=12.7 g/L, (IgG1=4.53, IgG2=3.93, IgG4=3.34) [laboratory normal ranges not provided, typical normal ranges;[9, 10] CH50 (63-145 U/mL); IgA (0.5-3.5 g/L); IgG (5.0-12.0 g/L)].

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

The investigator assessed the serious adverse event for subject 502/1069 as possibly related to study medication. The event was considered a serious adverse event because it met the following criteria: required or prolonged hospitalization and was medically important. The Applicant commented that the clinical picture *is clouded by the presence of an apparent infectious process as well as concomitant medications including kefurion that offer alternative explanations. However, the clinical picture is compatible with a hypersensitivity reaction. The findings of eosinophilia and hepatitis on liver biopsy are consistent with a drug-related etiology* (8:v251:p196-7).

> **MO Comment:** As noted previously the Applicant subsequently clarified that patient 502/1069 did not receive kefurion. (Please see earlier MO Comment.)

The patient underwent a "routine check-up" on — and was found to have an ALT=1331 U/L, T.Bili=25 umol/L (NR <20 umol/L). Eosinophilia was not present. Serologic testing for hepatitis A antibodies, HBs antigen, HBc antibodies, and HCV antibodies, was negative. EBV and CMV serology results were consistent with old inactive infection. Antinuclear and mitochondrial antibodies were negative. A serology for anti-smooth muscle antibodies yielded a titer of 1:1000. Serum immunoglobulin levels were IgG=18.1 g/L, IgA=5.48 g/L, IgM=2.07 g/L, IgE=471 kU/L [normal range not provided, typical normal ranges for IgA and IgG as noted, for IgM (0.3-2.3 g/L);[9] IgE (5-100 kU/L)[9] or IgE (0-380 kU/L)[11]]. An ultrasound examination of the liver was reported as normal. The only medication that the patient reported taking was paracetamol for headache. A percutaneous liver biopsy was performed on — and the results were reported by a pathologist as — as hepatitis with centrilobular liver cell depletion, no frank necrosis. His ALT reportedly normalized rapidly and was 43 U/L on —

On — the patient reportedly had normal LFTs, a negative ANA, and negative serologic tests for anti-smooth muscle, anti-microsomal, and anti-thyroglobulin antibodies. At a subsequent follow-up visit on — follow-up info notes "LFTs normalized."

Aventis Pharmaceuticals had the case of patient 1069 from center 502 in study 3000 reviewed by two expert hepatologists, — . At the request of the Agency, their expert reports were submitted to the NDA. Dr. — concluding paragraph from his 20 March 2000 report to Aventis is excerpted below:

> *The follow-up information, particularly the finding of the smooth muscle antibodies, does support the possibility that the patient has an underlying autoimmune hepatitis which is relatively mild. His hepatitis viral tests had all been negative. It would be worthwhile to follow-up with the patient further. It is not possible to exclude that telithromycin was the cause of the initial reaction. However, the subsequent time course and observations are supportive of a mild autoimmune hepatitis. It would be worthwhile to examine other cases of hepatotoxicity possibly related to telithromycin to see if similar events have occurred. There have been rare instances of*

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[9] System International (SI) units table. JAMA 1996;276:24-26.
[10] Kratz A, Lewandrowski KB. Normal reference laboratory values. NEJM 1998;339(15):1063-1072.
[11] Elin RJ. Reference intervals and laboratory values (Ch. 523). In *Cecil Textbook of Medicine*. Eds. Goldman L, Bennett JC. 21st Ed, Vol. 2. W.B. Saunders Co. Philadelphia. 2000. pp. 2299-2308.

elevations of smooth muscle antibody elevations in patients in whom a drug etiology was subsequently found.

Dr [redacted] concluding paragraphs from his consultation to Aventis Pharmaceuticals of 16 March 2000 are excerpted below:

The presence of ASMA at high titers is consistent with an autoimmune mechanism. Improvement of hepatitis without any important immunosuppressive regimen may suggest drug-induced rather than «idiopathic» autoimmunity.

Since the liver disease was different during both episodes (with fever, eosinophils and granulomata during the first episode but not the second), we cannot rule out the involvement of telithromycin during the first bout. Nevertheless, the use of paracetamol before both episodes may also suggest the possibility of paracetamol-induced autoimmunity.

It will be interesting to see whether the abstention of any paracetamol intake would prevent the recurrence of hepatitis flares in the future and could also progressively decrease ASMA titers.

MO Comment: If the patient uses acetaminophen in a pattern of chronic intermittent use on several occasions over a typical month each month throughout the year, acetaminophen use is likely to precede any event at any point in time, even in the absence of a causal association. Further information on the patient's medication use was requested from Aventis by the Agency on 09 Nov 2000. The patient's acetaminophen use is described as, *Para-Tabs (paracetamol) for unspecified aches when needed (dosage and exact dates unknown).*[12] The information provided doesn't provide a precise history or quantitation of acetaminophen use.

The slides of the patient's liver biopsies were requested by the Agency for review. In addition, a consultation with Dr. Senior of OPDRA to evaluate the case of patient 502/1069 and the hepatotoxic potential of *telithromycin* was requested. (Please see Dr. Senior's consultation for his comments and conclusions.)

The slides of the patient's liver biopsies were reviewed with [redacted]. The [redacted] diagnoses and findings from the report dated December 15, 2000 are as follows:

Diagnosis 99-4879 (N)[redacted] biopsy]: (1) Recent zone 3 ("centrilobular") necrosis with numerous tissue eosinophils, strongly suggestive of drug-induced liver disease. (2) History of telithromycin therapy.

Diagnosis 99-28804 (N)[redacted] biopsy]: Chronic hepatitis, probably autoimmune, with marked activity and extensive bridging fibrosis

The first biopsy (99-4879) shows a severe recent liver injury with extensive hepatocyte loss in acinar zone 3 ("centrilobular") and numerous macrophages and eosinophils in the areas of necrosis. There is also some patchy portal inflammation, but fibrosis is minimal. The character of the injury and the presence of eosinophils strongly suggest a hypersensitivity-type drug-related injury. Although the patient was reported to have taken acetaminophen, the histologic features do not suggest this as the cause. In view of the history of another drug (telithromycin), it seems more likely that this is the etiologic agent.

The second biopsy (99-28804) is quite different from the first. It shows extensive fibrosis with bridging. Much of the fibrosis is in zone 3, in the same location as the acute injury in the first biopsy, but there is also portal fibrosis with portal-portal and portal central bridging. In addition, there is ongoing hepatocellular injury with extensive interface hepatitis ("piecemeal necrosis"),

[12] Aventis response to request for information submitted November 20, 2000.

and the inflammatory infiltrate contains a predominance of plasma cells. Eosinophils are few. The histologic features of this biopsy strongly suggest autoimmune hepatitis, and the presence of smooth muscle antibodies and some hyperglobulinemia seem to support this diagnosis.

The precise relationship between the diseases suggested by the two biopsies is unclear. It is possible. The fact that the patient's aminotransferase levels were slightly elevated before taking the drug suggests that he may have had an underlying, relatively quiescent autoimmune hepatitis.

As noted above in the excerpt from Dr —— report, the first biopsy strongly suggests drug-induced liver disease.

MO Comment: The description of the histopathologic findings on examination of liver tissue in some of the reported cases of trovafloxacin-associated acute liver disease are similar to the findings on patient 502/1069's first liver biopsy. The biopsy findings reported for patients with trovafloxacin-associated acute hepatitis have shown centrilobular necrosis and eosinophilic infiltration.[13, 14]

The liver biopsy findings for this patient (502/1069) were found to be strongly suggestive of a hypersensitivity-type drug-related injury, a pathologic picture similar to what was seen in some of the patients with trovafloxacin-associated hepatitis. It is remarkable that such a case was observed to occur within the relatively small population within the NDA database. While this patient had a mildly elevated ALT at study entry, the biopsy findings from this case suggest that telithromycin may be capable of inducing serious liver injury by a hypersensitivity mechanism.

[13] Chen HJL, Bloch KJ, Maclean JA. Acute eosinophilic hepatitis from trovafloxacin. NEJM 2000, 342 (5):359.

[14] Lucena MI, Andrade, RJ, Rodrigo L, Salmeron J, et. al. Trovafloxacin-induced acute hepatitis. Clin Infect Dis. 2000. 30(2):400-1.

Phase III – Deaths due to Hepatic Adverse Events

In the comparative phase III studies there were 2 deaths in the telithromycin treated group and 4 deaths in the comparator treated group. In the non-comparative studies there were 5 additional deaths in patients treated with telithromycin. Review of the deaths in the safety database did not reveal any patientts who expired because of an event that appeared to be primarily the result of a telithromycin drug induced hepatic adverse event.

Of the 11 deaths, 2 involved patients with marked hepatic laboratory abnormalities. The first of these was patient 0703/1466 from Study 3000 who died with renal failure, hemolytic anemia, sepsis, and liver insufficiency due to acute leptospirosis (diagnosed serologically). The second of the two patients with notable hepatic abnormalities (patient 0369/108 from Study 3009) was a cachectic 37-year-old female admitted to Study 3009 at a study center in —— with pneumonia, severe dyspnea, and respiratory distress. At the time of admission to study, her transaminases were ALT 1235 U/L and AST 806 U/L. She received 7 days of telithromycin at 800 mg po daily. On her seventh day of study therapy she was diagnosed with HIV infection and transferred to a specialist hospital where she expired four days later. Also noted on her second hospital day was that the subject developed leg pain with the following associated findings "blue toes" bilaterally, "swollen" and "tender" legs bilaterally with non-pitting edema (Review of the subject's CRF does not reveal the use of any vasopressors). The investigator's diagnosis for the adverse event involving her lower extremities was severe lower leg vasculitis not thought to be related to study therapy.

> **MO Comment:** Patient 0369/108's pre-existing liver disease in the setting of pneumonia with severe dyspnea/respiratory distress in an HIV-positive patient make it unlikely that telithromycin played a primary role in the patient's liver abnormalities or subsequent death due to multiorgan failure.

There was another patient (patient 0803/1520 from study 3000) that expired in the non-comparative studies that did not have a hepatic adverse event preceding his death. However, it is interesting that 3 days after he completed his 9-day course of telithromycin he developed a rash and microscopic hematuria and proteinuria. A biopsy of the rash showed findings on histopathology consistent with leukocytoclastic vasculitis (an event that may result form any of a number of conditions one of which is drug-induced hypersensitivity). At the time of onset of his rash the investigator considered the subject a cure. He was treated with prednisone and hydroxizine and his rash resolved within 11 days of its onset on —— . Also on —— the patient became hypotensive and was diagnosed with an acute myocardial infarction by serum CPK enzymes and ECGs. He expired on —— with the listed diagnoses of gram-negative sepsis, severe congestive heart failure, and acute myocardial infarction.

Laboratory Abnormalities for ALT, AST, T. Bilirubin, and Alkaline Phosphatase – Phase III Studies

Multiple analyses were performed to investigate laboratory abnormalities for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (T. Bili.), and alkaline phosphatase (Alk. Phos.). The first set of analyses were conducted on the population of patients from the phase III studies that were normal for the analyte being evaluated at baseline and then in a separate group of analyses for patients abnormal for the analyte of interest at baseline. These analyses examined changes in liver function tests during the "During Treatment" period – study entry through end of treatment + 7 days. In addition to the aforementioned analyses, a number of supplemental analyses of liver function tests were also performed. These supplemental analyses examined rates of elevation at each of the visit timepoints (on-therapy, post-therapy, and late post-therapy) whereas the first set of analyses examined only the composite timepoint of "During Treatment," which was defined as pretherapy/entry through end of treatment + 7 days. The findings from these analyses and several of the key tables are presented within this section examining laboratory abnormalities.

The data from the analyses of patients normal for the analyte being evaluated at baseline and their LFT changes During Treatment are presented first for ALT, AST, T. Bili., and Alk. Phos. These results are presented separately for patients from the CAP studies and patients from studies other than CAP (Non-CAP studies). For both the CAP and non-CAP studies the data were also analyzed by the following strata; age (<65 vs. ≥65 years), concomitant intake of CYP3A4 inhibitors (Yes vs. No), weight (≤50 vs. >50 kg), and gender. The analyses are performed in the group of patients with normal values for the analyte of interest at baseline and in a separate analysis for those with an abnormal value for the analyte of interest at baseline.

Patients with normal baseline values for the analyte of interest – CAP Studies
In the controlled CAP studies, in patients with a normal baseline value for the lab analyte being evaluated, a greater proportion of telithromycin treated than comparator-treated patients developed elevations in ALT, AST, or T. Bili. During Treatment (Table 14). These differences are largely the result of a greater number of telithromycin treated patients with elevations in the range of >ULN & ≤2xULN (ALT, AST, and T. Bili.) and >2xULN & ≤3xULN (ALT & AST). The proportion of excess elevations appears to be greatest for AST rather than ALT or T. Bili. The number of patients experiencing elevations in the categories >3xULN are small in both treatment groups. The results from the uncontrolled CAP studies were similar.

