

APPENDIX B: PHASE III SAFETY DATA

Deaths in controlled studies

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Narratives: Deaths in controlled Phase III studies

Narratives: Deaths in open-label Phase III studies

Criteria of clinically noteworthy abnormal laboratory values (CNALV)

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DEATHS IN CONTROLLED STUDIES

*Subject Age	Study Drug	Causal Event	Day of Event	Day of Death	Medical History
3001/1002/027 71/F	TEL	Multiorgan Failure	3	4	COPD, CAD, Dorsal Scoliosis
3001/1301/004 80/M	TEL	Cardiac Failure	10	10	CAD, Atrial Fibrillation, Cerebrovascular disease, Diabetes, Liver disease
3001/0111/004 52/M	AMOX	Severe bronchospasm	34	34	Asthma
3004/1306/008 55/F	PEN-V	Acute lymphoid leukemia	2	47	Mild Hearing Loss, Splenectomy, Elevated Leukocytes Pretherapy
3006/0060/002 70/F	CLA	Bronchial neoplasm	21	155	Schizophrenia, Hypothyroidism, Seizures, COPD, Tobacco Use and Small Bowel Resection
3006/0386/018 43/F	CLA	Pneumonia	3	Unknown	Diabetes
3013/0101/022 90/F	CLA	Neoplasm NOS	48	Unknown	Neoplasm of an unspecified origin
3013/0601/003 79/F	CLA	Chronic Obstructive Airways Disease Cardiac dysrhythmia	54	54	Cigarette Smoking, Neoplasm, Coronary Atherosclerosis, Congestive Heart Failure, Chronic Airway Disease
3013/1403/003 88F	CLA	Cardio-Respiratory Arrest	82	82	Cigarette Smoking, Chronic Airway Obstruction, and Other Pulmonary
3013/1203/004 79/F	TEL	Chest Pain	127	127	COPD, Tobacco Use
3013/1403/004 81/F	TEL	Acute Myocardial Infarction	127	127	Cigarette Smoking, Chronic Airway Obstruction
3013/0201/006 80F	TEL	Cardiac Failure	29	32	Chronic Airway Obstruction

*Subject Age	Study Drug	Causal Event	Day of Event	Day of Death	Medical History
70F					Obstruction, Hypertension
3013/00101/0010 82/F	TEL	Superinfection Lung	80	81	Diabetes Mellitus, Cerebrovascular Accident, Neoplasm of the Colon and Right Nephrectomy
4003/3657/025 41/M	TEL	Bacterial Sepsis	1	3	Alcohol Dependency, Hemoptysis
4003/3410/004 78/F	TEL	Cardiac Arrest	3	3	Heart Failure, Ventricular Arrhythmia, Renal Insufficiency, Cardiomegaly
4003/3652/003 30/M	TEL	Convulsions Headache Vomiting	7	8	None
4003/3402/007 83/F	CLA	Myocardial Infarction	13	13	Angina Pectoris
4003/3128/002 57/M	CLA	Lung Cancer	30	39	Prostate Cancer

*Please note that these subjects were enrolled in a controlled study

DEATHS IN OPEN LABEL STUDIES

*Subject Age	Study Drug	Causal Event	Day of Event	Day of Death	Medical History
3000/0703/1466 57/M	TEL	Leptospirosis Acute Respiratory Distress Syndrome Sepsis	3 4	24 24	Hypertension
3000/0803/1520 65/M	TEL	Myocardial Infarction	20	32	Coronary Artery Disease, Chronic Obstructive Pulmonary Disease, Chronic Septicemia, Osteomyelitis, Stroke
3009/0369/108 37/F	TEL	Pneumonia, Cardiomyopathy, Sepsis Immunosuppression Respiratory Failure Liver Failure	5 5 6 6 7 7	Unknown Unknown Unknown Unknown Unknown Unknown	HIV, Positive Pneumonia Respiratory distress
3010/0473/009 77/M	TEL	Aspiration Acute	5	5	Congestive Heart Failure, Foreign Body in Larynx
3010/0537/009 44/M	TEL	Acute Myocardial Infarction	1	2	Myocardial Infarction Pre- Therapy, Sinus Tachycardia
3012/2004/004 84/F	TEL	Worsening Respiratory Distress	1	1	Hypertension
3012/4002/022 70/F	TEL	Cardiac Failure	3	3	COPD, Heart Failure, Cor Pulmonale
3012/4003/013 46/M	TEL	Pneumonia	6	8	HIV Infection
3012/4003/040 56/M	TEL	Lobar Pneumonia	8	12	Chronic Obstructive Airway Disease, Pneumoconiosis (1987), Unspecified Visual and Hearing Problems

*Subject Age	Study Drug	Causal Event	Day of Event	Day of Death	Medical History
3012/4003/022 43/M	TEL	Pneumonia	15	17	AIDS-related complex

*Please note that the subjects in these cases were enrolled in an uncontrolled study

NARRATIVES: DEATHS IN CONTROLLED PHASE III STUDIES*STUDY A3001*

Telithromycin 10-day for CAP

Subject 3001/1002/027 was a 71-year-old white female with history of COPD, coronary artery disease (CAD) and dorsal scoliosis, who was admitted to a frail nursing care unit at study entry. Pretherapy chest X-ray showed single lobe consolidation on the right side. Sputum cultures were positive for *S. pneumoniae*, β -lactamase-producing *H. influenzae*, and *S. aureus* (subsequently identified resistant to telithromycin). The following day, the subject's clinical condition worsened (severe lobar pneumonia, with associated hypotension, cyanosis, and altered mental state). Antimicrobial therapy with iv gentamycin and Rocephin (ceftriaxone) was started. Severe multiorgan (circulatory, kidney, and respiratory) failure developed and was the primary cause of death on Day 4.

Subject 3001/1301/004 was an 80-year-old white male with history of CAD, atrial fibrillation, cerebrovascular disease, diabetes mellitus and unspecified liver disease. On Day 10 the subject developed dyspnea and hypotension (BP: 100/70 mm Hg). Intensive medical care was given, but the subject died that day with the primary cause of death as cardiac insufficiency.

Amoxicillin for CAP

Subject 3001/0111/004 was a 52-year-old white male with a longstanding history of asthma. Study medication was discontinued on Day 8 due to low creatinine clearance at study entry (exclusion criteria). Subsequent amoxicillin therapy was started on 3 August 1998 to treat the pneumonia. On Day 34, the subject experienced severe bronchospasm and died while being transported to the hospital. No autopsy was performed.

STUDY A3004

Penicillin VK for tonsillitis/pharyngitis

Subject 3004/1306/008 was a 55-year-old white female with a history of mild hearing loss and splenectomy and elevated leukocytes (215 x10⁹/L) pretherapy. On Day 2, the subject had fever and weakness. The subject was diagnosed with severe acute lymphoid leukemia, treatment was changed to amoxicillin (Day 4), the subject was withdrawn from the study (Day 5) and transferred to another hospital. She died 44 days after the last dose of study medication of acute lymphoid leukemia.

Clarithromycin for CAP

Subject 3006/0060/002 was a 70-year-old white female with a medical history of schizophrenia, hypothyroidism, seizures, COPD, 2 ½ pack-per-day tobacco use, and small bowel resection. The subject died 5 months post-treatment of malignant bronchial neoplasm.

Subject 3006/0386/018 was a 43-year-old white female with a history of diabetes. Pretherapy sputum culture revealed normal flora. Three days after completing study medication, the subject developed worsening pneumonia. Therapy with ceftriaxone was started. On Day 21, the subject was hospitalized for worsening pneumonia with associated dyspnea, tachypnea, increased sputum production, chest pain, nausea, and mild pleural effusion. Antimicrobial therapy with clindamycin, cefotaxime, ceftazidime, and amikacin was started to treat the pneumonia. The subject died on Day 30, with the primary cause of death as pneumonia (organism not identified).

Clarithromycin for AECB

Subject 3013/0101/022 was a 90-year-old white female who died on Day 48 (post-treatment) with the cause tentatively diagnosed as a neoplasm. An autopsy was not performed. Two weeks prior to the subject's death, all medications were stopped due to swallowing problems. The subject had been cachectic with a deteriorating overall condition. The subject's medical history included neoplasm of an unspecified origin.