In the subset of patients ≥65 years of age from the controlled CAP studies with a normal baseline value for the analyte being evaluated, the proportion of telithromycin treated patients with an elevation in AST was greater than for patients <65 years of age. There was a slightly greater proportion of telithromycin treated patients experiencing elevations in ALT in the ≥65 years of age group, although the number of patients in the ≥ 65 years of age group is small. Additional analyses of lab value abnormalities for ALT, AST, and T. Bili. in the analyses stratified by gender, concomitant intake of CYP3A4 inhibitors

(Yes vs. No), and weight (≤50 vs. >50 kg), within the group of patients with a normal value for the analyte of interest at baseline showed the following trends. In general, a greater proportion of men developed abnormal values for ALT or AST During Treatment. Similar rates of ALT or T. Bili. abnormalities were observed in patients taking concomitant drugs known to inhibit CYP 3A4 compared to patients not taking CYP3A4 inhibitors. There was a very slightly greater proportion of telithromycin treated patients with AST elevations in the subgroup taking concomitant drugs known to inhibit CYP 3A4 compared to those not taking CYP3A4 inhibitors. There were no clearly discernible differences between the very small number of patients in the subgroup with weight ≤50kg compared to those with weight >50kg.

The results for the overall population and for the subset of patients of age ≥ 65 years of age are presented in Tables 14 and 15.

Table 14. ALT, AST, or T. Bili. Lab Values Occurring During Treatment* in Subjects with a Normal Value for the Analyte of Interest at Baseline – CAP Studies

Analysis	Telithromycin † n/N	(%)	All Comparators†† n/N	(%)
Controlled CAP Studies Baseline ALT is Normal and Follow-up ALT is				
≤ULN	309/395	(78.2)	317/388	(81.7)
>ULN & ≤ 2 x ULN	72/395	(18.2)	64/388	(16.5)
>2 x ULN & ≤ 3 x ULN	10/395	(2.5)	4/388	(1.0)
>3 x ULN & ≤ 5 x ULN	3/395	(0.8)	2/388	(0.5)
>5 x ULN & ≤ 8 x ULN	1/395	(0.3)	1/388	(0.3)
>8 x ULN	0/395	(0.0)	0/388	(0.0)
Uncontrolled CAP Studies Baseline ALT is Normal and Follow-up ALT is				
≤ULN	549/671	(81.8)		
>ULN & ≤ 2 x ULN	93/671	(13.9)		
>2 x ULN & ≤ 3 x ULN	21/671	(3.1)		
>3 x ULN & ≤ 5 x ULN	7/671	(1.0)		
>5 x ULN & ≤ 8 x ULN	0/671	(0.0)		
>8 x ULN	1/671	(0.1)		
Controlled CAP Studies Baseline AST is Normal and Follow-up AST is				
≤ULN	344/411	(83.7)	358/394	(90.9)
>ULN & ≤ 2 x ULN	59/411	(14.4)	32/394	(8.1)
>2 x ULN & ≤ 3 x ULN	4/411	(1.0)	1/394	(0.3)
>3 x ULN & ≤ 5 x ULN	3/411	(0.7)	3/394	(0.8)
>5 x ULN & ≤ 8 x ULN	1/411	(0.2)	0/394	(0.0)
>8 x ULN	0/411	(0.0)	0/394	(0.0)
Uncontrolled CAP Studies Baseline AST is Normal and Follow-up AST is				
≤ULN	527/643	(82.0)		
>ULN & ≤ 2 x ULN	100/643	(15.6)		
>2 x ULN & ≤ 3 x ULN	12/643	(1.9)		
>3 x ULN & ≤ 5 x ULN	3/643	(0.5)		
>5 x ULN & ≤ 8 x ULN	1/643	(0.2)		
>8 x ULN	0/643	(0.0)		
Controlled CAP Studies Baseline T Bili is Normal and Follow-up T Bili is				
≤ULN	444/452	(98.2)	428/432	(99.1)
>ULN & ≤ 2 x ULN	8/452	(1.8)	3/432	(0.7)
>2 x ULN & ≤ 3 x ULN	0/452	(0.0)	0/432	(0.0)
>3 x ULN & ≤ 5 x ULN	0/452	(0.0)	0/432	(0.0)
>5 x ULN & ≤ 8 x ULN	0/452	(0.0)	1/432	(0.2)
>8 x ULN	0/452	(0.0)	0/432	(0.0)
Uncontrolled CAP Studies Baseline T Bili is NORMAL and Follow-up T Bili is				
≤ULN	688/701	(98.1)		
>ULN & ≤ 2 x ULN	12/701	(1.7)		
>2 x ULN & ≤ 3 x ULN	0/701	(0.0)		
>3 x ULN & ≤ 5 x ULN	1/701	(0.1)		
>5 x ULN & ≤ 8 x ULN	0/701	(0.0)		
>8 x ULN	0/701	(0.0)		

* During Treatment = from pretherapy/entry through end of treatment + 7 days

† The telithromycin regimens for the Controlled CAP (comparative) studies were telithromycin 800 mg po QD x 10 days (Studies 3006 and 3001) and telithromycin 800 mg po QD x 7-10 days (Study 3009). The telithromycin regimen for the uncontrolled CAP studies were telithromycin 800 mg po QD x 7-10 days (Study 3000 and 3009OL) and telithromycin 800 mg po QD x 7 days (Study 3010).

†† Comparators for the controlled CAP studies were: clarithromycin 500 mg po BID x 10 days (Study 3006); trovafloxacin 200 mg po QD x 7-10 days (Study 3009); amoxicillin 1000 mg po TID x 10 days (Study 3001)

Adapted from Applicant's Tables v10/0000042t.1[a] 19 February 2001; v10/0000060t.1[a] 19 February 2001; v10/0000096t.1[a] 19 February 2001

Table 15. ALT, AST, or T. Bili. Lab Values Occurring During Treatment* in Subjects ≥ 65 Years of Age with a Normal Value for the Analyte of Interest at Baseline – CAP Studies

Analysis	Telithromycin † n/N	(%)	All Comparators†† n/N	(%)
Controlled CAP Studies Baseline ALT is Normal and Follow-up ALT is				
≤ULN	53/69	(76.8)	61/70	(87.1)
>ULN & ≤ 2 x ULN	12/69	(17.4)	9/70	(12.9)
>2 x ULN & ≤ 3 x ULN	3/69	(4.3)	0/70	(0.0)
>3 x ULN & ≤ 5 x ULN	0/69	(0.0)	0/70	(0.0)
>5 x ULN & ≤ 8 x ULN	1/69	(1.4)	0/70	(0.0)
>8 x ULN	0/69	(0.0)	0/70	(0.0)
Uncontrolled CAP Studies Baseline ALT is Normal and Follow-up ALT is				
≤ULN	69/88	(78.4)		
>ULN & ≤ 2 x ULN	13/88	(14.8)		
>2 x ULN & ≤ 3 x ULN	4/88	(4.5)		
>3 x ULN & ≤ 5 x ULN	1/88	(1.1)		
>5 x ULN & ≤ 8 x ULN	0/88	(0.0)		
>8 x ULN	1/88	(1.1)		
Controlled CAP Studies Baseline AST is Normal and Follow-up AST is				
≤ULN	50/67	(74.6)	61/67	(91.0)
>ULN & ≤ 2 x ULN	15/67	(22.4)	6/67	(9.0)
>2 x ULN & ≤ 3 x ULN	1/67	(1.5)	0/67	(0.0)
>3 x ULN & ≤ 5 x ULN	0/67	(0.0)	0/67	(0.0)
>5 x ULN & ≤ 8 x ULN	1/67	(1.5)	0/67	(0.0)
>8 x ULN	0/67	(0.0)	0/67	(0.0)
Uncontrolled CAP Studies Baseline AST is Normal and Follow-up AST is				
≤ULN	69/85	(81.2)		
>ULN & ≤ 2 x ULN	11/85	(12.9)		
>2 x ULN & ≤ 3 x ULN	3/85	(3.5)		
>3 x ULN & ≤ 5 x ULN	1/85	(1.2)		
>5 x ULN & ≤ 8 x ULN	1/85	(1.2)		
>8 x ULN	0/85	(0.0)		
Controlled CAP Studies Baseline T Bili is Normal and Follow-up T Bili is				
≤ULN	76/76	(100.0)	68/69	(98.6)
>ULN & ≤ 2 x ULN	0/76	(0.0)	1/69	(1.4)
>2 x ULN & ≤ 3 x ULN	0/76	(0.0)	0/69	(0.0)
>3 x ULN & ≤ 5 x ULN	0/76	(0.0)	0/69	(0.0)
>5 x ULN & ≤ 8 x ULN	0/76	(0.0)	0/69	(0.0)
>8 x ULN	0/76	(0.0)	0/69	(0.0)
Uncontrolled CAP Studies Baseline T Bili is Normal and Follow-up T Bili is				
≤ULN	83/87	(95.4)		
>ULN & ≤ 2 x ULN	4/87	(4.6)		
>2 x ULN & ≤ 3 x ULN	0/87	(0.0)		
>3 x ULN & ≤ 5 x ULN	0/87	(0.0)		
>5 x ULN & ≤ 8 x ULN	0/87	(0.0)		
>8 x ULN	0/87	(0.0)		

Adapted from Applicant's Tables v10/0000045t.1[a] 5 February 2001; v10/0000063t.1[a] 16 March 2001; v10/0000099t.1[a] 16 March 2001

*During Treatment = from pretherapy/entry through end of treatment + 7 days

† The telithromycin regimens for the Controlled CAP (comparative) studies were telithromycin 800 mg po QD x 10 days (Studies 3006 and 3001) and telithromycin 800 mg po QD x 7-10 days (Study 3009). The telithromycin regimen for the uncontrolled CAP studies were telithromycin 800 mg po QD x 7-10 days (Study 3000 and 3009OL) and telithromycin 800 mg po QD x 7 days (Study 3010).

†† Comparators for the controlled CAP studies were: clarithromycin 500 mg po BID x 10 days (Study 3006); trovafloxacin 200 mg po QD x 7-10 days (Study 3009); amoxicillin 1000 mg po TID x 10 days (Study 3001)

Patients with abnormal baseline values for the analyte of interest – CAP Studies
Changes in liver-related lab analytes During Treatment for the subset of patients with an abnormal value for the analyte of interest at baseline were also examined. The number of patients that fell into this category was considerably fewer than the number of patients with normal values at baseline. The analyses took all patients with an abnormal value for the liver-related analyte of interest at baseline and categorized the subject by category of abnormality during treatment.

> **MO Comment:** This type of analysis does not examine how a subject's lab analyte changed over time, rather it simply looks at the category for a subject's During Treatment value for the analyte of interest. (The Applicant also performed line plots for patients in order to graphically display lab analyte changes over time.) The supplemental hepatic analyses that were performed examine the change in patients' lab analytes (LFTs) that occur by Visit.

The population of patients with abnormal lab values at baseline is a smaller population than the population of patients with normal values at baseline. The size of this smaller population and the lack of major differences in the laboratory findings limit the conclusions that can be drawn from these data. From the controlled CAP studies, there is a slightly greater proportion of telithromycin treated patients with an abnormal ALT During Treatment. The proportion of patients with an abnormal T. bilirubin during treatment in the controlled CAP studies is greater for comparator treated patients although the number of patients with an abnormal T. bilirubin at baseline is small.

Similar analyses stratified by gender, age, CYP3A4 inhibitor intake, and weight were also conducted for patients with an abnormal value for the analyte of interest at baseline. The analyses are somewhat limited by the small size of some of the subgroups. ALT and AST abnormalities during treatment among telithromycin treated subjects were more frequent in male patients. There were no marked differences in ALT or AST in patients taking CYP3A4 inhibitors. There were insufficient numbers of patients with weight $\leq$50 kg, or age $\geq$65 years to make comparisons for ALT and AST for these strata.

Comparisons of the T. Bilirubin values for the aforementioned strata were markedly limited by the small numbers of patients in the baseline abnormal T. Bilirubin population.

The results for the patients from the CAP studies with an abnormal value for the analyte of interest are presented in Table 16.

Table 16. ALT, AST, or T. Bili. Lab Values Occurring During Treatment* in Subjects with an Abnormal Value for the Analyte of Interest at Baseline – CAP Studies

Analysis	Telithromycin † n/N	(%)	All Comparators†† n/N	(%)
Controlled CAP Studies Baseline ALT is Abnormal and Follow-up ALT is				
≤ULN	18/101	(17.8)	25/96	(26.0)
>ULN & ≤ 2 x ULN	57/101	(56.4)	43/96	(44.8)
>2 x ULN & ≤ 3 x ULN	18/101	(17.8)	16/96	(16.7)
>3 x ULN & ≤ 5 x ULN	6/101	(5.9)	8/96	(8.3)
>5 x ULN & ≤ 8 x ULN	2/101	(2.0)	3/96	(3.1)
>8 x ULN	0/101	(0.0)	1/96	(1.0)
Uncontrolled CAP Studies Baseline ALT is Abnormal and Follow-up ALT is				
≤ULN	20/146	(13.7)		
>ULN & ≤ 2 x ULN	71/146	(48.6)		
>2 x ULN & ≤ 3 x ULN	27/146	(18.5)		
>3 x ULN & ≤ 5 x ULN	25/146	(17.1)		
>5 x ULN & ≤ 8 x ULN	1/146	(0.7)		
>8 x ULN	2/146	(1.4)		
Controlled CAP Studies Baseline AST is Abnormal and Follow-up AST is				
≤ULN	32/85	(37.6)	36/89	(40.4)
>ULN & ≤ 2 x ULN	40/85	(47.1)	34/89	(38.2)
>2 x ULN & ≤ 3 x ULN	7/85	(8.2)	12/89	(13.5)
>3 x ULN & ≤ 5 x ULN	4/85	(4.7)	6/89	(6.7)
>5 x ULN & ≤ 8 x ULN	2/85	(2.4)	0/89	(0.0)
>8 x ULN	0/85	(0.0)	1/89	(1.1)
Uncontrolled CAP Studies Baseline AST is Abnormal and Follow-up AST is				
≤ULN	45/173	(26.0)		
>ULN & ≤ 2 x ULN	73/173	(42.2)		
>2 x ULN & ≤ 3 x ULN	30/173	(17.3)		
>3 x ULN & ≤ 5 x ULN	20/173	(11.6)		
>5 x ULN & ≤ 8 x ULN	4/173	(2.3)		
>8 x ULN	1/173	(0.6)		
Controlled CAP Studies Baseline T. Bili is Abnormal and Follow-up T. Bili is				
≤ULN	28/32	(87.5)	32/42	(76.2)
>ULN & ≤ 2 x ULN	4/32	(12.5)	9/42	(21.4)
>2 x ULN & ≤ 3 x ULN	0/32	(0.0)	1/42	(2.4)
>3 x ULN & ≤ 5 x ULN	0/32	(0.0)	0/42	(0.0)
>5 x ULN & ≤ 8 x ULN	0/32	(0.0)	0/42	(0.0)
>8 x ULN	0/32	(0.0)	0/42	(0.0)
Uncontrolled CAP Studies Baseline T Bili is Abnormal and Follow-up T Bili is				
≤ULN	53/62	(85.5)		
>ULN & ≤ 2 x ULN	6/62	(9.7)		
>2 x ULN & ≤ 3 x ULN	3/62	(4.8)		
>3 x ULN & ≤ 5 x ULN	0/62	(0.0)		
>5 x ULN & ≤ 8 x ULN	0/62	(0.0)		
>8 x ULN	0/62	(0.0)		

*During Treatment = from pretherapy/entry through end of treatment + 7 days

† The telithromycin regimens for the Controlled CAP (comparative) studies were telithromycin 800 mg po QD x 10 days (Studies 3006 and 3001) and telithromycin 800 mg po QD x 7-10 days (Study 3009). The telithromycin regimen for the uncontrolled CAP studies were telithromycin 800 mg po QD x 7-10 days (Study 3000 and 3009OL) and telithromycin 800 mg po QD x 7 days (Study 3010).

†† Comparators for the controlled CAP studies were: clarithromycin 500 mg po BID x 10 days (Study 3006); trovafloxacin 200 mg po QD x 7-10 days (Study 3009); amoxicillin 1000 mg po TID x 10 days (Study 3001)

Adapted from Applicant's v10/0000042t.1[a] 19 February 2001, v10/0000060t.1[a] 19 February 2001, v10/0000096t.1[a] 19 February 2001

Patients with normal baseline values for the analyte of interest – Non-CAP studies
The Applicant's analyses of levels of elevation in transaminases During Treatment for patients in the controlled Non-CAP studies reveals a pattern of a small proportion of patients with low levels of AST or ALT elevations that are quite similar between telithromycin and comparators (Table 17). There is a greater proportion of telithromycin treated patients with elevations of T. Bili. [telithromycin 22/1348 (1.6%); comparators 6/997 (0.6%)]; all of these elevations (both for telithromycin and comparators) are in the category >ULN & ≤2x ULN.

Examination of elevations of ALT, AST, stratified by age (<65y vs. ≥65y) reveals no clear effect of age in this population. The proportion of telithromycin treated patients with AST elevations is greater for telithromycin treated males than females. A similar but smaller difference was also observed for comparator treated males compared to comparator treated females. The analyses stratifying by the presence or absence of concomitant intake of a drug known to inhibit CYP3A4 reveals no marked differences between the telithromycin and comparator treated patients with regards to the proportions and levels of ALT or AST elevations. Comparison of telithromycin treated patients with CYP3A4 inhibitor intake vs. telithromycin treated patients not taking CYP3A4 does not reveal differences in the proportion of patients or the levels of ALT or AST elevations. In the analysis stratifying by weight of ≤50 kg vs. >50 kg there are no marked differences in the proportion of patients or levels of elevation for ALT or AST between telithromycin treated patients and comparator treated patients in each of the weight strata. There are also no marked differences in the proportion of subjects and levels of elevations for ALT or AST between the telithromycin treated patients from the ≤50 kg weight strata compared to the telithromycin treated patients from the >50 kg weight strata (note the number of patients in the < 50 kg weight strata is small).

Examining the stratifications of the analyses for T. bilirubin elevations reveals the following. Comparison of the proportion of patients with elevations of T. bilirubin for telithromycin treated patients between genders finds a greater proportion of male patients with low level T. bilirubin elevations (the same is also true for male compared to female patients treated with comparators). The proportion of patients with T. bilirubin elevations was slightly greater in the subset of patients less than 65 years of age for both telithromycin and comparator although the numbers were small. In the subset of patients with concomitant intake of CYP3A4 inhibitors, there was a slightly greater proportion of telithromycin treated patients with low-level elevations of T. bilirubin. Comparing the subset of telithromycin treated patients with concomitant intake of CYP3A4 inhibitors to those without concomitant intake of CYP3A4 inhibitors, the proportion with T. bilirubin elevations is slightly greater in the subset of patients without concomitant CYP3A4 inhibitor intake (this is similar to what is found in the comparator group.) There were no marked differences in the proportion of patients with T. bilirubin elevations in the subset of patients with weight ≤50 kg either between telithromycin and comparators or between telithromycin treated patients with weight ≤50 kg compared to those with weight >50 kg (however, the number of patients with weight ≤50 kg is small).

Table 17. ALT, AST, or T. Bili. Lab Values Occurring During Treatment* in Subjects with Normal Values for the Analyte of Interest at Baseline – Non-CAP Studies

Analysis	Telithromycin † n/N	(%)	All Comparators†† n/N	(%)
Controlled Non-CAP Studies Baseline ALT is Normal and Follow-up ALT is				
≤ULN	1126/1251	(90.0)	836/936	(89.3)
>ULN & ≤ 2 x ULN	117/1251	(9.4)	92/936	(9.8)
>2 x ULN & ≤ 3 x ULN	5/1251	(0.4)	6/936	(0.6)
>3 x ULN & ≤ 5 x ULN	2/1251	(0.2)	2/936	(0.2)
>5 x ULN & ≤ 8 x ULN	0/1251	(0.0)	0/936	(0.0)
>8 x ULN	1/1251	(0.1)	0/936	(0.0)
Uncontrolled Non-CAP Studies Baseline ALT is Normal and Follow-up ALT is				
≤ULN	241/265	(90.9)		
>ULN & ≤ 2 x ULN	24/265	(9.1)		
>2 x ULN & ≤ 3 x ULN	0/265	(0.0)		
>3 x ULN & ≤ 5 x ULN	0/265	(0.0)		
>5 x ULN & ≤ 8 x ULN	0/265	(0.0)		
>8 x ULN	0/265	(0.0)		
Controlled Non-CAP Studies Baseline AST is Normal and Follow-up AST is				
≤ULN	1252/1333	(93.9)	931/1000	(93.1)
>ULN & ≤ 2 x ULN	75/1333	(5.6)	66/1000	(6.6)
>2 x ULN & ≤ 3 x ULN	3/1333	(0.2)	1/1000	(0.1)
>3 x ULN & ≤ 5 x ULN	0/1333	(0.0)	0/1000	(0.0)
>5 x ULN & ≤ 8 x ULN	3/1333	(0.2)	1/1000	(0.1)
>8 x ULN	0/1333	(0.0)	1/1000	(0.1)
Uncontrolled Non-CAP Studies Baseline AST is Normal and Follow-up AST is				
≤ULN	270/288	(93.8)		
>ULN & ≤ 2 x ULN	16/288	(5.6)		
>2 x ULN & ≤ 3 x ULN	1/288	(0.3)		
>3 x ULN & ≤ 5 x ULN	1/288	(0.3)		
>5 x ULN & ≤ 8 x ULN	0/288	(0.0)		
>8 x ULN	0/288	(0.0)		
Controlled Non-CAP Studies Baseline T Bili Normal and Follow-up T Bili is				
≤ULN	1326/1348	(98.4)	991/997	(99.4)
>ULN & ≤ 2 x ULN	22/1348	(1.6)	6/997	(0.6)
>2 x ULN & ≤ 3 x ULN	0/1348	(0.0)	0/997	(0.0)
>3 x ULN & ≤ 5 x ULN	0/1348	(0.0)	0/997	(0.0)
>5 x ULN & ≤ 8 x ULN	0/1348	(0.0)	0/997	(0.0)
>8 x ULN	0/1348	(0.0)	0/997	(0.0)
Uncontrolled Non-CAP Studies Baseline T Bili Normal and Follow-up T Bili is				
≤ULN	287/295	(97.3)		
>ULN & ≤ 2 x ULN	8/295	(2.7)		
>2 x ULN & ≤ 3 x ULN	0/295	(0.0)		
>3 x ULN & ≤ 5 x ULN	0/295	(0.0)		
>5 x ULN & ≤ 8 x ULN	0/295	(0.0)		
>8 x ULN	0/295	(0.0)		

*During Treatment = from pretherapy/entry through end of treatment + 7 days

† The telithromycin regimens for the Controlled Non-CAP (comparative) studies were telithromycin 800 mg po QD x 5 days (Studies 3003, 3004, 3007, 3008, and 3011) and telithromycin 800 mg po QD x 5 days and telithromycin 800 mg po QD x 10 days (in Study 3005 a 3-arm study). The telithromycin regimen for the uncontrolled Non-CAP study was telithromycin 800 mg po QD x 5 days vs. telithromycin 800 mg po QD x 10 days (Study 3002).

†† Comparators for the controlled Non-CAP studies were: cefuroxime axetil 500 mg po BID x 10 days (Study 3007); Amoxicillin/clavulanic acid 500/125 mg po QD x 10 days (Studies 3003 and 3005); penicillin VK 500 mg po TID x 10 days (Study 3004), clarithromycin 250 mg po BID x 10 days (Study 3008), cefuroxime 250 mg po BID x 10 days (Study 3011).

Adapted from the Applicant's Tables v10/0000051t.1[st] 2 February 2001; v10/0000069t.1[st] 2 February 2001; v10/00000105t.1[st] 19 February 2001

Table 18. ALT, AST, or T. Bili. Lab Values Occurring During Treatment* in Subjects ≥ 65 Years of Age with a Normal Value for the Analyte of Interest at Baseline – Non-CAP Studies