Subject 3013/0601/003 was a 79-year-old white female who died on Day 54 (post-treatment) due to a severe exacerbation of chronic obstructive pulmonary disease and cardiac dysrhythmia with onset on the day of death. Study medication had been completed on Day 10. The subject's medical history included cigarette smoking, neoplasm, coronary atherosclerosis, congestive heart failure, and chronic airway disease.

Subject 3013/1403/003 was an 88-year-old white female who experienced cardiopulmonary arrest on Day 82 (post-treatment) that resulted in death on the same day. Study medication was completed on Day 10. An autopsy was not performed. The subject's medical history included cigarette smoking, chronic airway obstruction, and other pulmonary insufficiency. The subject had been taking multiple concomitant medications including diltiazem, pantoprazole, Duo-CVP® , ipratropium/albuterol, prednisone, Ravotril® , Aerogastrol® , and Hidrium® . The cardiopulmonary arrest was assessed by the investigator as not related to study medication.

STUDY A3013

Telithromycin 5-day for AECB

Subject 3013/1203/004 was a 79-year-old white female with a history of COPD and tobacco use. On Day 127 (post-treatment) she died following severe acute precordial chest pain that had started that day. No autopsy was performed, but the investigator considered myocardial infarction the most likely cause of death.

Subject 3013/1403/004 was a 81-year-old white female who experienced a severe acute myocardial infarction on Day 127 (post-treatment) that resulted in death on the same day. Although an autopsy was not performed, the investigator considered the myocardial infarction as the most likely cause of death. The subject's medical history included cigarette smoking and chronic airway obstruction.

Subject 3013/0201/006 was a 70-year-old female who experienced putative cardiac decompensation 29 days post treatment that resulted in hospitalization. She died 3 days later. Although an autopsy was not performed, the cause of death was attributed to right cardiac decompensation. The subject's medical history included chronic airway obstruction, hypertension, hypothyroidism, cor pulmonale, and diabetes mellitus. The cardiac decompensation was assessed by the investigator as not related to study medication.

Subject 3013/0101/0010 was an 82-year-old white female who received treatment from 11 Oct 2001 to 20 Oct 2001. On 08 Jan 2002, approximately 80 days post treatment, she experienced a superinfection (as defined by the investigator, no organism was isolated) of her chronic obstructive pulmonary disease (COPD) that resulted in death one day later. Although no autopsy was performed, the investigator considered the primary cause of death to be respiratory failure related to COPD. The subject's medical history included diabetes mellitus cerebrovascular accident, neoplasm of the colon, and right nephrectomy. The superinfection was assessed by the investigator as not related to study medication, but instead due to underlying illness.

STUDY A4003

Telithromycin 5-day

Subject 4003/3657/025 was a 41-year-old male, with a history of alcohol dependency and hemoptysis, who experienced gram negative septicemia due to *Klebsiella* spp and subsequently died. On Day 1, prior to study entry, the subject presented to the hospital with worsening respiratory signs, tachypnea, crepitations, and delirium. The subject was enrolled into the study before laboratory results were available. On Day 3, the culture results showed *Klebsiella pneumoniae* resistant to telithromycin and clarithromycin. Study medication was discontinued and therapy with cefuroxime iv and gentamycin iv was started but the subject died on Day 3 due to septicemia.

Telithromycin 7-day

Subject 4003/3410/004 was a 78-year-old white female who experienced an adverse event of cardiac arrest on Day 3 that resulted in death. On study entry, this subject had CAP with a Fine score of IV and clinical findings including renal insufficiency (estimated creatinine clearance = 29 mL/min) and a chest X-ray showing cardiac enlargement. An ECG done 4.5 hours after the first dose of study medication showed 1st degree atrioventricular block (PR interval = 0.22 sec) and a QTc interval of 440 ms, within normal limits. Medical history included heart failure treated with furosemide and unspecified ventricular arrhythmia treated with amiodarone. Concomitant medications included heparin, salbutamol and oxygen (all begun on Day 1 at time of hospitalization). Sputum culture results identified *S. pneumoniae* as the causative pathogen with a telithromycin MIC of 0.008 μ g/mL and sensitive to penicillin G, erythromycin A, and clarithromycin. On the morning of Day 3, the subject was found with no pulse and no spontaneous respiration. The cause of death was listed as cardiac arrest. An autopsy was not performed.