Analysis	Telithromycin † n/N	(%)	All Comparators†† n/N	(%)
Controlled CAP Studies Baseline ALT is Normal and Follow-up ALT is				
≤ULN	138/148	(93.2)	137/148	(92.6)
>ULN & ≤ 2 x ULN	10/148	(6.8)	11/148	(7.4)
>2 x ULN & ≤ 3 x ULN	0/148	(0.0)	0/148	(0.0)
>3 x ULN & ≤ 5 x ULN	0/148	(0.0)	0/148	(0.0)
>5 x ULN & ≤ 8 x ULN	0/148	(0.0)	0/148	(0.0)
>8 x ULN	0/148	(0.0)	0/148	(0.0)
Uncontrolled CAP Studies Baseline ALT is Normal and Follow-up ALT is				
≤ULN	3/3	(100.0)		
>ULN & ≤ 2 x ULN	0/3	(0.0)		
>2 x ULN & ≤ 3 x ULN	0/3	(0.0)		
>3 x ULN & ≤ 5 x ULN	0/3	(0.0)		
>5 x ULN & ≤ 8 x ULN	0/3	(0.0)		
>8 x ULN	0/3	(0.0)		
Controlled CAP Studies Baseline AST is Normal and Follow-up AST is				
≤ULN	133/146	(91.1)	139/151	(92.1)
>ULN & ≤ 2 x ULN	13/146	(8.9)	12/151	(7.9)
>2 x ULN & ≤ 3 x ULN	0/146	(0.0)	0/151	(0.0)
>3 x ULN & ≤ 5 x ULN	0/146	(0.0)	0/151	(0.0)
>5 x ULN & ≤ 8 x ULN	0/146	(0.0)	0/151	(0.0)
>8 x ULN	0/146	(0.0)	0/151	(0.0)
Uncontrolled CAP Studies Baseline AST is Normal and Follow-up AST is				
≤ULN	3/3	(100.0)		
>ULN & ≤ 2 x ULN	0/3	(0.0)		
>2 x ULN & ≤ 3 x ULN	0/3	(0.0)		
>3 x ULN & ≤ 5 x ULN	0/3	(0.0)		
>5 x ULN & ≤ 8 x ULN	0/3	(0.0)		
>8 x ULN	0/3	(0.0)		
Controlled CAP Studies Baseline T Bili is Normal and Follow-up T Bili is				
≤ULN	151/152	(99.3)	155/155	(100.0)
>ULN & ≤ 2 x ULN	1/152	(0.7)	0/155	(0.0)
>2 x ULN & ≤ 3 x ULN	0/152	(0.0)	0/155	(0.0)
>3 x ULN & ≤ 5 x ULN	0/152	(0.0)	0/155	(0.0)
>5 x ULN & ≤ 8 x ULN	0/152	(0.0)	0/155	(0.0)
>8 x ULN	0/152	(0.0)	0/155	(0.0)
Uncontrolled CAP Studies Baseline T Bili is Normal and Follow-up T Bili is				
≤ULN	3/3	(100.0)		
>ULN & ≤ 2 x ULN	0/3	(0.0)		
>2 x ULN & ≤ 3 x ULN	0/3	(0.0)		
>3 x ULN & ≤ 5 x ULN	0/3	(0.0)		
>5 x ULN & ≤ 8 x ULN	0/3	(0.0)		
>8 x ULN	0/3	(0.0)		

*During Treatment = from pretherapy/entry through end of treatment + 7 days

† The telithromycin regimens for the Controlled Non-CAP (comparative) studies were telithromycin 800 mg po QD x 5 days (Studies 3003, 3004, 3007, 3008, and 3011) and telithromycin 800 mg po QD x 5 days and telithromycin 800 mg po QD x 10 days (in Study 3005 a 3-arm study). The telithromycin regimen for the uncontrolled Non-CAP study was telithromycin 800 mg po QD x 5 days vs. telithromycin 800 mg po QD x 10 days (Study 3002).

†† Comparators for the controlled Non-CAP studies were: cefuroxime axetil 500 mg po BID x 10 days (Study 3007); Amoxicillin/clavulanic acid 500/125 mg po QD x 10 days (Studies 3003 and 3005); penicillin VK 500 mg po TID x 10 days (Study 3004), clarithromycin 250 mg po BID x 10 days (Study 3008), cefuroxime 250 mg po BID x 10 days (Study 3011).

Adapted from the Applicant's Tables v10/0000054t.1[st] 5 February 2001; v10/0000072t.1[st] 5 February 2001; v10/00000108t.1[st] 16 March 2001

Patients with abnormal baseline values for the analyte of interest – Non-CAP studies
The analyses comparing During Treatment values of ALT and AST for telithromycin treated versus comparator treated patients found the distribution of lab abnormalities for ALT and AST to be similar between treatment groups (Table 19). There was a greater proportion of T. bilirubin elevations during treatment for the telithromycin treated patients compared to comparators in the small population of patients with abnormal T. Bilirubin at baseline.

Similar subgroup analyses were conducted for each of the analytes. The number of patients older than 65 years of age or less than 50 kg in weight were too small to allow comparisons between age and weight strata respectively. For telithromycin treated patients comparing gender groups for ALT abnormalities during treatment there were no marked differences. The proportion of telithromycin treated patients with AST abnormalities during treatment was greater among male than female patients (this was also true when comparing male to female comparator treated patients). The number of subjects in the population with an abnormal T. bilirubin at baseline was insufficient to allow comparisons between strata.

Table 19. ALT, AST, or T. Bili. Lab Values Occurring During Treatment* in Subjects with an Abnormal Value for the Analyte of Interest at Baseline – Non-CAP Studies

Analysis	Telithromycin† n/N	(%)	All Comparators†† n/N	(%)
Controlled Non-CAP Studies Baseline ALT Normal and Follow-up ALT is				
≤ULN	31/182	(17.0)	25/130	(19.2)
>ULN & ≤ 2 x ULN	115/182	(63.2)	74/130	(56.9)
>2 x ULN & ≤ 3 x ULN	22/182	(12.1)	19/130	(14.6)
>3 x ULN & ≤ 5 x ULN	12/182	(6.6)	9/130	(6.9)
>5 x ULN & ≤ 8 x ULN	1/182	(0.5)	1/130	(0.8)
>8 x ULN	1/182	(0.5)	2/130	(1.5)
Uncontrolled Non-CAP Studies Baseline ALT Normal and Follow-up ALT is				
≤ULN	12/34	(35.3)		
>ULN & ≤ 2 x ULN	17/34	(50.0)		
>2 x ULN & ≤ 3 x ULN	4/34	(11.8)		
>3 x ULN & ≤ 5 x ULN	1/34	(2.9)		
>5 x ULN & ≤ 8 x ULN	0/34	(0.0)		
>8 x ULN	0/34	(0.0)		
Controlled Non-CAP Studies Baseline AST is Normal and Follow-up AST is				
≤ULN	35/103	(34.0)	23/66	(34.8)
>ULN & ≤ 2 x ULN	50/103	(48.5)	33/66	(50.0)
>2 x ULN & ≤ 3 x ULN	12/103	(11.7)	2/66	(3.0)
>3 x ULN & ≤ 5 x ULN	4/103	(3.9)	6/66	(9.1)
>5 x ULN & ≤ 8 x ULN	0/103	(0.0)	1/66	(1.5)
>8 x ULN	2/103	(1.9)	1/66	(1.5)
Uncontrolled Non-CAP Studies Baseline AST is Normal and Follow-up AST is				
≤ULN	5/11	(45.5)		
>ULN & ≤ 2 x ULN	4/11	(36.4)		
>2 x ULN & ≤ 3 x ULN	2/11	(18.2)		
>3 x ULN & ≤ 5 x ULN	0/11	(0.0)		
>5 x ULN & ≤ 8 x ULN	0/11	(0.0)		
>8 x ULN	0/11	(0.0)		
Controlled Non-CAP Studies Baseline T. Bili Normal and Follow-up T. Bili is				
≤ULN	21/37	(56.8)	33/41	(80.5)
>ULN & ≤ 2 x ULN	14/37	(37.8)	7/41	(17.1)
>2 x ULN & ≤ 3 x ULN	1/37	(2.7)	1/41	(2.4)
>3 x ULN & ≤ 5 x ULN	1/37	(2.7)	0/41	(0.0)
>5 x ULN & ≤ 8 x ULN	0/37	(0.0)	0/41	(0.0)
>8 x ULN	0/37	(0.0)	0/41	(0.0)
Uncontrolled Non-CAP Studies Baseline T. Bili Normal and Follow-up T Bili is				
≤ULN	0/3	(0.0)		
>ULN & ≤ 2 x ULN	3/3	(100.0)		
>2 x ULN & ≤ 3 x ULN	0/3	(0.0)		
>3 x ULN & ≤ 5 x ULN	0/3	(0.0)		
>5 x ULN & ≤ 8 x ULN	0/3	(0.0)		
>8 x ULN	0/3	(0.0)		

*During Treatment = from pretherapy/entry through end of treatment + 7 days

† The telithromycin regimens for the Controlled Non-CAP (comparative) studies were telithromycin 800 mg po QD x 5 days (Studies 3003, 3004, 3007, 3008, and 3011) and telithromycin 800 mg po QD x 5 days and telithromycin 800 mg po QD x 10 days (in Study 3005 a 3-arm study). The telithromycin regimen for the uncontrolled Non-CAP study was telithromycin 800 mg po QD x 5 days vs. telithromycin 800 mg po QD x 10 days (Study 3002).

†† Comparators for the controlled Non-CAP studies were: cefuroxime axetil 500 mg po BID x 10 days (Study 3007); Amoxicillin/clavulanic acid 500/125 mg po QD x 10 days (Studies 3003 and 3005); penicillin VK 500 mg po TID x 10 days (Study 3004), clarithromycin 250 mg po BID x 10 days (Study 3008), cefuroxime 250 mg po BID x 10 days (Study 3011).

Adapted from Applicant's Tables v10/0000051t.1[st] 2 February 2001; v10/0000069t.1[st] 2 February 2001; v10/00000105t.1[st] 19 February 2001

Analysis of Alkaline Phosphatase Laboratory Values – CAP Studies

The Applicant analyzed laboratory values for alkaline phosphatase During Treatment in the population of patients with normal alkaline phosphatase values at baseline and separately in the population of patients with abnormal alkaline phosphatase values at baseline. In the patients from the controlled CAP studies with normal baseline alkaline phosphatase values, there are no marked differences between telithromycin and comparator in the proportion of patients and distribution of abnormal alkaline phosphatase values During Treatment (Table 20). In the group of patients with abnormal values for alkaline phosphatase at baseline there is a greater proportion of patients with abnormal values for alkaline phosphatase During Treatment in the comparator group (Table 21).

Table 20. Alkaline Phosphatase Lab Values During Treatment* in Patients with a Normal Alkaline Phosphatase at Baseline – CAP Studies

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin†		Comparators††		Telithromycin †	
	n/N	(%)	n/N	(%)	n/N	(%)
Baseline Alk. Phos. Normal and Follow-up Alk. Phos. is						
≤ ULN	406/431	(94.2)	396/426	(93.0)	687/725	(94.8)
> ULN & ≤ 2x ULN	24/431	(5.6)	28/426	(6.6)	37/725	(5.1)
> 2x ULN & ≤ 3x ULN	0/431	(0.0)	1/426	(0.2)	1/725	(0.1)
> 3x ULN & ≤ 5x ULN	1/431	(0.2)	0/426	(0.0)	0/725	(0.0)
> 5x ULN & ≤ 8x ULN	0/431	(0.0)	1/426	(0.2)	0/725	(0.0)
> 8x ULN	0/431	(0.0)	0/426	(0.0)	0/725	(0.0)

*During Treatment = from pretherapy/entry through end of treatment + 7 days ULN= upper limit of normal for the analyte being evaluated
† The telithromycin regimens for the Controlled CAP (comparative) studies were telithromycin 800 mg po QD x 10 days (Studies 3006 and 3001) and telithromycin 800 mg po QD x 7-10 days (Study 3009). The telithromycin regimen for the uncontrolled CAP studies were telithromycin 800 mg po QD x 7-10 days (Study 3000 and 3009OL) and telithromycin 800 mg po QD x 7 days (Study 3010).
†† Comparators for the controlled CAP studies were: clarithromycin 500 mg po BID x 10 days (Study 3006); trovafloxacin 200 mg po QD x 10 days (Study 3009); amoxicillin 1000 mg po TID x 10 days (Study 3001)
Adapted from the Applicant's Table v10/0000078t.1[st] 19 February 2001

Table 21. Alkaline Phosphatase Lab Values During Treatment* in Patients With an Abnormal Alkaline Phosphatase at Baseline – CAP Studies

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin †		Comparators††		Telithromycin †	
	n/N	(%)	n/N	(%)	n/N	(%)
Baseline Alk. Phos. Abnormal and Follow-up Alk. Phos. is						
≤ ULN	18/67	(26.9)	13/68	(19.1)	19/118	(16.1)
> ULN & ≤ 2x ULN	41/67	(61.2)	45/68	(66.2)	83/118	(70.3)
> 2x ULN & ≤ 3x ULN	7/67	(10.4)	6/68	(8.8)	10/118	(8.5)
> 3x ULN & ≤ 5x ULN	1/67	(1.5)	3/68	(4.4)	4/118	(3.4)
> 5x ULN & ≤ 8x ULN	0/67	(0.0)	0/68	(0.0)	2/118	(1.7)
> 8x ULN	0/67	(0.0)	1/68	(1.5)	0/118	(0.0)

*During Treatment = from pretherapy/entry through end of treatment + 7 days ULN= upper limit of normal for the analyte being evaluated
† The telithromycin regimens for the Controlled CAP (comparative) studies were telithromycin 800 mg po QD x 10 days (Studies 3006 and 3001) and telithromycin 800 mg po QD x 7-10 days (Study 3009). The telithromycin regimen for the uncontrolled CAP studies were telithromycin 800 mg po QD x 7-10 days (Study 3000 and 3009OL) and telithromycin 800 mg po QD x 7 days (Study 3010).
†† Comparators for the controlled CAP studies were: clarithromycin 500 mg po BID x 10 days (Study 3006); trovafloxacin 200 mg po QD x 10 days (Study 3009); amoxicillin 1000 mg po TID x 10 days (Study 3001)
Adapted from the Applicant's Table v10/0000078t.1[st] 19 February 2001

Analysis of Alkaline Phosphatase Laboratory Values – Non-CAP Studies

The proportion of patients and distribution of alkaline phosphatase values During Treatment for the group of patients with normal alkaline phosphatase values at baseline was similar between telithromycin and comparators in the controlled Non-CAP studies (Table 22). In the group of patients with an abnormal baseline value for alkaline phosphatase, more patients treated with comparator have an abnormal alkaline phosphatase value During Treatment (Table 23). While the proportion of patients with an abnormal value for alkaline phosphatase is greater for comparator treated patients, there are a few patients treated with telithromycin that have higher values for alkaline phosphatase During Treatment.

Table 22. Alkaline Phosphatase Lab Values During Treatment* in Patients with a Normal Alkaline Phosphatase at Baseline – Non-CAP Studies

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

*During Treatment = from pretherapy/entry through end of treatment + 7 days ULN= upper limit of normal for the analyte being evaluated
† The telithromycin regimens for the Controlled Non-CAP (comparative) studies were telithromycin 800 mg po QD x 5 days (Studies 3003, 3004, 3007, 3008, and 3011) and telithromycin 800 mg po QD x 5 days and telithromycin 800 mg po QD x 10 days (in Study 3005 a 3-arm study). The telithromycin regimen for the uncontrolled Non-CAP study was telithromycin 800 mg po QD x 5 days vs. telithromycin 800 mg po QD x 10 days (Study 3002).
†† Comparators for the controlled Non-CAP studies were: cefuroxime axetil 500 mg po BID x 10 days (Study 3007); Amoxicillin/clavulanic acid 500/125 mg po QD x 10 days (Studies 3003 and 3005); penicillin VK 500 mg po TID x 10 days (Study 3004), clarithromycin 250 mg po BID x 10 days (Study 3008), and cefuroxime axetil 250 mg po BID x 10 days (Study 3011).
Adapted from the Applicant's Table v10/0000087t.1# 5 February 2001

Table 23. Alkaline Phosphatase Lab Values During Treatment* in Patients with an Abnormal Alkaline Phosphatase at Baseline – Non-CAP Studies

Analysis Category	Controlled Non-CAP Studies				Uncontrolled Non-CAP Studies	
	Telithromycin †		Comparator††		Telithromycin†	
	n/N	(%)	n/N	(%)	n/N	(%)
Baseline Alk. Phos. Abnormal and Follow-up Alk. Phos. is						
≤ ULN	19/95	(20.0)	8/65	(12.3)	3/11	(27.3)
> ULN & ≤ 2x ULN	73/95	(76.8)	57/65	(87.7)	8/11	(72.7)
> 2x ULN & ≤ 3x ULN	1/95	(1.1)	0/65	(0.0)	0/11	(0.0)
> 3x ULN & ≤ 5x ULN	2/95	(2.1)	0/65	(0.0)	0/11	(0.0)
> 5x ULN & ≤ 8x ULN	0/95	(0.0)	0/65	(0.0)	0/11	(0.0)
> 8x ULN	0/95	(0.0)	0/65	(0.0)	0/11	(0.0)

*During Treatment = from pretherapy/entry through end of treatment + 7 days ULN= upper limit of normal for the analyte being evaluated
† The telithromycin regimens for the Controlled Non-CAP (comparative) studies were telithromycin 800 mg po QD x 5 days (Studies 3003, 3004, 3007, 3008, and 3011) and telithromycin 800 mg po QD x 5 days and telithromycin 800 mg po QD x 10 days (in Study 3005 a 3-arm study). The telithromycin regimen for the uncontrolled Non-CAP study was telithromycin 800 mg po QD x 5 days vs. telithromycin 800 mg po QD x 10 days (Study 3002).
†† Comparators for the controlled Non-CAP studies were: cefuroxime axetil 500 mg po BID x 10 days (Study 3007); Amoxicillin/clavulanic acid 500/125 mg po QD x 10 days (Studies 3003 and 3005); penicillin VK 500 mg po TID x 10 days (Study 3004), clarithromycin 250 mg po BID x 10 days (Study 3008), and cefuroxime axetil 250 mg po BID x 10 days (Study 3011).
Adapted from the Applicant's Table v10/0000087t.1# 5 February 2001

Supplemental Hepatic Laboratory Analyses

Additional "supplemental hepatic laboratory analyses" were also requested that examined abnormalities in ALT, AST, alkaline phosphatase, and/or T. Bili. from baseline to on-therapy, baseline to post-therapy, and baseline to late post-therapy/follow-up in patients from the phase III studies (CAP and Non-CAP studies) (Tables 24-35). (Note: results for the late post-therapy time point for the Non-CAP studies for patients abnormal at baseline are only presented for the sinusitis studies.)

In patients with normal ALT, AST, and T. bilirubin at baseline from the controlled CAP studies, there was a slightly greater proportion of patients with abnormalities in AST or ALT in telithromycin treated patients at on-therapy. This difference between treatment groups in AST or ALT abnormalities was also present at the post-therapy assessment. The proportion of missing data at the late post-therapy assessment was large (approx. 50%). In the subjects for whom data was available at the late post-therapy visit, there was a slightly greater proportion of patients with an abnormal AST or ALT in the comparator treated patients than in the telithromycin treated patients. From the patients in the CAP studies normal at baseline, there were a few telithromycin treated patients with predominantly low level T. Bili. elevations.

Within the smaller population of CAP patients not normal for AST, ALT, and T. Bili at baseline a slightly greater proportion of comparator treated patients had AST and ALT elevations at On-Therapy. At the Post-Therapy and Late Post-Therapy time points there was a slightly greater proportion of comparator treated patients with AST elevations, whereas changes in ALT were similar between treatment groups. Elevations in T. Bili. were similar at On-Therapy, were slightly more common in telithromycin treated patients at Post-Therapy and slightly more common in comparator treated patients at Late Post-Therapy. With regards to combination abnormalities for AST and T. Bili. or ALT and T. Bili., the proportion of telithromycin treated patients experiencing combination abnormalities was either similar or more in the telithromycin treated patients at the time points evaluated.

In patients with normal ALT, AST, and T. bilirubin at baseline from the Non-CAP studies, the proportion of patients with an abnormal ALT was slightly greater in telithromycin treated patients at On-Therapy and slightly greater in comparator treated patients at Post-Therapy and Late Post-Therapy. Changes in ALT were similar between telithromycin and comparator treated patients at On-Therapy and Post-Therapy and slightly more common in comparator treated patients at Late Post-Therapy. T. Bili. elevations were either similar or slightly more common in telithromycin treated patients at the three time points evaluated.

In patients without normal ALT, AST, and T. Bilirubin at baseline, there were no marked differences in changes in AST or ALT between treatment groups at the On-Therapy or Post-Therapy assessments. A greater proportion of telithromycin treated patients experienced T. Bili. elevations than comparator treated patients at the On-Therapy assessment. This difference was also noted for combined ALT and T. Bili. elevations and AST and T. Bili. elevations at the On-Therapy visit. Changes in LFT's were similar

between telithromycin and comparators at the Post-Therapy time point. Analyses for Non-CAP patients from the Late Post-Therapy time point were only available for the subset of patients from the sinusitis studies. In this smaller population with data not available for over half of the patients there were no marked differences in values for LFTs.

> **MO Comment:** The slight excess of abnormalities in AST, ALT, and T. bilirubin noted in telithromycin treated patients occurring while patients were receiving therapy suggests the potential for mild direct injury to the hepatocyte by telithromycin.

In the population of CAP patients and in the patients from the sinusitis studies (a subset of the Non-CAP studies) with a normal alkaline phosphatase value at baseline, there were no marked differences in alkaline phosphatase elevations between treatment groups at on-therapy, post therapy and late post therapy.

Table 24. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and ALT or T. Bilirubin and AST Abnormalities at On-Therapy – CAP Studies – Patients with Normal Values for AST, ALT, and T. Bilirubin at Baseline

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	n	(%)	n	(%)
Total numbers of patients exposed	339		335		562	
Missing ALT at On -Therapy	19		21		36	
Missing AST at On-Therapy	19		21		36	
Missing T. Bilirubin at On-Therapy	23		30		69	
Missing AST or T. Bilirubin at On-Therapy	23		30		69	
Missing ALT or T. Bilirubin at On-Therapy	23		30		69	
Total number of patients with						
ALT ≤ ULN	279	87.2	283	90.1	473	89.9
ALT > ULN and ≤ 2*ULN	35	10.9	28	8.9	45	8.6
ALT > 2*ULN and ≤ 3*ULN	5	1.6	2	0.6	6	1.1
ALT > 3*ULN and ≤ 5*ULN	1	0.3	0	0.0	2	0.4
ALT > 5*ULN and ≤ 8*ULN	0	0.0	1	0.3	0	0.0
ALT > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
AST ≤ ULN	284	88.8	293	93.3	461	87.6
AST > ULN and ≤ 2*ULN	33	10.3	18	5.7	54	10.3
AST > 2*ULN and ≤ 3*ULN	1	0.3	1	0.3	8	1.5
AST > 3*ULN and ≤ 5*ULN	2	0.6	2	0.6	3	0.6
AST > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
AST > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
T. Bili. ≤ ULN	315	99.7	304	99.7	489	99.2
T. Bili. > ULN and ≤ 2*ULN	1	0.3	1	0.3	4	0.8
T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili) > ULN	316	100.0	305	100.0	491	99.6
ALT and T. Bili. > ULN and ≤ 2*ULN	0	0.0	0	0.0	2	0.4
ALT and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (AST and T. Bili.) > ULN	316	100.0	305	100.0	491	99.6
AST and T. Bili. > ULN and ≤ 2*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	1	0.2
AST and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	1	0.2
AST and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-30 v10/0000445t.1st 22 February 2001

Table 25. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and AST or ALT Abnormalities at Post-Therapy – CAP Studies – Patients with Normal Values for AST, ALT, and T. Bilirubin at Baseline

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	n	(%)	n	(%)
Total numbers of patients exposed	339		335		562	
Missing ALT at Post-Therapy	43		42		186	
Missing AST at Post-Therapy	43		42		186	
Missing T. Bilirubin at Post-Therapy	50		49		207	
Missing AST or T. Bilirubin at Post-Therapy	50		49		207	
Missing ALT or T. Bilirubin at Post-Therapy	50		49		207	
Total number of patients with						
ALT ≤ ULN	256	86.5	265	90.4	314	83.5
ALT > ULN and ≤ 2*ULN	36	12.2	27	9.2	51	13.6
ALT > 2*ULN and ≤ 3*ULN	4	1.4	0	0.0	7	1.9
ALT > 3*ULN and ≤ 5*ULN	0	0.0	1	0.3	4	1.1
ALT > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
ALT > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
AST ≤ ULN	275	92.9	287	98.0	335	89.1
AST > ULN and ≤ 2*ULN	18	6.1	6	2.0	38	10.1
AST > 2*ULN and ≤ 3*ULN	2	0.7	0	0.0	2	0.5
AST > 3*ULN and ≤ 5*ULN	1	0.3	0	0.0	0	0.0
AST > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	1	0.3
AST > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
T. Bili. ≤ ULN	286	99.0	284	99.3	352	99.2
T. Bili. > ULN and ≤ 2*ULN	3	1.0	1	0.3	3	0.8
T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	1	0.3	0	0.0
T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) > ULN	287	99.3	286	100	352	99.2
ALT and T. Bili. > ULN and ≤ 2*ULN	2	0.7	0	0.0	2	0.6
ALT and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	1	0.3
ALT and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (AST and T. Bili.) > ULN	289	100.0	286	100	353	99.4
AST and T. Bili. > ULN and ≤ 2*ULN	0	0.0	0	0.0	2	0.6
AST and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-31 v10/0000446t.1st 22 February 2001

Table 26. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and AST or ALT Abnormalities at Late Post-Therapy or Follow-up – CAP Studies – Patients with a Normal Baseline AST, ALT, and T. Bilirubin

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	n	(%)	n	(%)
Total numbers of patients exposed	339		335		562	
Missing ALT at Late Post-Therapy or Follow-up	187		183		137	
Missing AST at Late Post-Therapy or Follow-up	187		183		137	
Missing T. Bilirubin at Late Post-Therapy or Follow-up	188		185		159	
Missing AST or T. Bilirubin at Late Post-Therapy or Follow-up	188		185		159	
Missing ALT or T. Bilirubin at Late Post-Therapy or Follow-up	188		185		159	
Total number of patients with						
ALT ≤ ULN	141	92.8	143	94.1	378	88.9
ALT > ULN and ≤ 2*ULN	8	5.3	7	4.6	42	9.9
ALT > 2*ULN and ≤ 3*ULN	2	1.3	2	1.3	5	1.2
ALT > 3*ULN and ≤ 5*ULN	1	0.7	0	0.0	0	0.0
ALT > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
ALT > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
AST ≤ ULN	144	94.7	142	93.4	393	92.5
AST > ULN and ≤ 2*ULN	7	4.6	9	5.9	32	7.5
AST > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
AST > 3*ULN and ≤ 5*ULN	1	0.7	0	0.0	0	0.0
AST > 5*ULN and ≤ 8*ULN	0	0.0	1	0.7	0	0.0
AST > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
T. Bili. ≤ ULN	150	99.3	150	100	399	99.0
T. Bili. > ULN and ≤ 2*ULN	1	0.7	0	0.0	3	0.7
T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	1	0.2
T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) > ULN	151	100.0	150	100.0	403	100.0
ALT and T. Bili. > ULN and ≤ 2*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (AST and T. Bili.) > ULN	151	100.0	150	100.0	402	99.8
AST and T. Bili. > ULN and ≤ 2*ULN	0	0.0	0	0.0	1	0.2
AST and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-32 v10/0000447t.1[st] 22 February 2001