Subject 4003/3652/003 was a 30-year-old black male who developed a headache, vomiting and then convulsions on the evening of Day 7 (he had discontinued study medication 2 days earlier). The subject was brought to the hospital the following morning in extremis where he continued to convulse. Treatment with diazepam, cefazolin iv, gentamycin iv, and iv fluids of lactated ringers solution were initiated. On Day 8, 15 hours after the convulsions began, the subject died from suspected acute meningitis. No autopsy was performed.

Clarithromycin

Subject 4003/3402/007 was a 83-year-old white female with a history of angina pectoris who experienced myocardial infarction (MI) resulting in death on Day 13, 3 days after the last dose of study medication. The subject presented to the emergency room (ER) with edema, shortness of breath, and altered consciousness. She was treated in the ER (unspecified) and an ECG indicated a myocardial infarction.

Subject 4003/3128/002 was a 57-year-old white male with prostate cancer who was diagnosed with lung cancer (type and stage unspecified) on Day 30 (post-treatment) resulting in death on Day 39.

NARRATIVES: DEATHS IN OPEN LABEL PHASE III STUDIES*Study A3000*

Telithromycin

Subject 3000/0703/1466 was a 57-year-old white male who was diagnosed on Day 3 with acute leptospirosis (confirmed by serology) associated with renal failure, hemolytic anemia, sepsis, and liver insufficiency. The subject subsequently died of sepsis and adult respiratory distress syndrome (ARDS).

Subject 3000/0803/1520 was a 65-year-old white male, with history of CAD, diabetes, COPD, chronic osteomyelitis and stroke, who completed study treatment with a return to the preinfection state. On Day 12 (3 days post-treatment) he presented with a nonpruritic rash on upper and lower extremities, confirmed as leukocytoclastic vasculitis on biopsy. Urinalysis showed microscopic hematuria and chest X-ray showed bilateral infiltrates, which were identified in the chest CT scan as pleural fluid. On Day 20, the subject had an acute myocardial infarction and died on Day 31 due to gram-negative septicemia.

Study A3009OL

Telithromycin

Subject 3009OL/0369/108 was a 37-year-old black female who experienced a worsening of pneumonia with severe dyspnea and respiratory distress on Day 5. On Day 6 she developed clinical jaundice and complained of painful lower legs. Laboratory test results revealed abnormal liver function tests (AST 806 U/L, ALT 1235 U/L, alkaline phosphatase 326 U/L, total bilirubin 26 μ mol/L). The following day, she became dyspneic with peripheral edema and hepatomegaly, HIV tests were positive. The subject was withdrawn from the study and transferred to another hospital, and died on Day 12, 5 days after the last dose of study medication. The investigator assessed these events as unrelated to the study medication. The reported cause of death was respiratory failure, cardiomyopathy, liver failure, and immunosuppression, considered due to the underlying/concomitant illness.

Study A3010

Telithromycin 7-day

Subject 3010/0473/009 was a 77-year old white male who presented to the emergency room at study entry with increased shortness of breath, cough with productive purulent sputum, chest discomfort, and mild chills for 2 to 3 days. An entry diagnosis of mild renal insufficiency was initially felt to be compromised due to pneumonia and underlying congestive heart failure. On Day 3 the subject showed improvement in clinical signs and symptoms of pneumonia (confirmed by chest X-ray). However, renal insufficiency increased from mild to moderate secondary to vomiting and poor intake. On Day 5 the subject experienced labored respirations and shortness of breath secondary to acute aspiration, was transferred to the intensive care unit and died a short time later due to acute aspiration, later changed to foreign body in larynx.

Subject 3010/0537/009 was a 44-year old black male who experienced acute myocardial infarction on Day 1. Pretherapy, the subject was hospitalized due to presentation with pleuritic chest pain, cough, dyspnea, tachypnea, fever and chest X-ray revealing consolidation. No causative pathogen was isolated. Review of the pretherapy/entry ECG indicated evidence of a new myocardial infarction (Q waves in leads V1-V3, ST segment elevations in leads V1-V4, PR segment depressions in lead II, QTc of 470 ms) and sinus tachycardia at 130 beats per minute. The subject died on Day 2. The investigator assessed the event as not related to the study medication, but rather to an underlying or concomitant illness (acute myocardial infarction).

Study A3012

Telithromycin 7-day

Subject 3012/2004/004 was an 84-year-old white female with a history of hypertension who was treated with study medication approximately 18 hours after hospital admission for suspected pneumonia. Approximately 1.5 hours later the subject's clinical condition deteriorated with worsening respiratory distress, subsequent arrest, unsuccessful resuscitative attempts and death approximately 8 hours later.

Subject 3012/4002/022 was a 70-year-old female with medical history of chronic obstructive pulmonary disease, heart failure, and cor pulmonale. On Day 1 the subject started furosemide for her heart failure, which worsened on Day 3, and resulted in death the same day despite counteractive measures.

Subject 3012/4003/013 was a 46-year-old black male with a history of HIV infection. Initial clinical improvement was noted on Day 3, but the subject subsequently worsened and died on Day 8.

Subject 3012/4003/040 was a 56-year-old black male with medical history of chronic obstructive airways disease, pneumoconiosis (1987), unspecified visual and hearing loss, and nonsmoking status. Study medication was completed on Day 7. On Day 12, the subject was hospitalized for worsening bilateral upper lobe pneumonia and died the same day.

Subject 3012/4003/022 was a 43-year-old black male with history of AIDS-related complex with immunocompromized status and tobacco use. On Day 8, the subject developed diarrhea attributed to an unspecified toxic herbal treatment. On Day 11, the subject visited his Sangoma (witch doctor) who advised him not to continue the study as the study medication was considered poison. The investigator suspected that the subject drank a toxic substance provided by the Sangoma. On Day 15, the pneumonia worsened, CD4 count was 44 U/L. On Day 17, the subject was prescribed ciprofloxacin and an unspecified tuberculosis therapy, but died before treatment was started.

Table 1 – Criteria for PCA CNALV

Variable	Unit ^a	Predefined Change Abnormal	CNALV
Hemoglobin	mmol/L	-1.2412 mmol/L	PCA
	g/dL	-2 g/dL	PCA
Leukocytes	G/L	-2 G/L	<LLN and < 3.0 G/L or < 3G/L when normal range given as a percentage
	/mm ³	-2000 /mm ³	<3000 /mm ³
Lymphocytes	G/L	-20% ^b	<LLN and <2.0 G/L or <2 G/L when normal range given as a percentage
	/mm ³	-20% ^b	<2000/mm ³
Neutrophils	G/L	-20% ^b	<LLN and <1.5 G/L or <1.5 G/L when normal range given as a percentage
	/mm ³	-20% ^b	<1500/mm ³
Eosinphils	G/L	+20% ^b	>1.0 G/L
	/mm ³	+20% ^b	>1000/mm ³
Platelets	G/L	-100 G/L	<100 G/L
	/mm ³	-100,000/mm ³	<100,000/mm ³
ALT/SGPT	U/L	+2 ULN	>3 ULN
AST/SGOT	U/L	+2 ULN	>3 ULN
Alkaline phosphatase	U/L	+5.0 ULN	PCA
Total bilirubin	µmol/L	+0.5 ULN	>2 ULN
Serum creatinine	µmol/L	+0.3 ULN	>2 ULN
Creatinine clearance	mL/sec	-0.5 mL/sec	<0.8333 mL/sec
	mL/min	-30 mL/min	<50 mL/min
Serum potassium	mmol/L	+1.0 mmol/L or -1.0 mmol/L	<3.0 or 5.5 mmol/L

G: Giga, 10⁹

ULN: Upper Limit of Normal LLN: lower limit normal using laboratory normal range

^a When 2 units are provided for each analyte, the first is the SI units and the second is the corresponding alternative unit in clinical use^b Percent of absolute value for lymphocytes, neutrophils, and eosinophils

**Table 1 - QT interval data for telithromycin vs. clarithromycin
(controlled Studies 3006, 3008 and 3113)**

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

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

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

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

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

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

Source: Table 7 – 14 from Section 7.2.6.2 of Advisory Committee Meeting Briefing Document, January 2003.