Table 27. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and AST or ALT Abnormalities at On-Therapy – CAP Studies – Patients with an Abnormal Baseline AST, ALT, or T. Bilirubin

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	n	(%)	n	(%)
Total numbers of patients exposed	155		162		261	
Missing ALT at On -Therapy	5		9		25	
Missing AST at On-Therapy	5		8		24	
Missing T. bilirubin at On-Therapy	6		10		38	
Missing AST or T. bilirubin at On-Therapy	6		11		38	
Missing ALT or T. bilirubin at On-Therapy	6		10		38	
Total number of patients with						
ALT ≤ baseline (BL)	85	56.7	80	52.3	123	52.1
ALT > BL and ≤ BL + Δ	52	34.7	60	39.2	86	36.4
ALT > BL + Δ and ≤ BL + 2Δ	9	6.0	9	5.9	19	8.1
ALT > BL + 2Δ and ≤ BL + 4Δ	3	2.0	2	1.3	7	3.0
ALT > BL + 4Δ and ≤ BL + 7Δ	1	0.7	1	0.7	0	0.0
ALT > BL + 7Δ	0	0.0	1	0.7	1	0.4
Total number of patients with						
AST ≤ baseline (BL)	105	70.0	99	64.3	146	61.6
AST > BL and ≤ BL + Δ	39	26.0	50	32.5	76	32.1
AST > BL + Δ and ≤ BL + 2Δ	3	2.0	3	1.9	11	4.6
AST > BL + 2Δ and ≤ BL + 4Δ	1	0.7	1	0.6	3	1.3
AST > BL + 4Δ and ≤ BL + 7Δ	2	1.3	0	0.0	1	0.4
AST > BL + 7Δ	0	0.0	1	0.6	0	0.0
Total number of patients with						
T. Bili. ≤ baseline (BL)	121	81.2	126	82.9	182	81.6
T. Bili. > BL and ≤ BL + Δ	28	18.8	26	17.1	40	17.9
T. Bili. > BL + Δ and ≤ BL + 2Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	1	0.4
T. Bili. > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) ≥ baseline (BL)	139	93.3	143	94.7	202	90.6
ALT and T. Bili.						
> BL and ≤ BL + Δ	8	5.4	5	3.3	13	5.8
> BL + Δ and ≤ BL + 2Δ	2	1.3	1	0.7	4	1.8
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	4	1.8
> BL + 4Δ and ≤ BL + 7Δ	0	0.0	1	0.7	0	0.0
> BL + 7Δ	0	0.0	1	0.7	0	0.0
Total number of patients with						
Without (AST and T. Bili.) ≥ baseline (BL)	139	93.3	146	96.1	206	92.4
AST and T. Bili.						
> BL and ≤ BL + Δ	9	6.0	3	2.0	13	5.8
> BL + Δ and ≤ BL + 2Δ	0	0.0	2	1.3	3	1.3
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	1	0.4
> BL + 4Δ and ≤ BL + 7Δ	1	0.7	0	0.0	0	0.0
> BL + 7Δ	0	0.0	1	0.7	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-33 v10/0000454t.1[st] 22 February 2001

Table 28. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and AST or ALT Abnormalities at Post-Therapy – CAP Studies – Patients with an Abnormal Baseline AST, ALT, or T. Bilirubin

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	n	(%)	n	(%)
Total numbers of patients exposed	155		162		261	
Missing ALT at Post -Therapy	17		30		79	
Missing AST at Post -Therapy	17		29		79	
Missing T. bilirubin at Post -Therapy	18		30		89	
Missing AST or T. bilirubin at Post -Therapy	18		31		89	
Missing ALT or T. bilirubin at Post -Therapy	18		30		89	
Total number of patients with						
ALT ≤ baseline (BL)	86	62.3	82	62.1	95	52.2
ALT > BL and ≤ BL + Δ	46	33.3	43	32.6	70	38.5
ALT > BL + Δ and ≤ BL + 2Δ	4	2.9	6	4.5	12	6.6
ALT > BL + 2Δ and ≤ BL + 4Δ	1	0.7	1	0.8	4	2.2
ALT > BL + 4Δ and ≤ BL + 7Δ	1	0.7	0	0.0	0	0.0
ALT > BL + 7Δ	0	0.0	0	0.0	1	0.5
Total number of patients with						
AST ≤ baseline (BL)	99	71.7	100	75.2	125	68.7
AST > BL and ≤ BL + Δ	37	26.8	32	24.1	51	28.0
AST > BL + Δ and ≤ BL + 2Δ	1	0.7	1	0.8	2	1.1
AST > BL + 2Δ and ≤ BL + 4Δ	1	0.7	0	0.0	4	2.2
AST > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
AST > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
T. Bili. ≤ baseline (BL)	107	78.1	108	81.8	140	81.4
T. Bili. > BL and ≤ BL + Δ	30	21.9	24	18.2	31	18.0
T. Bili. > BL + Δ and ≤ BL + 2Δ	0	0.0	0	0.0	1	0.6
T. Bili. > BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) ≥ baseline (BL)	124	90.5	122	93.1	156	90.7
ALT and T. Bili.						
> BL and ≤ BL + Δ	11	8.0	8	6.1	13	7.6
> BL + Δ and ≤ BL + 2Δ	2	1.5	1	0.8	2	1.2
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	0	0.0
> BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
> BL + 7Δ	0	0.0	0	0.0	1	0.6
Total number of patients with						
Without (AST and T. Bili.) ≥ baseline (BL)	126	92.0	126	95.5	159	92.4
AST and T. Bili.						
> BL and ≤ BL + Δ	11	8.0	6	4.5	11	6.4
> BL + Δ and ≤ BL + 2Δ	0	0.0	0	0.0	1	0.6
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	1	0.6
> BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
> BL + 7Δ	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-34 v10/0000455t.1[a] 22 February 2001

Table 29. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and AST or ALT Abnormalities at Late Post-Therapy or Follow-up – CAP Studies – Patients with an Abnormal Baseline AST, ALT, or T. Bilirubin

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	n	(%)	n	(%)
Total numbers of patients exposed	155		162		261	
Missing ALT at Late Post-Therapy or Follow-up	83		76		66	
Missing AST at Late Post-Therapy or Follow-up	83		76		66	
Missing T. bilirubin at Late Post-Therapy or Follow-up	85		77		81	
Missing AST or T. bilirubin at Late Post-Therapy or Follow-up	85		77		81	
Missing ALT or T. bilirubin at Late Post-Therapy or Follow-up	85		77		81	
Total number of patients with						
ALT ≤ baseline (BL)	51	70.8	63	73.3	124	63.6
ALT > BL and ≤ BL + Δ	19	26.4	21	24.4	63	32.3
ALT > BL + Δ and ≤ BL + 2Δ	2	2.8	2	2.3	3	1.5
ALT > BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	2	1.0
ALT > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	2	1.0
ALT > BL + 7Δ	0	0.0	0	0.0	1	0.5
Total number of patients with						
AST ≤ baseline (BL)	58	80.6	65	75.6	140	71.8
AST > BL and ≤ BL + Δ	14	19.4	20	23.3	48	24.6
AST > BL + Δ and ≤ BL + 2Δ	0	0.0	1	1.2	3	1.5
AST > BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	2	1.0
AST > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	2	1.0
AST > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
T. Bili. ≤ baseline (BL)	51	72.9	68	80.0	139	77.2
T. Bili. > BL and ≤ BL + Δ	19	27.1	17	20.0	40	22.2
T. Bili. > BL + Δ and ≤ BL + 2Δ	0	0.0	0	0.0	1	0.6
T. Bili. > BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) ≥ baseline (BL)	65	92.9	83	97.6	162	90.0
ALT and T. Bili.						
> BL and ≤ BL + Δ	4	5.7	1	1.2	15	8.3
> BL + Δ and ≤ BL + 2Δ	1	1.4	1	1.2	0	0.0
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	1	0.6
> BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	1	0.6
> BL + 7Δ	0	0.0	0	0.0	1	0.6
Total number of patients with						
Without (AST and T. Bili.) ≥ baseline (BL)	67	95.7	82	96.5	163	90.6
AST and T. Bili.						
> BL and ≤ BL + Δ	3	4.3	2	2.4	15	8.3
> BL + Δ and ≤ BL + 2Δ	0	0.0	1	1.2	0	0.0
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	1	0.6
> BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	1	0.6
> BL + 7Δ	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-35 v10/0000456t.1[a] 22 February 2001

Table 30. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and ALT or T. Bilirubin and AST Abnormalities at On-Therapy – Non-CAP Studies – Patients with Normal Values for AST, ALT, and T. Bilirubin at Baseline

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	n	(%)	n	(%)
Total numbers of patients exposed	1194		889		263	
Missing ALT at On -Therapy	62		50		26	
Missing AST at On-Therapy	61		49		25	
Missing T. Bilirubin at On-Therapy	81		64		25	
Missing AST or T. Bilirubin at On-Therapy	82		65		26	
Missing ALT or T. Bilirubin at On-Therapy	81		64		25	
Total number of patients with						
ALT ≤ ULN	1060	93.6	799	95.2	228	96.2
ALT > ULN and ≤ 2*ULN	68	6.0	36	4.3	9	3.8
ALT > 2*ULN and ≤ 3*ULN	3	0.3	4	0.5	0	0.0
ALT > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
ALT > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
ALT > 8*ULN	1	0.1	0	0.0	0	0.0
Total number of patients with						
AST ≤ ULN	1089	96.1	811	96.5	232	97.5
AST > ULN and ≤ 2*ULN	42	3.7	28	3.3	6	2.5
AST > 2*ULN and ≤ 3*ULN	1	0.1	1	0.1	0	0.0
AST > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
AST > 5*ULN and ≤ 8*ULN	1	0.1	0	0.0	0	0.0
AST > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
T. Bili. ≤ ULN	1106	99.4	822	99.6	233	97.9
T. Bili. > ULN and ≤ 2*ULN	7	0.6	3	0.4	5	2.1
T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) > ULN	1111	99.9	824	100.0	237	100.0
ALT and T. Bili. > ULN and ≤ 2*ULN	1	0.1	0	0.0	0	0.0
ALT and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (AST and T. Bili.) > ULN	1113	100.0	825	100.0	238	100.0
AST and T. Bili. > ULN and ≤ 2*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-42 v10/0000448t.1[s] 22 February 2001

Table 31. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and AST or ALT Abnormalities at Post-Therapy – Non-CAP Studies – Patients with Normal Values for AST, ALT, and T. Bilirubin at Baseline

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	n	(%)	n	(%)
Total numbers of patients exposed	1194		889		263	
Missing ALT at Post -Therapy	258		151		23	
Missing AST at Post-Therapy	259		151		23	
Missing T. Bilirubin at Post-Therapy	274		160		23	
Missing AST or T. Bilirubin at Post-Therapy	274		160		23	
Missing ALT or T. Bilirubin at Post-Therapy	275		160		23	
Total number of patients with						
ALT ≤ ULN	878	93.8	674	91.3	221	92.1
ALT > ULN and ≤ 2*ULN	56	6.0	61	8.3	19	7.9
ALT > 2*ULN and ≤ 3*ULN	1	0.1	1	0.1	0	0.0
ALT > 3*ULN and ≤ 5*ULN	1	0.1	2	0.3	0	0.0
ALT > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
ALT > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
AST ≤ ULN	913	97.6	717	97.2	231	96.3
AST > ULN and ≤ 2*ULN	19	2.0	19	2.6	8	3.3
AST > 2*ULN and ≤ 3*ULN	1	0.1	0	0.0	0	0.0
AST > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	1	0.4
AST > 5*ULN and ≤ 8*ULN	2	0.2	1	0.1	0	0.0
AST > 8*ULN	0	0.0	1	0.1	0	0.0
Total number of patients with						
T. Bili. ≤ ULN	907	98.6	725	99.5	234	97.5
T. Bili. > ULN and ≤ 2*ULN	13	1.4	4	0.5	6	2.5
T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) > ULN	920	100.0	729	100.0	238	99.2
ALT and T. Bili. > ULN and ≤ 2*ULN	0	0.0	0	0.0	2	0.8
ALT and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (AST and T. Bili.) > ULN	919	100.0	729	100.0	239	99.6
AST and T. Bili. > ULN and ≤ 2*ULN	0	0.0	0	0.0	1	0.4
AST and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-43 v10/0000449t.1st 22 February 2001