**Table 2 - QT interval data for telithromycin vs. non-macrolide comparators
in controlled Phase III studies**

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

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

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

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

^c ΔQTc interval on-therapy minus QTc interval pretherapy

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

Source: Table 7 – 15 from Section 7.2.6.2 of Advisory Committee Meeting Briefing Document, January 2003.

NARRATIVES FOR SERIOUS HEPATIC CASES (6)

3000/0502/069

Case **199910127RUPV** Involved a 54 year-old male patient who experienced **Hepatitis** 3 days after discontinuing an 11day course of telithromycin for pneumonia. Concomitant medications included salbutamol, fluticasone, paracetamol, ipratropium, salmeterol, and prednisolone. Relevant medical history included asthma and diabetes mellitus. On 15-Feb-1999, the ALT was 354, which increased to 1529 on 25-Feb-1999. Alkaline phosphatase 169, total bilirubin 29. Eosinophilia increased from 774 on 02-Feb-1999 to 2856 on 08-Mar-1999. On 15-Feb-1999, he visited family who had gastroenteritis-like disease with fever. The patient underwent tests for serum markers of recent viral infection, which were negative. Hepatitis B, EBV infection, hepatitis C, hepatitis A antibodies anti-HAV IgM, HIV, toxoplasma, F-para-O, tularemia, legionella, brucella, mycoplasma were also all negative. Liver biopsy revealed extensive liver necrosis, predominantly centrolobular liver necrosis and granulomata-like structures with infiltration of eosinophilic granulocytes. It is noteworthy that ALT was already high at inclusion into the study (1.6 N) but it could be related to the underlying diabetes (liver steatosis). In view of the context (i.e. multiple cases of gastroenteritis and granulocytes on liver biopsy), the subject's clinical course is suggestive of parasitic infestation (larva migrans syndrome) rather than drug induced hepatocellular injury. The patient had been exposed to macrolides in the past, roxithromycin and azithromycin. Repeat biopsy in Dec 1999 (no re-exposure to telithromycin) revealed hepatitis with centrilobular liver cell depletion; no frank necrosis. Investigator considered the findings consistent with autoimmune hepatitis. Latest ALT value in April 2005 was 35IU/ml. Patient without symptoms.

3012/1027/006

Case **200212006US** involved a 19 –year-old male who experienced **Worsening Transaminases, Aminotransferase Increase and Lactate Dehydrogenase Increase** while receiving a 4- day course of telithromycin and concomitant medication acetaminophen for pneumonia. The patient has no significant medical history. The following elevated laboratory values were reported ALT 160, AST 318, and LDH 652. His transaminase levels were high prior to entering study and worsened after starting telithromycin. It was noted that the transaminitis were most likely due to acetaminophen use in the 3 days prior to study entry. The levels peaked with an ALT of 447 and AST of 690. They were declining at the time of discharge. Telithromycin was discontinued on 14-Feb-02 for this event. The patient recovered on 22-May-2002.

3010/0473/001

Case **200011081HMRI** involved a 54-year-old male who experienced **Pancreatitis, Pancreatic Mass, Gall stones, Biliary Tract Occlusion Small Cell Carcinoma of the**

Lung and Hyponatremia 122 while taking a 7 day course of telithromycin for pneumonia. Concomitant medications included salbutamol, doxazosin, metoprolol, clorazepate, acetylsalicylic acid, and oxycodone. Medical history included pneumonia, hypertension, borderline diabetes mellitus, ulcers, right upper quadrant pain and alcohol abuse. The patient was hospitalized for persistent abdominal pain. Amylase was 4,174, and lipase was 35,600. CT scan of the abdomen showed gallstone, enlargement of the head of the pancreas with dilated common bile duct and dilated intrahepatic ducts, suggesting possible neoplasm of the head of the pancreas. Cytology of the pancreatic mass revealed no atypical cells. Thorascopic biopsies of mediastinal lymph nodes revealed small cell carcinoma. The patient underwent stent, ERCP, bile duct brushing and mediastinal biopsy. After stent placement, the bilirubin returned to normal and the patient was asymptomatic. The event of pancreatic mass is not resolved. A bone marrow aspirate revealed no evidence of metastatic tumor. The small cell carcinoma of the lung is not resolved.