Table 32. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and AST or ALT Abnormalities at Late Post-Therapy or Follow-up – CAP Studies – Patients with a Normal Baseline AST, ALT, and T. Bilirubin

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	n	(%)	n	(%)
Total numbers of patients exposed	1194		889		263	
Missing ALT at Late Post-Therapy or Follow-up	792		575		212	
Missing AST at Late Post-Therapy or Follow-up	791		575		212	
Missing T. Bilirubin at Late Post-Therapy or Follow-up	802		576		212	
Missing AST or T. Bilirubin at Late Post-Therapy or Follow-up	802		576		212	
Missing ALT or T. Bilirubin at Late Post-Therapy or Follow-up	802		576		212	
Total number of patients with						
ALT ≤ ULN	382	95.0	293	93.3	45	88.2
ALT > ULN and ≤ 2*ULN	17	4.2	19	6.1	5	9.8
ALT > 2*ULN and ≤ 3*ULN	2	0.5	0	0.0	0	0.0
ALT > 3*ULN and ≤ 5*ULN	1	0.2	2	0.6	0	0.0
ALT > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	1	2.0
ALT > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
AST ≤ ULN	397	98.5	299	95.2	48	94.1
AST > ULN and ≤ 2*ULN	3	0.7	15	4.8	2	3.9
AST > 2*ULN and ≤ 3*ULN	3	0.7	0	0.0	0	0.0
AST > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	1	2.0
AST > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
AST > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
T. Bili. ≤ ULN	386	98.5	311	99.4	50	98.0
T. Bili. > ULN and ≤ 2*ULN	6	1.5	2	0.6	1	2.0
T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) > ULN	392	100.0	313	100.0	51	100.0
ALT and T. Bili. > ULN and ≤ 2*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
ALT and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (AST and T. Bili.) > ULN	392	100.0	313	100.0	51	100.0
AST and T. Bili. > ULN and ≤ 2*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 2*ULN and ≤ 3*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 3*ULN and ≤ 5*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 5*ULN and ≤ 8*ULN	0	0.0	0	0.0	0	0.0
AST and T. Bili. > 8*ULN	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-44 v10/0000450t.1st 22 February 2001

Table 33. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and AST or ALT Abnormalities at On-Therapy – Non-CAP Studies – Patients with an Abnormal Baseline AST, ALT, or T. Bilirubin

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	N	(%)	n	(%)	n	(%)
Total numbers of patients exposed	246		186		42	
Missing ALT at On -Therapy	15		12		7	
Missing AST at On-Therapy	15		12		7	
Missing T. Bilirubin at On-Therapy	23		18		8	
Missing AST or T. Bilirubin at On-Therapy	23		18		8	
Missing ALT or T. Bilirubin at On-Therapy	23		18		8	
Total number of patients with						
ALT ≤ baseline (BL)	121	52.4	92	52.9	22	62.9
ALT > BL and ≤ BL + Δ	101	43.7	72	41.4	13	37.1
ALT > BL + Δ and ≤ BL + 2Δ	8	3.5	8	4.6	0	0.0
ALT > BL + 2Δ and ≤ BL + 4Δ	0	0.0	1	0.6	0	0.0
ALT > BL + 4Δ and ≤ BL + 7Δ	1	0.4	1	0.6	0	0.0
ALT > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
AST ≤ baseline (BL)	132	57.1	101	58.0	24	68.6
AST > BL and ≤ BL + Δ	94	40.7	71	40.8	11	31.4
AST > BL + Δ and ≤ BL + 2Δ	3	1.3	1	0.6	0	0.0
AST > BL + 2Δ and ≤ BL + 4Δ	2	0.9	1	0.6	0	0.0
AST > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
AST > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
T. Bili. ≤ baseline (BL)	132	59.2	125	74.4	22	64.7
T. Bili. > BL and ≤ BL + Δ	91	40.8	43	25.6	12	35.3
T. Bili. > BL + Δ and ≤ BL + 2Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) ≥ baseline (BL)	179	80.3	148	88.1	27	79.4
ALT and T. Bili.						
> BL and ≤ BL + Δ	38	17.0	18	10.7	7	20.6
> BL + Δ and ≤ BL + 2Δ	5	2.2	1	0.6	0	0.0
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	1	0.6	0	0.0
> BL + 4Δ and ≤ BL + 7Δ	1	0.4	0	0.0	0	0.0
> BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (AST and T. Bili) ≥ baseline (BL)	184	82.5	150	89.3	29	85.3
AST and T. Bili.						
> BL and ≤ BL + Δ	35	15.7	18	10.7	5	14.7
> BL + Δ and ≤ BL + 2Δ	2	0.9	0	0.0	0	0.0
> BL + 2Δ and ≤ BL + 4Δ	2	0.9	0	0.0	0	0.0
> BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
> BL + 7Δ	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-45 v10/0000457t.1[st] 22 February 2001

Table 34. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and AST or ALT Abnormalities at Post-Therapy – Non-CAP Studies – Patients with an Abnormal Baseline AST, ALT, or T. Bilirubin

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	N	(%)	n	(%)
Total numbers of patients exposed	246		186		42	
Missing ALT at Post-Therapy	67		43		6	
Missing AST at Post-Therapy	67		43		6	
Missing T. Bilirubin at Post-Therapy	70		44		7	
Missing AST or T. Bilirubin at Post-Therapy	70		44		7	
Missing ALT or T. Bilirubin at Post-Therapy	70		44		7	
Total number of patients with						
ALT ≤ baseline (BL)	108	60.3	81	56.6	28	77.8
ALT > BL and ≤ BL + Δ	65	36.3	57	39.9	6	16.7
ALT > BL + Δ and ≤ BL + 2Δ	5	2.8	3	2.1	2	5.6
ALT > BL + 2Δ and ≤ BL + 4Δ	1	0.6	2	1.4	0	0.0
ALT > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
ALT > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
AST ≤ baseline (BL)	117	65.4	90	62.9	26	72.2
AST > BL and ≤ BL + Δ	59	33.0	50	35.0	9	25.0
AST > BL + Δ and ≤ BL + 2Δ	3	1.7	1	0.7	1	2.8
AST > BL + 2Δ and ≤ BL + 4Δ	0	0.0	2	1.4	0	0.0
AST > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
AST > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
T. Bili. ≤ baseline (BL)	119	67.6	99	69.7	18	51.4
T. Bili. > BL and ≤ BL + Δ	57	32.4	43	30.3	17	48.6
T. Bili. > BL + Δ and ≤ BL + 2Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) ≥ baseline (BL)	157	89.2	127	89.4	31	88.6
ALT and T. Bili.						
> BL and ≤ BL + Δ	18	10.2	14	9.9	3	8.6
> BL + Δ and ≤ BL + 2Δ	1	0.6	1	0.7	1	2.9
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	0	0.0
> BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
> BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (AST and T. Bili.) ≥ baseline (BL)	159	90.3	129	90.8	30	85.7
AST and T. Bili.						
> BL and ≤ BL + Δ	15	8.5	12	8.5	4	11.4
> BL + Δ and ≤ BL + 2Δ	2	1.1	0	0.0	1	2.9
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	1	0.7	0	0.0
> BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
> BL + 7Δ	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-46 v10/0000458t.1[a] 22 February 2001

Table 35. Laboratory Values for ALT or AST and T. Bilirubin and Concomitant T. Bilirubin and AST or ALT Abnormalities at Late Post-Therapy or Follow-up – Sinusitis Studies – Patients with an Abnormal Baseline AST, ALT, or T. Bilirubin

Analysis Category	Controlled CAP Studies				Uncontrolled CAP Studies	
	Telithromycin		Comparator		Telithromycin	
	n	(%)	N	(%)	n	(%)
Total numbers of patients exposed	95		70		53	
Missing ALT at Late Post-Therapy or Follow-up	52		46		37	
Missing AST at Late Post-Therapy or Follow-up	52		46		37	
Missing T. Bilirubin at Late Post-Therapy or Follow-up	56		46		38	
Missing AST or T. Bilirubin at Late Post-Therapy or Follow-up	56		46		38	
Missing ALT or T. Bilirubin at Late Post-Therapy or Follow-up	56		46		38	
Total number of patients with						
ALT ≤ baseline (BL)	28	65.1	16	66.7	12	75.0
ALT > BL and ≤ BL + Δ	14	32.6	8	33.3	3	18.8
ALT > BL + Δ and ≤ BL + 2Δ	1	2.3	0	0.0	1	6.3
ALT > BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	0	0.0
ALT > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
ALT > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
AST ≤ baseline (BL)	25	58.1	15	62.5	8	50.0
AST > BL and ≤ BL + Δ	18	41.9	8	33.3	7	43.8
AST > BL + Δ and ≤ BL + 2Δ	0	0.0	0	0.0	0	0.0
AST > BL + 2Δ and ≤ BL + 4Δ	0	0.0	1	4.2	1	6.3
AST > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
AST > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
T. Bili. ≤ baseline (BL)	24	61.5	14	58.3	6	40.0
T. Bili. > BL and ≤ BL + Δ	15	38.5	10	41.7	9	60.0
T. Bili. > BL + Δ and ≤ BL + 2Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
T. Bili. > BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (ALT and T. Bili.) ≥ baseline (BL)	35	89.7	21	87.5	13	86.7
ALT and T. Bili.						
> BL and ≤ BL + Δ	4	10.3	3	12.5	2	13.3
> BL + Δ and ≤ BL + 2Δ	0	0.0	0	0.0	0	0.0
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	0	0.0	0	0.0
> BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
> BL + 7Δ	0	0.0	0	0.0	0	0.0
Total number of patients with						
Without (AST and T. Bili.) ≥ baseline (BL)	30	76.9	19	79.2	11	73.3
AST and T. Bili.						
> BL and ≤ BL + Δ	9	23.1	4	16.7	4	26.7
> BL + Δ and ≤ BL + 2Δ	0	0.0	0	0.0	0	0.0
> BL + 2Δ and ≤ BL + 4Δ	0	0.0	1	4.2	0	0.0
> BL + 4Δ and ≤ BL + 7Δ	0	0.0	0	0.0	0	0.0
> BL + 7Δ	0	0.0	0	0.0	0	0.0

Note: ULN = upper limit of normal for the analyte being evaluated The percentages calculated exclude the patients with missing values
For combinations of abnormal analytes the most abnormal value is taken into account
Adapted from the Applicant's Table SS-55 v10/0000705t.1[st] 22 February 2001

The supplemental hepatic analyses also queried the laboratory data for the occurrence of concomitant increases in T. bilirubin and ALT; T. bilirubin and AST; or T. Bilirubin and AST and ALT in patients who had a normal ALT, AST, and T. bilirubin at baseline. In the controlled phase III studies in the original NDA there were 3 telithromycin treated subjects [3/1349 (0.2%)] with elevations of ALT and T. bilirubin occurring on the same day and zero in the comparator arms [0/1139 (0.0%)] (Table 36). From the uncontrolled studies in the original NDA population and study 3009OL, there were several additional telithromycin treated patients with low level elevations involving either or both transaminases and T. Bilirubin. (Table 36).

Table 36. Concomitant ALT and T. Bilirubin or AST and T. Bilirubin or ALT and AST and T. Bilirubin Elevations During Treatment in Patients with Normal AST, ALT, and T. Bilirubin at Baseline – Patients in Original NDA and Study 3009OL

Analysis	Controlled Phase III Studies				Uncontrolled Phase III Studies	
	Telithromycin		Comparator		Telithromycin	
	n/N	(%)	n/N	(%)	n/N	(%)
Total number of patients with						
ALT and T. bilirubin > ULN & ≤ 2x ULN	3/1349	(0.2)	0/1139	(0.0)	6/538	(1.1)
ALT and T. bilirubin > 2x ULN & ≤ 3x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and T. bilirubin > 3x ULN & ≤ 5x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and T. bilirubin > 5x ULN & ≤ 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and T. bilirubin > 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
Total number of patients with						
AST and T. bilirubin > ULN & ≤ 2x ULN	0/1349	(0.0)	0/1139	(0.0)	4/538	(0.7)
AST and T. bilirubin > 2x ULN & ≤ 3x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
AST and T. bilirubin > 3x ULN & ≤ 5x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
AST and T. bilirubin > 5x ULN & ≤ 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
AST and T. bilirubin > 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
Total number of patients with						
ALT and AST and T. bilirubin > ULN & ≤ 2x ULN	0/1349	(0.0)	0/1139	(0.0)	4/538	(0.7)
ALT and AST and T. bilirubin > 2x ULN & ≤ 3x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and AST and T. bilirubin > 3x ULN & ≤ 5x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and AST and T. bilirubin > 5x ULN & ≤ 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)
ALT and AST and T. bilirubin > 10x ULN	0/1349	(0.0)	0/1139	(0.0)	0/538	(0.0)

Note: ULN=upper limit of normal for the analyte being evaluated.
Adapted from Applicant's Tables x10/0000202t.1[st] 20 November 2000 and x10/0000312t.1[st] 20 November 2000

Concomitant Transaminase Elevations >3x ULN and T. Bilirubin elevations >1.5x ULN

There were no telithromycin treated patients with normal LFTs at baseline that precisely met the criteria of transaminase elevations ≥3x ULN and T. Bilirubin elevations ≥1.5x ULN. There were two telithromycin treated patients normal at baseline who were close and one notable patient with an abnormal ALT at baseline that achieved an ALT elevation in excess of 3x ULN and T. Bilirubin >1.5x ULN. (This is the same patient whose liver biopsy results were discussed in the serious adverse event section.)