3008/0259/005

Case **199911578HMRI** involved a 19-year-old male who experienced ***Liver Injury and Diarrhea 2*** days after completing a 5-day course of telithromycin for group A beta-hemolytic streptococcal pharyngitis/tonsillitis. The patient has no relevant medical history. Concomitant medications included Zinc and ascorbic acid. The night before laboratory tests were drawn, the patient admits to going out, “partied” and consumed an excessive amount of alcohol, SGOT 273, SGPT 124, GGT 37, LDH 592, serum alcohol level was not provided. Serology results reveal nonreactive hepatitis A, B, and C, with positive serology for CMV but with IgG. Repeat liver function tests returned to normal 8 days after the event.

3006/0060/039

Case **199911017HMRI** involved a **76-year-old female who experienced *Liver Injury*** while receiving a 6-day course of telithromycin for pneumonia. Concomitant medications included cefuroxime, pravastatin, and allopurinol. Relevant medical history included amygdalectomy, hyperlipidemia and hyperuricemia. On Feb. 15, 1999, the patient developed asymptomatic liver injury (based on elevated liver enzymes), which the investigator felt could be related to telithromycin or pravastatin or a combination of telithromycin and pravastatin. The following laboratory values were elevated; Alkaline Phosphatase was 306, ALT 418, AST 295, and GGT was 73. Anti Hepatitis A, B, C and HBS AG were all non-reactive. Cytomegalovirus IgG is pending. The patient reported that she has no history of liver or gallbladder problems. The patient recovered on 22-Feb-1999.

3006/0425/011

Case **199920661HMRI** included a 61-year-old male patient who experienced ***Icteric Syndrome and Disseminated Neoplasm 5*** days after completing an 11-day course of clarithromycin for pneumonia. Concomitant medications included digoxin. Relevant

medical history included alcohol abuse, anemia and hypoalbuminemia. On 17-Aug-1999, the patient presented with fever, choluria, and jaundice. The following laboratory values were elevated, platelets 785, potassium 6.4 and GGT 457. CT scan revealed hepatic tumor and disseminated neoplasm throughout abdominal and thoracic cavities (no biopsy results were provided). The investigator assessed the event of disseminated neoplasms as not related to clarithromycin and gave an alternative explanation of underlying concomitant illness. The platelet and potassium increase are considered complications of the disease progression.

NARRATIVES FOR SERIOUS SYCOPE CASE

Case 200114103EU involved an 83-year-old male patient who experienced *Syncope, Dysregulation of Anticoagulation Therapy and Important Intra-Muscular Hematoma* 2 days after completing a 5-day course of telithromycin for acute exacerbation of chronic bronchitis. Concomitant medications included warfarin, ranitidine, selegiline, methylprednisolone, acetylcysteine, paroxetine, lorazepam, levodopa, clonazepam, bumetanide, fenoterol and lactulose. Relevant medical history included respiratory insufficiency, cardiac failure, atrial fibrillation, Parkinson's disease and lung embolism. On 06-August-2001, eight days prior to starting telithromycin the patient's INR was 3.5. On 20-Aug-2001 and 22 Aug-2001, the patient's (onset date of events), INR was >9. The investigator states that the INR was already too high prior to telithromycin administration because of liver interference between concomitant drugs and telithromycin. It was also reported that the patient required cane and or wheelchair and experienced various fall episodes since that date, most probably linked to the severe underlying Parkinson's disease. After clinical review of hospital reports, the investigator considered the important intramuscular hematoma as not related to study treatment, but due to fall and worsened by disequilibrium of anticoagulant therapy, and was considered by the investigator as not related to study treatment, but due to concomitant therapy with corticoids. The patient recovered on 22-August-2001.