The two patients that were close to the aforementioned levels for transaminase and T. Bilirubin elevations had lab values as follows. Patient 367/102 from Study 3009OL had an AST 2.8x ULN and a T. Bilirubin elevation of 1.48x ULN. This patient also had a notable increase in alkaline phosphatase of 3.7x ULN. The other patient was patient 473/009 from Study 3010. He achieved a maximum AST level of 3.1x ULN and a T. Bili. level of 1.47x ULN. This patient expired on Day 4 with a primary cause of death of "Acute Aspiration–Fatal." On autopsy he was noted to have very mild fatty liver with passive congestion.

There was another noteworthy patient, patient 502/1069 from Study 3000. He had a slightly elevated ALT at baseline of 81 (ULN<49). He achieved an ALT level of 19x ULN and a T. Bili. elevation of 1.55x ULN. This case is discussed in detail in the serious adverse events section of this review.

PCAs LPCAs and CNALVs for Liver-Related Laboratory Values

The Applicant tabulated lab values that were abnormal by a pre-defined amount (pre-defined change abnormal (PCAs)), lab values that were abnormal by a pre-defined amount at the subjects last determination (last evaluation pre-defined change abnormal (LPCAs)), and lab values that were either PCAs or considered medically important by the Sponsor according to predefined criteria (clinically noteworthy abnormal laboratory values (CNALVs)) (Table 37).

Although the number of events were small, there was a slightly greater proportion of patients with PCAs for AST and ALT for telithromycin than comparator in the controlled CAP studies. Again, although the numbers are small, there is a slightly greater proportion of patients with alkaline phosphatase and total bilirubin PCAs among the comparator-treated patients in the controlled CAP studies. The PCAs for the Non-CAP studies are similar between the telithromycin treated groups (considered together) compared to comparator. The smaller number of patients exposed to 10 days of telithromycin do not appear to be experiencing PCAs more frequently than the 5-day telithromycin treated group. However, the number of patients in the 10-day treatment group is small. The result for analyses for CNALVs by treatment group are similar except for the CNALVs for alkaline phosphatase which were greater for comparator in the controlled CAP studies and the CNALVs for ALT which were greater for telithromycin in the non-CAP controlled studies.

Table 37. PCA, LPCA, and CNALV Laboratory Value Abnormalities

Analyte/ PC Amount Direction	PCA/ LPCA/ CNALV	Number n/N (%) of Subjects										
		CAP Controlled Studies					Non-CAP Controlled Studies					
		Telithromycin 7-10d		Comparator 7-10d			Telithromycin 5d		Telithromycin 10d*		Comparator 10d	
		n/N	(%)	n/N	(%)		n/N	(%)	n/N	(%)	n/N	(%)
SGPT/ALT	PCA	10/496	(2.0)	8/484	(1.7)		8/1190	(0.7)	0/243	(0.0)	7/1066	(0.7)
Increase	LPCA (Day 5)	-	-	-	-		5/1155	(0.4)	0/242	(0.0)	5/1065	(0.5)
200% of NR	LPCA (Day 10)	5/496	(1.0)	5/484	(1.0)		6/1190	(0.5)	0/243	(0.0)	5/1066	(0.5)
U/L	CNALV	16/527	(3.0)	17/532	(3.2)		13/1256	(1.0)	4/254	(1.6)	14/1130	(1.2)
SGOT/AST	PCA	8/496	(1.6)	5/483	(1.0)		6/1193	(0.5)	0/243	(0.0)	5/1066	(0.5)
Increase	LPCA (Day 5)	-	-	-	-		3/1158	(0.3)	0/242	(0.0)	3/1065	(0.3)
200% of NR	LPCA (Day 10)	5/496	(1.0)	2/483	(0.4)		5/1193	(0.4)	0/243	(0.0)	5/1066	(0.5)
U/L	CNALV	12/527	(2.3)	10/532	(1.9)		8/1256	(0.6)	1/254	(0.4)	10/1130	(0.9)
Total Bilirubin	PCA	0/484	(0.0)	2/474	(0.4)		1/1146	(0.1)	0/239	(0.0)	1/1038	(0.1)
Increase	LPCA (Day 5)	-	-	-	-		0/1108	(0.0)	0/238	(0.0)	1/1038	(0.1)
50% of NR	LPCA (Day 10)	0/484	(0.0)	2/474	(0.4)		1/1146	(0.1)	0/239	(0.0)	1/1038	(0.1)
µmol/L	CNALV	0/527	(0.0)	2/530	(0.4)		2/1248	(0.2)	0/254	(0.0)	1/1125	(0.1)
Alkaline Phos.	PCA	8/498	(1.6)	14/494	(2.8)		3/1212	(0.2)	0/247	(0.0)	2/1075	(0.2)
Increase	LPCA (Day 5)	-	-	-	-		1/1180	(0.1)	0/245	(0.0)	2/1074	(0.2)
50% of NR	LPCA (Day 10)	4/498	(0.8)	8/494	(1.6)		3/1212	(0.2)	0/247	(0.0)	2/1075	(0.2)
U/L	CNALV	8/527	(1.5)	14/532	(2.6)		3/1255	(0.2)	0/254	(0.0)	2/1130	(0.2)
Eosinophils (Abs.)	PCA	7/478	(1.5)	6/469	(1.3)		5/1149	(0.4)	0/240	(0.0)	12/1037	(1.2)
Increase	LPCA (Day 5)	-	-	-	-		3/1091	(0.3)	0/239	(0.0)	10/1035	(1.0)
20 – G/L[% of BL]	LPCA (Day 10)	4/478	(0.8)	5/469	(1.1)		5/1149	(0.4)	0/240	(0.0)	10/1037	(1.0)
G/L	CNALV	10/527	(1.9)	8/532	(1.5)		9/1253	(0.7)	1/254	(0.4)	15/1130	(1.3)

* Data in this column from sinusitis study HMR 3647A/3005 only.
Note PCA=predefined change abnormal; LPCA=predefined change abnormal at last evaluation; CNALV=clinically noteworthy abnormal laboratory value
Controlled CAP studies are HMR 3647A/3006, HMR3647A/3009, and HMR 3647A/3001
Controlled Non-CAP studies are HMR 3647A/3007, HMR 3647A/3003, HMR 3647A/3005, HMR 3647A/3008, HMR 3647A/3004, HMR3647/3011
Adapted from Applicant's Table SS-129 from 1:v117:p122-3 v10/0000015t.1[st] 6 February 2001

Summary of Hepatic Findings

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

In phase III studies, the proportion of patients experiencing hepatic adverse events or treatment discontinuation because of a hepatic adverse event were similar between the Ketek and comparator treatment groups. In the comparative studies there were 2 serious hepatic AEs in the Ketek treated patients and one serious hepatic AE in comparator treated patients. There was one additional serious hepatic AE from the noncomparative Ketek studies. One of these serious adverse events in the Ketek treated group was a patient with a liver biopsy showing centrilobular necrosis and eosinophilic infiltration, changes strongly suggestive of a hypersensitivity type drug-related liver injury (this patients baseline labs included an ALT of 81 U/L (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.[15,16,17] The pathologic changes for some of the cases of trovafloxacin-associated hepatitis were described as centrilobular necrosis and eosinophilic infiltration on liver biopsy.[18,19]) Several months later this patient went on to have an episode of elevations in his ALT and AST noted at a "routine check-up" and a second liver biopsy was performed showing changes consistent with chronic hepatitis, probably autoimmune.

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

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[15] Steigbigel NH. Macrolides and Clindamycin. In Principles and Practices of Infectious Diseases, 5th Ed. Mandell GL, Bennett JE, and Dolin R. Churchill Livingstone. Philadelphia. 2000. p. 366-382

[16] Pessayre D, Larrey D. Acute and chronic drug induced hepatitis. Bailliere's Clinical Gastroenterology. 1988:(2):385-422.

[17] Diehl AM, et al. Cholestatic hepatitis from erythromycin ethylsuccinate: report of two cases. Am J Med. 1984:(76); 931-4.

[18] Chen HJL, Bloch KJ, Maclean JA. Acute eosinophilic hepatitis from trovafloxacin. NEJM 2000, 342 (5):359.

[19] Lucena MI, Andrade, RJ, Rodrigo L, Salmeron J, et. al. Trovafloxacin-induced acute hepatitis. Clin Infect Dis. 2000. 30(2):400-1.

Medical Officer's Final Comments and Recommendations

The findings from the preclinical studies and the data from human studies support the capacity of telithromycin to induce injury to the hepatocyte. These findings combined with the adverse event of the patient developing hepatitis with pathologic changes consistent with a drug-induced immunoallergic event is concerning. Within a safety database of 3265 telithromycin treated patients, one case of drug-induced hepatitis with a biopsy showing centrilobular necrosis and eosinophilic infiltration is remarkable. The nature of this injury, an immunoallergic injury resulting in centrilobular necrosis, is also of concern.

The nature of this serious hepatic event is concerning because of the pathologic changes that were observed and also because the event occurred at a time subsequent to completion of therapy. On the risk side, it isn't clear from the available information that a particular "at risk" group can be clearly identified. In addition, the event occurred at a time subsequent to the completion of drug therapy, leaving no opportunity to cease drug therapy as a means of preventing or modifying the course of events. An additional practical concern is that if a serious hepatic event occurs only after drug therapy has been completed, in certain circumstances, the potential connection to preceding drug therapy that may be causally related to the event may not be recognized.

Because of the potential serious nature of drug-induced hepatic injury and the liver-related safety profile of telithromycin, the risks of telithromycin should be carefully weighed against the benefits. (The reader is referred to the reviews for each of the indications for discussions of efficacy). In addition to the hepatic profile of telithromycin, other risks such as the potential effects of telithromycin on the QT interval, the potential for drug interactions, and pharmacologic variability in the setting of these effects should also be considered in weighing the risks and benefits (these risks are discussed in Dr. Ross's Medical Officer's Safety Review). Taking the risks and benefits of telithromycin based upon the available data within the NDA into consideration, a satisfactory risk-benefit ratio for telithromycin is not supported. It is possible that with further information defining the risks of telithromycin and/or supporting additional benefits, that a satisfactory risk-benefit ratio could be achieved for populations in which telithromycin provides specific benefits.

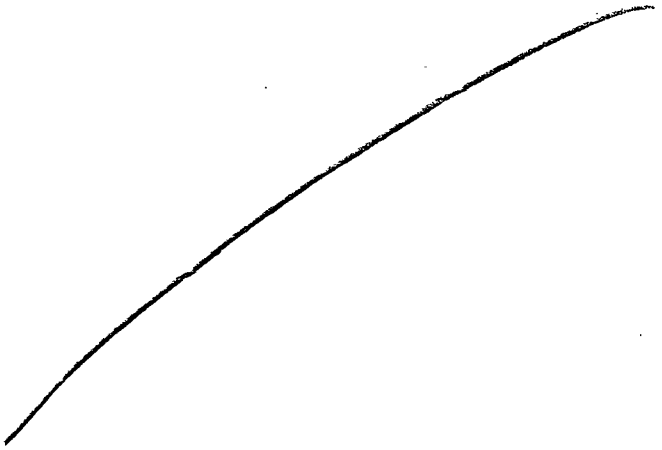
Recommendations for Additional and/or Phase IV Studies

Studying infrequent serious adverse events such as serious hepatic toxicity poses significant challenges. One could consider a very large trial to attempt to further characterize the rate and character of hepatic adverse events that occur in the setting of Ketek therapy. Either alternatively or additionally, if data can be presented supporting additional benefit for Ketek, it may be possible to achieve a satisfactory risk-benefit profile for Ketek. In any future studies additional information on the hepatic effects of telithromycin should be obtained. Any additional data to identify at risk groups or means of mitigating the risk of serious hepatic AEs could also help support an acceptable risk-benefit ratio. In future studies where monitoring for hepatic adverse events is considered, the possible delay in time between the completion of therapy and the occurrence of the hepatic adverse event should be considered in the design of the study.

Medical Officer's Recommended Changes to the Applicant's Proposed Labeling for Hepatic-Related Safety for Ketek

The Applicant's hepatic-related safety labeling is provided below:

ADVERSE REACTIONS



MO Comment/Recommendation: The data from the NDA regarding hepatic effects support that Ketek may be associated with serious hepatic adverse reactions. Therefore it would be appropriate to add language to the WARNINGS section describing the potential serious hepatic effects. The MO's proposed addition to the WARNINGS section is as follows: