FDA Briefing Document

Solithromycin Oral Capsule and Injection

Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

November 4, 2016

The committee will discuss new drug applications (NDAs) 209006 and 209007 for solithromycin oral capsule and injection, submitted by Cempra Pharmaceuticals, for the proposed indication of treatment of community acquired bacterial pneumonia.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought solithromycin oral capsule and injection to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Introduction

This briefing document describes the review of safety and efficacy data for solithromycin oral capsule and injection, prepared by the FDA for the panel members of the Advisory Committee. We would like the committee to discuss whether the data are adequate to support safety and efficacy of solithromycin for the treatment of community-acquired bacterial pneumonia (CABP).

2 Solithromycin Product Information

Solithromycin (CEM-101; SOLITHERA®) is a semi-synthetic antibacterial drug of the macrolide class/ketolide subclass developed by Cempra Pharmaceuticals, Inc. for the treatment of CABP caused by *Streptococcus pneumoniae, Haemophilus influenzae*, *Moraxella catarrhalis,* methicillin-susceptible *Staphylococcus aureus, Legionella pneumophila and Mycoplasma pneumoniae*. As with other macrolides, solithromycin binds to bacterial 23S ribosomal RNA to disrupt protein synthesis. In addition, it binds to an extra site on the rRNA that has potential to confer activity against bacteria with macrolide-resistance mechanisms. It differs structurally from telithromycin, the only other approved ketolide, mainly by the presence of a fluorine group at Carbon-2 of the macrolactone ring and loss of the pyridine group on the alkyl aryl side chain.

Solithromycin capsule is a white opaque 200 mg capsule. The recommended dose is 800 mg PO once on day 1, followed by 400 mg PO once daily on days 2-5. Solithromycin for Injection, 400 mg, is a sterile white to off-white lyophilized powder in 50 mL clear glass single-dose vials. Each vial must be reconstituted with sterile water for injection and subsequently diluted with 0.45% or 0.9% sodium chloride or Lactated Ringers solution, and administered as an intravenous infusion over 60 minutes. The recommended dose is 400 mg IV once a day for 7 days; when switching to oral solithromycin, the applicant proposes a loading dose of 800 mg PO, followed by 400 mg PO daily to complete the 7-day course.

3 Solithromycin Clinical Development and Regulatory History

The proposed indication for solithromycin is for the treatment of CABP caused by *S. pneumoniae, H. influenzae*, *M. catarrhalis,* methicillin-susceptible *S. aureus, L. pneumophila* and *M. pneumoniae*.

The investigational new drug (IND) application for solithromycin capsules was submitted on April 4, 2008**.** The following safety/pharmacokinetic/efficacy issues were identified and discussed with FDA during clinical development of solithromycin:

- Nonclinical evidence of hepatotoxicity

- Significant elevations of ALT in 3/6 subjects at 600 mg dose level in the multiple ascending dose phase 1 study in healthy volunteers
- Narrow therapeutic margin potential
- Potential for subtherapeutic concentrations/therapeutic failure due to significant variability in absorption
- Significant drug-drug interactions affecting solithromycin exposure and exposure of companion drugs
- Imprecise PK/PD model for target attainment assessment
- Projected size of the premarketing safety database (detection of adverse events occurring in ≥0.3% of patients receiving solithromycin for 5-7 days [n=924] and in ≥ 0.8% of patients receiving a single dose of solithromycin [n=355])
- Mechanisms for ketolide toxicities (hepatic, ocular, neurological)
- Cholestatic hepatitis and transaminase elevation cases from extended treatment duration (up to 13 weeks) COPD and NASH trials
- Exposure-related ALT elevations

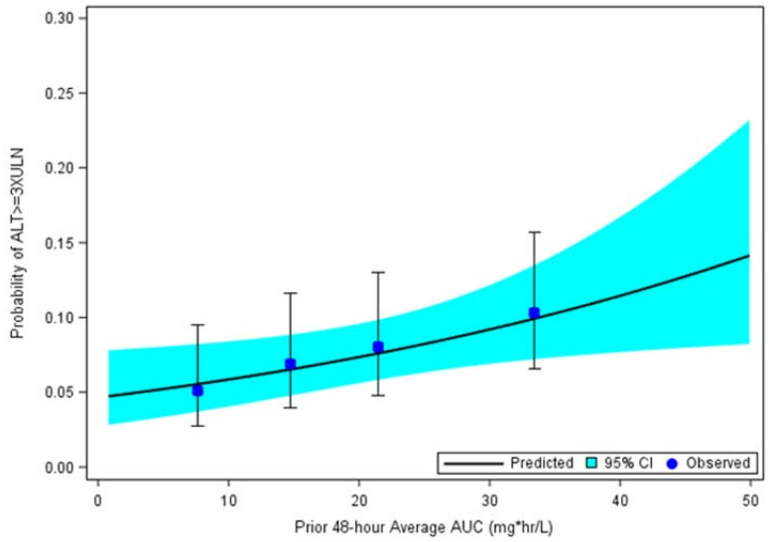
4 Clinical Pharmacology

The pharmacokinetics (PK) of solithromycin were characterized in phase 1, 2, and 3 trials. There was no dose-ranging evaluation in phase 2 (Study CE01-200). The dose selected for Study CE01-200 (i.e., 800 mg oral loading dose, followed by 400 mg oral once daily for 4 more days) was based on the PK/PD relationship derived from nonclinical infection models, MIC distribution data, human PK data for solithromycin following single and multiple oral doses in healthy subjects, and Monte Carlo simulation. The oral-only dosing regimen studied in phase 2 was further evaluated in phase 3 (Study CE01-300). The IV-only or IV-to-oral dosing was evaluated in the phase 3 study CE01-301. The three dosing regimens (Oral-only for 5 days, IV-only for 7 days, or IV-to-oral for 7 days) are the final proposed regimens for adult CABP patients.

Exposure-Response Analyses:
Population PK (PopPK) and exposure-response (E-R) analyses for both safety and efficacy were conducted using pooled data from phase 1 trials and two phase 3 trials (Studies CE01-300 and CE01-301). The E-R analysis for efficacy suggested that AUC:MIC ratio as the PK/PD index predictive for solithromycin efficacy in phase 3 is on the flat portion of the E-R curve for efficacy.

The E-R analysis for safety suggested that increase in AUC was associated with increase in the incidence of alanine transaminase (ALT) elevation (≥3×ULN). See Figure 4.1.

Figure 4.1: Relationship between the Probability of Patients with ALT > 3×ULN in Study CE01-300 and CE01-301 and Prior 48-hour Average AUC



Note: Plotted data points are observed quartile means (95% CI). The shaded areas are model-estimated 95% CI based on a logistic regression analysis

Absorption:

Due to nonlinear PK, the absolute oral bioavailability value is dose dependent. The absolute oral bioavailability of solithromycin capsules administered as a single 400 mg dose (2 × 200 mg capsules) was estimated to be 62%, when 400 mg IV solithromycin was used as the reference. Solithromycin is both a substrate and an inhibitor for P-gp. Time-dependent inhibition of CYP3A, the enzyme responsible for hepatic elimination of solithromycin, and saturation of intestinal P-glycoprotein are likely causes for the nonlinear PK.

Food has little effect on the bioavailability of solithromycin following a single oral dose of 400 mg. T_{max} is generally observed 2 to 4 hours post oral dose.

Solithromycin has moderate to high PK variability in CABP patients: 46 % and 61% CV% for C_{max} for IV-only and oral-only regimens, respectively; 65% and 79% CV% for AUC for IV-only and oral-only regimens respectively.

Distribution:

The plasma protein binding of solithromycin is approximately 81% (78-84%). The volume of distribution is approximately 400 L (349 -554 L) following 400 mg IV infusion. Solithromycin concentrations in epithelial lining fluid (ELF) and alveolar macrophages (AM) were estimated to be higher than the time-matched plasma concentrations, based on preliminary PK data from healthy subjects; however, this could not be confirmed because of a lack of assay validation.

Metabolism:

Solithromycin is primarily metabolized via oxidation with involvement of CYP3A and minimal contribution from other CYPs. Solithromycin is both a substrate and an inhibitor of

CYP3A4, and it inhibits its own metabolism. Multiple metabolites in feces, plasma, and urine were detectable after a single oral dose of 800 mg [^{14}C]-solithromycin in solution. Solithromycin was the major component in plasma samples from the mass balance study (approximately 80% by radioactivity), followed by the side chain metabolites N-acetylated solithromycin and hydroxyl destriazolyl-phenylamino solithromycin, which are present at 5.3% and 4.8% of parent AUC, respectively.

Excretion:

Solithromycin is predominantly metabolized and then excreted in the feces (approximately 77% of total radioactivity). Urinary excretion (14%) is a minor contributor to the overall elimination, with approximately 10% excreted as unchanged solithromycin. The terminal half-life is approximately 8.5 hours (7.2-11.2 hours) following the proposed IV dosing regimen in healthy subjects.

Effect of intrinsic/extrinsic factors

Intrinsic factors:

Elderly/Sex

Based on the PopPK and E-R analyses results, age and sex have minimal impact on the exposure of solithromycin, and thus no dose adjustment is required based on patient age or sex.

Renal Impairment

A dedicated PK study in subjects with moderate or severe renal impairment showed that there was an approximately 100% increase in solithromycin AUC on Day 5 in subjects with severe renal impairment but not on hemodialysis and an approximately 27% increase in subjects with moderately reduced renal function, relative to subjects with normal renal function, following oral administration of 800 mg solithromycin on Day 1 and 400 mg once daily on Days 2 to 5. High variability in solithromycin AUC (> 65 % CV) was observed in this study. PopPK analysis of data from healthy and CABP patients also showed that creatinine clearance (CLcr) impacts solithromycin exposure. Population predicted solithromycin AUC in subjects with moderate renal impairment was 53% higher than that in subjects with normal exposure. There were too few subjects (n=9) with severe renal impairment in the analysis to describe solithromycin exposures in this population, and the model-based simulations predict that solithromycin AUC is 86% higher in subjects with severe renal impairment compared to that in subjects with normal renal function.

Hepatic Impairment

In a dedicated PK study, solithromycin PK was evaluated in 24 adult subjects with mild, moderate, or severe hepatic impairment. Following oral administration of 800 mg solithromycin on Day 1 and 400 mg once daily on Days 2 to 5, the average AUC on Day 1 was not affected by degree of hepatic impairment. The mean exposure to solithromycin at Day 5 was lower by approximately 41% for subjects with severe hepatic impairment compared to subjects with normal hepatic function. The mean solithromycin AUC from patients with baseline hepatic impairment in the phase 3 trials (n=43; the severity of hepatic impairment for

each patient is unknown) was 11%-42% lower than those with normal baseline hepatic function (n=816). Despite these lower exposures, the response rates in patients with hepatic impairment were comparable to those in patients with normal baseline hepatic function in the phase 3 trials. Based on the dedicated PK study in subjects with normal or reduced hepatic function, the results from the phase 3 trials (lower exposure not associated with efficacy decrease), and the E-R relationship between exposure and ALT elevation, we concur with the applicant's proposal that no dose adjustment is needed for CABP patients with mild, moderate, or severe hepatic impairment.

Extrinsic factors:

Drug Interactions

- Co-administration with a potent CYP3A/P-gp inducer: Rifampin caused a > 97% decrease in both C_{max} and AUC of solithromycin. Given this observation, solithromycin should NOT be administered to patients on CYP3A/P-gp inducers, due to the risk of subtherapeutic exposure and loss of efficacy of solithromycin.

- Concomitant administration with a potent CYP3A inhibitor: Ketoconazole increased the single-dose solithromycin C_{max} and AUC by 1.6- and 2.6-fold, respectively. However, given that solithromycin inhibits its own metabolism via CYP3A4 auto-inhibition, solithromycin AUC was predicted to increase by approximately 25% in the presence of ketoconazole following multiple dosing of both drugs. Therefore, the effect of concomitantly administered CYP3A inhibitors on solithromycin PK following repeat dosing is not expected to be clinically significant.

- Co-administration with CYP3A substrates: The impact of multiple doses of oral solithromycin on the PK of midazolam (a substrate of CYP3A) showed that solithromycin is a strong CYP3A inhibitor, as it caused a 9-fold increase in midazolam AUC. Administration of solithromycin with drugs that are primarily CYP3A substrates could increase or prolong the therapeutic effect or adverse events of the concomitant drug. In vitro studies showed that solithromycin did not inhibit any other CYPs to a clinically meaningful degree.

- Co-administration with P-gp substrates: Concomitant administration of solithromycin with digoxin resulted in an increase in plasma digoxin $AUC_{0\text{-}tau}$ and C_{max} by approximately 38% and 46%, respectively. Administration of solithromycin with drugs that are P-gp substrates could increase or prolong the therapeutic effect or potentiate adverse events of the concomitant drug.

Effect on QT prolongation

The effect of solithromycin on cardiac repolarization was assessed in a randomized, positive- and placebo-controlled crossover study in 48 healthy subjects. Solithromycin did not prolong the QT interval to any clinically relevant extent at a single intravenous dose of two times the maximum recommended dose.

Dosing recommendations

The applicant's proposed dosing regimens and the Agency's recommendations are provided in Table 4.1. We are in agreement with the applicant's proposed oral-only and IV-only dosing regimens, dose reduction in CABP patients with severe renal impairment, and no dose adjustment in patients with mild or moderate renal impairment, or hepatic impairment. For the IV-to-oral dosing regimens, we question the need for the oral loading dose on the day of IV-to-oral switch and recommend dosing using the oral doses without a loading dose.

A. Rationale for removing the oral loading dose in the IV-to-oral regimens:

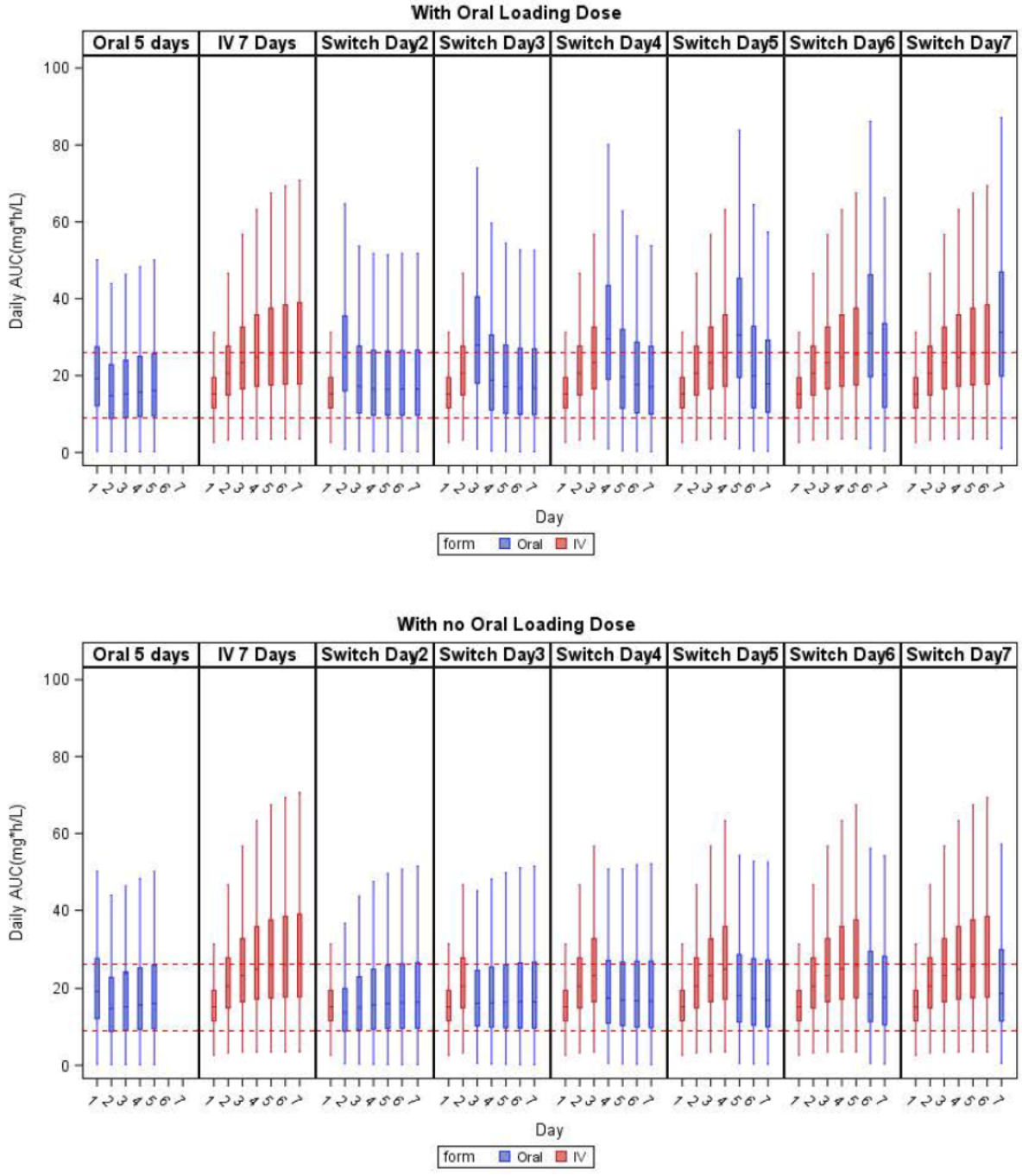
- As evidenced by the Daily-Exposure-Comparison data (see Figure 4.2) when patients meet the criteria (i.e., clinical improvement) for IV-to-oral switch, the use of an oral loading dose (800 mg) resulted in higher exposures on the day of switch, which may contribute to increased ALT elevation observed in CE01-301 as evidenced by the E-R relationship for safety (see Figure 4.1).
    - Note - It is important to recognize that the contribution of the high exposure produced by the 'oral load' on the day of IV-to-oral switch to the increased incidence of ALT elevation in Study CE01-301 could not be adequately assessed based on the available data. However, based on the relationship between AUC and efficacy, lowering exposure without sacrificing efficacy may be beneficial.

- Patients can transition without an oral loading dose of 800 mg (i.e., using 400 mg instead) and still maintain solithromycin at or exceeding Day 5 exposure observed in CE01-300, which was shown to be efficacious. Probability Target Attainment analysis (PTA) also predicts that the probability of achieving the desired PK/PD target at MIC of 0.25 mcg/mL on the day of IV-to-oral switch without a loading dose is similar to that following oral solithromycin treatment.
- The alternative IV-to-oral dosing regimen is simpler than the original proposal, and therefore may help reduce the potential for dosing errors.

Table 4.1: Solithromycin Dosing – Applicant and FDA Recommendations

	Applicant's proposal	**FDA recommendation** (Difference noted in **Bold)**
Patients with CLcr ≥ 30 mL/min	Oral only : 800 mg single dose Day 1; 400 mg once daily Day 2-5	Oral only: Same
	IV only: 400 mg infused over 60 min once daily for 7 days of treatment	IV only: Same
	IV-to-oral: 400 mg infused over 60 min once daily; 800 mg single oral dose on the day of switch; 400 mg oral once daily to the end of 7 days of treatment	**IV-to-oral: 400 mg infused over 60 min once daily; 400 mg oral dose once daily from the day of switch to the end of 7 days of treatment**
Patients with CLcr < 30 mL/min	Oral only : 800 mg single dose Day 1; 200 mg once daily Day 2-5	Oral only: Same
	IV only: 400 mg infused over 60 min Day 1; 200 mg infused over 60 min once daily for 7 days of treatment	IV only: Same
	IV-to-oral: 400 mg infused over 60 min Day 1; 200 mg infused over 60 min once daily until 400 mg single oral dose on the day of switch; 200 mg oral once daily to the end of 7 days of treatment	**IV-to-oral: 400 mg infused over 60 min Day 1; 200 mg infused over 60 min once daily; 200 mg oral once daily from the day of switch to the end of 7 days of treatment**

Figure 4.2: **Box-and whisker plots of simulated daily solithromycin exposure by dosing regimens – Oral-only 5 days, IV-only 7 days, or IV-to-oral <u>with</u> (upper graph) or <u>without</u> (lower graph) oral loading dose of 800 mg, for patients in phase 3 studies CE01-300 and CE01-301**



Note: Between two dotted lines is the interquartile range of the steady state exposure following the oral dosing regimen studied in CE01-300. In Study CE01-301, more than 30% patients switched to oral dose on Day 4.

B. Dose in patients with severe renal impairment (CLcr < 30 mL/min)

The rationale for dosing reduction for CABP patients with severe renal impairment is:

- The dedicated PK study, as described in the previous section- "*Renal impairment*" showed that solithromycin AUC ratio in subjects with severely reduced renal function relative to subjects with normal renal function is approximately 2 fold.
- PK data from phase 3 CABP patients showed that solithromycin exposure is correlated with the baseline CLcr. The PopPK model predicts that the solithromycin Day 5 AUC is 1.86 fold and 1.53 fold higher in CABP patients with severe renal impairment and moderate renal impairment, respectively, than that in CABP patients with normal renal function following the oral-only dosing regimen of 800 mg day one followed by 400 mg qd for 4 more days.
- A limited number of CABP patients with CLcr < 30 mL/min were enrolled in the phase 3 trials and received no dose adjustment; two out of four such subjects enrolled in Study CE01-301 had ALT elevation greater than 3×ULN.
- Both PopPK model and Physiologically-based PK model were used to explore the dosing regimens for CABP patients with severe renal impairment. The results support the proposed reduced dosing regimens in Table 4.1.

C. Dose in patients with moderate or mild renal impairment

There were 91 patients with moderate renal impairment and 288 patients with mild renal impairment enrolled in the phase 3 studies. The efficacy and the incidence of ALT elevation in these patients were comparable with that in patients with normal renal function despite the observed trend that solithromycin exposure increases with decreases in CLcr. These clinical data support that no dose adjustment is warranted for CABP patients with moderate or mild renal impairment.

5 Microbiology

Mechanism of Action

Solithromycin interferes with bacterial protein synthesis by binding to the 23S rRNA of the 50S ribosomal subunit. Domains within the 23S rRNA are categorized based on their unique helix structure. Domain II includes nucleotides 587-1250 and domain V includes nucleotides 2058-2610. Macrolides and ketolides interact with the central loop in domain V of 23S rRNA at A2058 and domain II at A752. Like macrolides and ketolides, solithromycin interacts with domain V and domain II in the 23S rRNA. It also has an additional third site of interaction with the bacterial ribosome at the C-2 fluorine. Solithromycin concentrates in phagocytes and exhibits activity against intracellular respiratory pathogens.

Activity in vitro

The in vitro activity of solithromycin was assessed against a number of US and European isolates associated with CABP (Table 5.1). The solithromycin MIC_{90} values against *S. pneumoniae, S. pyogenes, M. catarrhalis,* and *M. pneumoniae* were ≤ 0.25 mcg/mL. Against *S. aureus* the solithromycin MICs ranged from 0.008 to >32 mg/mL and showed a bimodal distribution (modes at 0.06 mcg/mL and >32 mcg/mL).

Table 5.1: In vitro Activity of Solithromycin against CABP Pathogens

Organisms	N	Solithromycin MICs in mcg/mL	
		MIC range	MIC_{90} range*/MIC_{90}
S. pneumoniae	10,692	0.002 -1.0	0.06 -0.25[a]
S. pyogenes	689	0.008 – 0.25	0.015
Methicillin sensitive S. aureus (MSSA))	10,632	0.008 - >32	0.06 -0.12
Methicillin resistant S. aureus (MRSA)	357	0.008 - >32	>32.0
Community acquired MRSA (USA300)	30	0.06 – 0.12	0.12
Hospital acquired MRSA	75	0.03 - >16	>16
H. influenzae	5680	≤0.03 -64	2.0
H. influenzae [b-lactamase positive]	347	0.12 - >8.0	2.0
H. influenzae [b-lactamase negative]	120	0.25 – 4.0	2.0
H. parainfluenzae	11	1.0 - 2.0	2.0
M. catarrhalis	1934	0.002 ->32	0.06 - 0.25
L. pneumophila[b]	573	≤0.000001 – 0.06	0.00006 – 0.031
M. pneumoniae	66	≤0.00000063 – 1.0	0.000125 – 0.5
C. pneumoniae[c]	10	0.25 – 1.0	0.25

*MIC_{90} range provided when MIC_{90} varied in the different studies.
[a] 2014 surveillance data MIC_{90} was 0.25 for isolates from USA.
[b] Different methods were used for susceptibility testing (agar or broth dilution). QC organisms were within range.
[c] using Hep2 cell culture susceptibility method.

Macrolide resistance occurs in *S. pneumoniae* mainly by three mechanisms: ribosomal methylation (encoded by the *erm* gene), macrolide efflux mechanisms (encoded by the *mef* gene), and mutations in ribosomal proteins (L4 or L22). The solithromycin MIC_{90s} for macrolide-resistant *S. pneumoniae* and penicillin-resistant *S. pneumoniae* were 0.25 mcg/mL (Table 5.2). The solithromycin MIC_{90} for *S. pneumoniae* isolates with *ermB* + *mefA* genotypes were 2-fold higher (0.5 mcg/mL) compared to isolates with either *ermB* or *mefA* genotypes (0.25 mcg/mL). Solithromycin retains ribosomal binding and antibacterial activity against some *erm*- and *mef*-containing *S. pneumoniae*.

Table 5.2: In vitro Activity of Solithromycin against Streptococci

Organisms (resistance/genotype)	N	Solithromycin MIC range in mcg/mL	Solithromycin MIC_{90} range*/ MIC_{90} in mcg/mL	Erythromycin MIC_{90} in mcg/mL	Azithromycin MIC_{90} in mcg/mL	Telithromycin MIC_{90} range*/ MIC_{90} in mcg/mL
S. pneumoniae						
Macrolide sensitive[a]	605	0.008 - 0.25	0.06	-	0.12	0.015
Erythromycin resistant	272	-	0.25	>16	-	-
Macrolide resistant[a]	644	0.008 -1.0	0.25	-	>32	0.5
Penicillin resistant[a]	246	0.004 – 1.0	0.25	-	>32	0.5
Telithromycin resistant	5	0.06 – 0.25	-	>256	-	8.0
Telithromycin intermediate	7	0.5 – 1.0	-	-	-	3.0
*erm*B	146	-	0.25	-	-	0.25
*mef*A	77	-	0.25	-	-	0.5
*erm*B + *mefA*	115	-	0.5	-	-	1.0
S. pyogenes						
Macrolide resistant	40	≤0.03 – 0.25	0.03 – 0.25	-	>32	0.5 -32

*MIC_{90} range provided when MIC_{90} varied in the different studies.
[a] 2014 surveillance data
Macrolide resistant (isolates with azithromycin MIC ≥2 mcg/mL or erythromycin MIC ≥1 mcg/mL)
Erythromycin resistant (isolates with MIC ≥1 mcg/mL)

Penicillin resistant (isolates with MIC ≥1 mcg/mL)
Telithromycin resistant (isolates with MIC≥4 mcg/mL)
Telithromycin intermediate (isolates with MIC >1 and <4 mcg/mL)
ermB = rRNA adenine N-6-methyltransferase;
mefA = major facilitator superfamily transporter

Resistance Development:
Resistance to solithromycin is mediated through mutations in the 23S rRNA gene. In single step mutation studies, solithromycin had a low rate of spontaneous mutations (10^{-9} to 10^{-10}) against *S. pneumoniae, S. pyogenes, and S. aureus*. Increases in MIC were observed in *S. pneumoniae* strains with both *ermB* and *mefA* genotype and *S. pyogenes* with *ermB* genotype. Erythromycin induces resistance to solithromycin in *S. aureus.*

Activity in vivo
Solithromycin was studied in two animal models of CABP: (a) the systemic infection mouse model, and (b) the tissue/organ model.

In the murine systemic infection model, treatment with solithromycin was associated with improved survival in animals infected with *S. pneumoniae*, *S. pyogenes* and *S. aureus*. The solithromycin *in vivo* activity against the pathogens was comparable to or exceeding that of comparator macrolides and ketolides. A higher solithromycin dose (20.6 to 23.6 mg/kg) was required to achieve 50% survival in animals infected with macrolide resistant *S. pneumoniae* including the isolate with *mefE* and *ermB* genotype (erythromycin MIC >32 mcg/mL; azithromycin MIC>32 mcg/mL) compared to macrolide sensitive *S. pneumoniae* (6.0 to 7.1 mg/kg).

In a pulmonary infection neutropenic mouse model, lower doses of solithromycin were required to achieve at least 2 $\log_{10}$ reduction in pulmonary bacterial counts in mice infected with macrolide-susceptible (6.9 - >30 mg/kg) and macrolide resistant (45-85 mg/kg) *S. pneumoniae* (*mefE* + *ermB* genotype, azithromycin and clarithromycin MIC >32 mcg/mL) compared to azithromycin (not tested and >100 mg/kg), clarithromycin (4.5 ->30 mg/kg and >100 mg/kg), and telithromycin (3.25 mg/kg and >100 mg/kg), for sensitive and resistant strains, respectively.

In the *H. influenzae* rat pulmonary infection neutropenic model, solithromycin reduced bacterial burden in the lung tissue at 24 hours and 48 hours post-treatment. Azithromycin was the most active compound against the *H. influenzae* strains.

6 Nonclinical Toxicology

Solithromycin undergoes significant hepatic metabolism in rats and monkeys and there is a large first pass effect following oral administration. It is metabolized by CYP3A4, but is also a potent inhibitor of this enzyme, thereby inhibiting its own metabolism following repeated dosing. Solithromycin is widely distributed to tissues with the highest levels found in liver, spleen, GI tract, and, after repeated dosing, lung. It accumulates in lysosomes and phospholipidosis (particularly in liver and lung) was observed after repeated dosing, similar to other macrolide drugs. In rats and monkeys, the active metabolites N-Acetyl-CEM-101

(formed by acetylation of the amino group of the aminophenyl-1,2,3-triazole moiety of solithromycin), and CEM-214 (formed through cleavage of the aminophenyl-1,2,3-triazole moiety) account for significant levels of exposure. Although these metabolites have been identified in human plasma, they each account for <7% exposure following oral administration. Following IV administration of solithromycin to monkeys, these metabolites were formed in much lower quantities than after oral administration. Elimination of solithromycin and its metabolites in the rat and monkey is primarily via the bile and feces with much less renal excretion (<10% after oral administration; <10% to <25% after IV).

Initial oral repeat-dose toxicity studies in rats and monkeys showed that the primary target organ of toxicity for solithromycin was the liver. In a 4-week oral rat study, mortality and biliary inflammation and centrilobular degeneration/necrosis were observed at 250 mg/kg dose. In contrast, a 125 mg/kg dose of solithromycin showed minimal to modest increases in AST, ALT, and ALP observed on Day 45 that did not progress with continued dosing and were not associated with adverse microscopic findings. In a 2-week oral monkey study, there was no mortality, but centrilobular vacuolation of hepatocytes was observed in animals that received the high dose of 200 mg/kg and the mid dose of 100 mg/kg, in conjunction with increases in AST and ALT. There were no adverse liver findings at 40 mg/kg in this study. In a 13-week oral monkey study, the high dose of 125 mg/kg was associated with body weight loss, centrilobular hepatocellular vacuolation, Kupffer cell hyperplasia, and moderate increases in AST, ALT, and GGT.

In the IV studies in monkeys and dogs (rats were not used for repeat dose IV studies due to unacceptable local tolerance), solithromycin infusion was primarily associated with local lesions at the infusion sites. There were no findings associated with systemic toxicity of solithromycin at the high dose of 25 mg/kg in the 4-week monkey study, although this dose caused exacerbation of local infusion site reactions compared with controls and lower doses (12.5 and 5 mg/kg). The high dose of 15 mg/kg in the 4-week IV dog study was associated with decreased food consumption and body weight. One dog in this group was sacrificed early due to poor clinical condition, but there were no histopathologic findings in this animal or any others in this dose group other than local lesions at the infusion site. As with the monkeys, high dose of solithromycin appeared to exacerbate local infusion site reactions compared with controls and the lower doses (5 and 10 mg/kg).

Oral solithromycin doses up to 220 mg/kg/day did not cause impairment of fertility in adult male or female rats. It did not affect early embryonic development of rat pups exposed *in utero* from conception to gestation day 13. Survival of F_1 pups from dams that received oral solithromycin doses up to 200 mg/kg/day from gestation day 6 to lactation day 20 were comparable to controls, although decreased mean pup weight was observed from birth to lactation day 7 at the high dose. Nonetheless, the solithromycin groups (50, 100, and 200 mg/kg/day) attained developmental landmarks at approximately the same rate as controls. Their behavior, motor activity, learning, and reproductive capacity did not differ from controls. Teratogenicity was not observed in a rat study at doses up to 220 mg/kg/day, the highest dose tested. Developmental toxicity studies conducted in rabbits were limited by maternal toxicity, not unusual for this type of antimicrobial drug. Although increased postimplantation loss secondary to maternal toxicity was observed at 200 mg/kg/day, there

was no indication of teratogenic potential. The no adverse effect level for developmental toxicity in rabbits was 110 mg/kg.

Solithromycin (regardless of metabolic activation) was negative in the Ames bacterial reverse mutation assay and mouse lymphoma assay. It did not induce chromosome aberrations in cultured human lymphocytes. Solithromycin doses of up to 2000 mg/kg (given orally) did not induce micronucleus formation in polychromatic erythrocytes in the bone marrow of rats.

Table 6.1: Comparison of Plasma PK Parameters for Solithromycin and Active Metabolites between Humans, Rats, Dogs, and Monkeys after Repeated Oral or IV Administration

	Cmax (ng/ml)			**$AUC_{0\text{-}24h}$ (ng·hr/ml)**		
	Soli	**NAC**	**214**	**Soli**	**NAC**	**214**
CABP Patients[#]	2200	---	---	26900	---	---
Monkeys 4 weeks daily dose IV						
5 mg/kg	1095	15	0	2840	25	---
12.5 mg/kg (NOAEL[@])	2975	68	109	7455	220	585
25 mg/kg	5860	347	692	20300	2300	6850
Dogs 4 weeks daily dose IV						
5 mg/kg	986	Q	R	4015	Q	R
10 mg/kg (NOAEL[@])	2070	Q	R	12750	Q	R
15 mg/kg	2980	Q	R	28650	Q	R
Rats 13 weeks daily dose Oral						
20 mg/kg	120	ND	ND	557	ND	ND
50 mg/kg	343	ND	ND	2310	ND	ND
125 mg/kg (NOAEL[@])	797	ND	ND	7575	ND	ND
Monkeys 13 weeks daily dose Oral						
20 mg/kg	245	92	254	1100	366	1072
50 mg/kg (NOAEL[@])	1029	642	882	12341	6578	13494
125 mg/kg	2765	1865	2065	60534	38769	46785

CABP IV 400 mg switch to oral 800 mg dosing regimen- parameters calculated first oral dose were used for comparison because the AUC value was highest. Only solithromycin was used to calculate human plasma PK parameters because it accounts for 90% of exposure.

[@] NOAEL, no observed adverse effect level

Soli=Solithromycin; NAC=N-acetyl-CEM-101; 214=CEM-214

Q=In dogs, NAC was below the 1 ng/ml limit of quantitation in most plasma samples. A few samples were just above this limit, but toxicokinetic analysis could not be performed.

R=Although CEM-214 was measurable in most dog plasma samples, the concentrations were low (5 mg/kg: <5 ng/ml; 10 mg/kg: <16 ng/ml; 15 mg/kg: <25 ng/ml and TK analysis was not performed.

ND=Not Done. At the time when the 13-week oral studies were conducted, the significant contribution of N-acetyl-CEM-101 and CEM-214 to exposure had not yet been recognized. Considering only solithromycin parent underestimates the estimation of total exposure in these studies. Monkey plasma samples were reanalyzed retrospectively.

7 Sources of Clinical Data

7.1 Overview of Solithromycin Clinical Program

The solithromycin development program included twenty-four phase 1 studies, one phase 2 trial, and two phase 3 trials (Table 7.1).

Table 7.1: Summary of Trials in the Solithromycin Development Program

Trials (N)	Solithromycin	Moxifloxacin or Levofloxacin	Phase 1 Control	Total
Phase 1[1] (24)	554	0	176	671[2]
Phase 2 (1)	64	68	NA	132
Phase 3 CABP (2)				
CE01-300	424	432	NA	856
CE01-301	432	426	NA	858
TOTAL	1474	926	176	2517

[1]CE01-113 and CE01-115 were phase 1 studies of solithromycin PK in patients with hepatic and renal impairment respectively; only the healthy subjects from these 2 studies are included

[2]The number of phase 1 subjects administered solithromycin plus comparator does not equal the total number of subjects because some subjects received both study drugs in some studies.

Studies for non-CABP conditions, specifically CE01-204 (solithromycin for reduction of airway inflammation in COPD, n=4) and CE01-205 (solithromycin for treatment of NASH, n=4) will be referenced in the safety overview.

Phase 2 and 3 clinical trials were randomized, double-blind, placebo-controlled trials in patients ≥ 18 years of age to evaluate efficacy and safety of solithromycin vs. comparator (levofloxacin in the phase 2 trial, moxifloxacin in the Phase 3 trials) for the treatment of CABP.

In the phase 2 trial, CE01-200, 132 subjects were randomized to receive either oral solithromycin, 800 mg on day 1, followed by 400 mg on days 2-5 (N=64), or oral levofloxacin, 750 mg on days 1-5 (N=68). They were treated as inpatients or outpatients, and were stratified by age (<50 or ≥50 years) and PORT score. The duration of the study was 30-35 days and included screening, 5 days of study drug administration, an End-of-Treatment (EOT) visit on day 5±1; a Test-of-Cure (TOC) visit 4-11 days after the last dose of study drug; and a long-term follow-up (LFU) visit 30-35 days after the first dose of study drug. All patients were from North America; most were male (50.8%), white (82.6%) with a mean age of 55.6 years. Most patients had PORT class II CABP (73.5%).

The co-primary efficacy outcomes were investigator-assessment of clinical response at TOC in the Intent-to-Treat (ITT) and Clinically Evaluable (CE) populations; clinical success (CS) at TOC was defined as continued improvement or complete resolution of baseline signs and symptoms and an improved or stable chest radiograph (if available) at EOT. CS was observed in 84.6% of patients in the solithromycin arm, and 86.5% of patients in the levofloxacin arm in the ITT population, and in 83.6% and 93.1% respectively in the CE population. More patients in the levofloxacin arm had ≥1 treatment-emergent adverse events (TEAEs) [45.6%] compared with the solithromycin arm [29.7%]; most were diarrhea, headache, arthralgia, nausea and vomiting. Three solithromycin recipients had syncope (2) or a fall (1) [total: 4.5%], 1 had AST/ALT elevation to >3xULN (1.5%), and 1 (1.5%) had hyponatremia.

Subsequent sections of this briefing document are focused primarily on the phase 3 CABP trials.

7.2 Phase 3 Trials

7.2.1 Study Designs

Two phase 3 trials, CE01-300 and Study CE01-301, were conducted between 2013 and 2015. Each was a randomized, double-blind, multi-center, multi-national, noninferiority trial comparing solithromycin to moxifloxacin. CE01-300 evaluated a 5-day oral solithromycin regimen while Study CE01-301 evaluated a 7-day intravenous-to-oral solithromycin regimen, as shown in the table below.

Table 7.2: Dosing in Phase 3 Trials

Trial	Solithromycin group	Moxifloxacin group
Study CE01-300 (oral)	Oral dose once a day: • 800 mg on Day 1 • 400 mg on Days 2-5 Total duration of 5 days*	Oral dose once a day: • 400 mg on Days 1-7 Total duration of 7 days
Study CE01-301 (intravenous-to-oral)	Intravenous: • 400 mg daily until oral switch criteria met After oral switch criteria: • 800 mg loading dose • 400 mg daily doses until Day 7 Total duration of 7 days	Intravenous: • 400 mg daily until oral switch criteria met After oral switch criteria: • 400 mg daily doses until Day 7 Total duration of 7 days

*To maintain blinding, solithromycin patients in Study CE01-300 received placebo on Days 6 and 7

Subjects in Study CE01-301 could be switched to oral therapy at investigator discretion if they met all of the following criteria: improvement in baseline clinical signs and symptoms, temperature <38°C orally (with adjustments for tympanic, axillary, or rectal measurements), respiratory rate ≤24 breaths per minute, systolic blood pressure ≥90 mmHg, and oxygen saturation determined by pulse oximetry ≥90% on room air or ≥pre-CABP baseline oxygen saturation on room air.

Subjects in both trials were randomized in a 1:1 ratio to solithromycin or moxifloxacin. The randomization was stratified by geographic region, history of asthma and/or chronic obstructive pulmonary disease, and PORT Risk Class (II versus III/IV).

Enrollment was capped in several ways: PORT Risk Class II at ≤50% in the oral trial and ≤25% in the intravenous-to-oral trial, subjects with receipt of a single dose of a short-acting antibacterial drug at ≤25%, subjects <65 years of age at ≤80%, and enrollment outside of North America at ≤75%.

Inpatient and outpatient male and female patients ≥18 years of age with PORT Risk Class II-IV were enrolled. The diagnosis of CABP required at least 3 signs and symptoms (cough, production of purulent sputum, dyspnea, and chest pain), and at least 1 of fever, hypothermia, or presence of pulmonary rales. There were also to be evidence of bacterial pneumonia on

pulmonary imaging within 48 hours of the first dose of study drug. Subjects received the assigned study drug for treatment of CABP, except in up to 25% of study subjects who were allowed to have received a single dose of a short-acting systemic antibiotic in the 7 days prior to enrollment.

Subjects with certain competing diagnoses such as ventilator-associated pneumonia were excluded. Among exclusion criteria were significant hepatic impairment, known history of myasthenia gravis, or significant renal or hematological impairment; the following laboratory parameters: creatinine clearance <30 mL/min calculated by the Cockcroft-Gault formula, aspartate aminotransferase or alanine aminotransferase >3x upper limit of normal (ULN), total bilirubin >2xULN, or platelet count <50,000 cells/mm^3; certain co-morbid conditions: HIV infection, hepatitis C infection, recent cytotoxic chemotherapy or radiation therapy, or life expectancy <30 days.

Study visits included a baseline visit, an early clinical response (ECR) visit at 72 (-12/+36) hours after the first dose of study drug, an end of treatment (EOT) visit on Day 7 (+2 days), the short-term follow-up (SFU) visit scheduled for Day 12-17, and a late follow-up visit on Day 28-35.

In each trial, the primary efficacy endpoint was ECR as described in the FDA's draft guidance document on developing drugs for treatment of CABP.[1] (Appendix 1)This endpoint was based on the 4 symptoms of cough, dyspnea, chest pain, and sputum production, each rated as absent, mild, moderate, or severe. To be classified as a responder for the primary endpoint, subjects were to have shown improvement from baseline on at least 2 out of the 4 symptoms, no worsening on other symptoms, not received an antibiotic for CABP from the first dose of study drug through 4.5 days (108 hours), and live through the late follow-up visit 28-35 days after the first dose of study drug. Subjects not meeting all of these criteria were classified as non-responders, and subjects had an indeterminate response if there was not enough information to determine if they met criteria for ECR. The sponsor pre-specified a 10% non-inferiority margin. The scientific justification for this margin based on the ECR endpoint is described in the FDA's draft guidance document.

Among secondary efficacy endpoints was early clinical response with improvement in vital signs at the ECR visit. In addition to meeting the criteria for the primary symptom-based endpoint, to be considered a responder for this secondary endpoint subjects were required at the ECR visit to show improvement in all vital signs abnormal at baseline. The abnormal vital signs were fever (body temperature >38°C orally, with adjustments for tympanic, rectal, or axillary measurements), hypotension (systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg), tachycardia (heart rate ≥100 beats per minute), and tachypnea (respiratory rate ≥20 breaths/minute).

Two other secondary efficacy endpoints were investigator assessment of clinical response at the EOT visit and SFU visit. These endpoints defined success as having complete or near-

[1] Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm123686.pdf

complete resolution of the baseline signs and symptoms of CABP, in the overall opinion of the investigator. Failure was defined if additional antibacterial treatment was required due to lack of resolution or worsening of baseline CABP-specific signs and symptoms, or development of new signs and symptoms, complications, or radiographic findings of CABP, or the study drug discontinuation due to an adverse event, or there was death from any cause. Failure for the EOT endpoint was carried forward to the SFU endpoint.

The protocols and statistical analysis plans for the two trials defined several analysis populations. The intent-to-treat (ITT) population was comprised of all randomized subjects. The safety population was comprised of randomized subjects who received any amount of study drug, and essentially overlapped with the ITT population. The microbiological intent-to-treat (mITT) population was comprised of all patients in the ITT population who received any amount of study drug and who had a baseline CABP pathogen in the 48 hour period before the first dose of study drug. Patients with either definitive or probable pathogen identifications could be included. Cultures of respiratory or blood specimens as well as rapid diagnostics such as urinary antigen tests could be used for pathogen identification for this population. Two clinically evaluable populations were defined, the CE-EOT and CE-SFU populations. These included subjects who met key inclusion and exclusion criteria, had non-indeterminate outcome assessments at the respective EOT and SFU visits, and sufficiently complied with the protocol and scheduled use of study drugs. An mITT-2 population where pathogen identification had relied primarily on traditional microbiological cultures was not defined after efficacy results were unblinded.

There were two prespecified co-primary efficacy analyses: (1) the early clinical response in the ITT population using a non-inferiority margin of 10% in each trial and (2) the early clinical response in the pooled mITT population using a non-inferiority margin of 15%. The potential improvement in assay sensitivity due to the greater likelihood of bacterial pneumonia led to the selection of mITT population for the second co-primary analysis; however, its size might not have provided sufficient power to test non-inferiority at a 10% margin. Indeterminate outcome values were handled as failures for the purposes of the primary statistical analyses.

The sample size of 860 subjects per trial was based on the response rate assumption of 73% for solithromycin and moxifloxacin. The trials did not plan to conduct interim efficacy analyses and did not provide for early stopping for futility or sample size modifications. An independent data monitoring committee did monitor safety throughout the studies, and recommended continuing trials following each meeting.

7.2.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics for each phase 3 trials are shown in the Table 7.3. Baseline characteristics were balanced between the solithromycin and moxifloxacin groups, although in the intravenous-to-oral trial CE01-301, the moxifloxacin arm had a greater proportion of males. Approximately 50% of subjects were male and 80% were white. The majority of subjects in both trials were enrolled in Europe, with subjects from the United States comprising approximately 20% of oral CE01-300 and 10% of intravenous-to-oral

CE01-301 trials. About 35% of subjects were ≥65 years old. In oral trial ~50% subjects were in PORT Risk Class II, while in intravenous-to-oral trial it was 25%. Prior antibacterial therapy was reported in 10% of subjects in the oral trail and 25% of subjects in the intravenous-to-oral trial. Among subjects in the United States, 187/190 (98%) had no prior therapy in Study CE01-300 and 70/96 (73%) had no prior therapy in Study CE01-301. The CABP symptoms of cough, dyspnea, chest pain, and sputum production were generally present at baseline. Thirty-six to fifty-five percent of subjects had microbiologically confirmed pneumonia at baseline and belonged to the mITT population. The predominant pathogen was *Streptococcus pneumoniae*, although in CE01-300 a relatively large fraction of subjects had *Haemophilus influenzae* or *Legionella pneumophila*. Quinolone resistance was uncommon, as no subjects had quinolone resistant *S. pneumoniae* and only 4 subjects had quinolone resistant *S. aureus*.

Table 7.3: Baseline Characteristics, ITT Population, CE01-300 and CE01-301Trials

Baseline characteristic	Study CE01-300 (oral therapy)		Study CE01-301 (IV-to-oral)	
	Solithromycin (n = 426)	Moxifloxacin (n =434)	Solithromycin (n = 434)	Moxifloxacin (n =429)
Male	53.3%	52.8%	48.8%	55.0%
Race				
White	81.5%	84.6%	79.3%	77.9%
Black or African American	10.8%	9.2%	5.1%	5.1%
Asian	0.9%	0.9%	14.1%	14.7%
Other	6.8%	5.3%	1.6%	2.3%
Age (years)				
<50	24.6%	29.0%	23.7%	20.3%
50-64	39.0%	39.4%	32.9%	33.8%
65-74	21.8%	17.1%	24.2%	28.0%
≥75	14.6%	14.5%	19.1%	17.9%
Region				
United States	21.6%	22.6%	10.6%	11.7%
Canada	1.6%	1.6%	1.4%	0.2%
Europe	52.3%	51.8%	69.4%	65.3%
Latin America	12.2%	12.4%	1.2%	2.6%
South Africa	12.2%	11.5%	3.5%	5.8%
Asia Pacific	0.0%	0.0%	14.1%	14.5%
PORT Risk Class				
II	50.0%	50.0%	25.1%	24.9%
III	39.4%	40.8%	49.5%	50.1%
IV	10.6%	9.2%	25.3%	24.9%
Creatinine clearance (mL/min)				
<50	9.6%	9.9%	13.6%	14.2%
50-80	34.0%	27.6%	32.9%	32.2%
>80	56.1%	62.4%	53.2%	52.7%
Prior antibacterial therapy	12.4%	10.1%	23.5%	25.6%
Bacteremia	1.4%	3.0%	3.2%	1.9%
Multilobar pneumonia	18.5%	23.5%	28.8%	26.8%
Current smoker	27.7%	27.6%	21.0%	22.6%
History of asthma or COPD	14.6%	14.7%	21.9%	21.4%
Symptoms present				
Cough	100%	100%	100%	99.8%

Baseline characteristic	Study CE01-300 (oral therapy)		Study CE01-301 (IV-to-oral)	
	Solithromycin (n = 426)	Moxifloxacin (n =434)	Solithromycin (n = 434)	Moxifloxacin (n =429)
Dyspnea	96.2%	94.9%	95.6%	96.3%
Chest pain	89.0%	86.9%	80.2%	79.5%
Sputum production	91.8%	95.4%	91.5%	90.2%
Fever	43.7%	45.6%	50.2%	46.2%
Baseline bacterial pathogens				
microbiological ITT	55.2%	52.1%	39.9%	35.7%
Streptococcus pneumoniae	22.5%	23.5%	18.2%	17.7%
Staphylococcus aureus	5.2%	3.2%	4.8%	3.7%
Haemophilus influenzae	18.8%	12.7%	4.1%	4.7%
Mycoplasma pneumoniae	8.7%	9.7%	9.0%	7.0%
Legionella pneumophila	14.3%	14.5%	4.1%	4.0%

8 Evaluation of Efficacy

In both phase 3 trials, solithromycin and moxifloxacin had almost identical response rates of slightly less than 80% for the early clinical response (ECR) primary endpoint in the ITT analysis population. Confidence intervals for the (solithromycin – moxifloxacin) differences in response rates ruled out losses of efficacy of more than 6%, and thus solithromycin met the pre-specified 10% non-inferiority margin in each phase 3 trial. Likewise, response rates for solithromycin and moxifloxacin were similar in the mITT population of the pooled trials, and solithromycin met the pre-specified 15% margin in this co-primary efficacy analysis.

Table 8.1: Early Clinical Response, ITT, CE01-300

Early clinical response	Solithromycin (n = 426)	Moxifloxacin (n = 434)	Difference	95% CI
Responder	333 (78.2%)	338 (77.9%)	0.3%	-5.5% to 6.1%
Nonresponder	81 (19.0%)	84 (19.4%)	-0.3%	
Indeterminate	12 (2.8%)	12 (2.8%)	0.1%	

Table 8.2: Early Clinical Response, ITT, CE01-301

Early clinical response	Solithromycin (n = 434)	Moxifloxacin (n = 429)	Difference	95% CI
Responder	344 (79.3%)	342 (79.7%)	-0.5%	-6.1% to 5.2%
Nonresponder	76 (17.5%)	78 (18.2%)	-0.7%	
Indeterminate	14 (3.2%)	9 (2.1%)	1.1%	

Table 8.3: Co-primary Analysis of Early Clinical Response, mITT, Pooled CE01-300 and CE01-301

Early clinical response	Solithromycin (n = 408)	Moxifloxacin (n = 379)	Difference	95% CI
Responder	315 (77.2%)	299 (78.9%)	-1.7%	-7.4% to 4.2%
Nonresponder	81 (19.9%)	72 (19.0%)		
Indeterminate	12 (2.9%)	8 (2.1%)		

Nonresponse was driven by inadequate improvement or worsening on the symptoms of cough, dyspnea, chest, pain, and sputum production. Rates of programmatically defined nonresponse

classification were rare when due to death (≤2% in both arms of each trial) or concomitant therapy (≤4% in both arms of each trial). The rates of indeterminate outcomes were in the 2-3% range for all primary analyses.

The rate of premature withdrawal from the phase 3 trials was approximately 5%. The overall rate of premature study drug discontinuation was 8%, with the most common reason being an adverse event. The most common protocol deviation was an error in the stratified randomization procedure (7%) due to miscalculation of the PORT score or asthma/COPD status, due to mismatches between electronic case report forms and the interactive web response system used for stratified randomization. However, this protocol violation would not be expected to impact the overall integrity of randomization because the trials in effect still stratified randomization, but with a noisier than intended covariate.

In non-inferiority trials it is important to examine efficacy in groups where there may be greater assay sensitivity to detect treatment effects. This ensures that findings of non-inferiority are not artificially driven by factors such as effective prior therapy, enrollment of subjects without bacterial pneumonia, or subjects with low severity of infection and high rates of spontaneous symptom resolution. Table 8.4 therefore displays results for subgroups of interest. Due to the observed lack of heterogeneity between the two trials and the similarity of the designs, these subgroup analyses pool the trials to decrease random variability. The subgroup results are supportive of efficacy, as solithromycin and moxifloxacin generally led to similar early clinical response rates.

Table 8.4: Early Clinical Response ITT Subgroups, Pooled CE01-300 and CE01-301

Subgroup	Solithromycin	Moxifloxacin	Difference	95% CI
Male	337/439 (76.8%)	368/465 (79.1%)	-2.4%	-8.0% to 3.3%
Female	340/421 (80.8%)	312/398 (78.4%)	2.4%	-3.4% to 8.1%
Age ≥65 years	270/343 (78.7%)	252/334 (75.4%)	3.3%	-3.4% to 9.9%
Age <65 years	407/517 (78.7%)	428/529 (80.9%)	-2.2%	-7.2% to 2.9%
Enrolled in US	103/138 (74.6%)	101/148 (68.2%)	6.4%	-4.7% to 17.5%
Enrolled ex-US	574/722 (79.5%)	579/715 (81.0%)	-1.5%	-5.7% to 2.8%
Prior therapy	124/155 (80.0%)	125/154 (81.2%)	-1.2%	-10.6% to 8.3%
No prior therapy	553/705 (78.4%)	555/709 (78.3%)	0.2%	-4.3% to 4.6%
Microbiological ITT	315/408 (77.2%)	299/379 (78.9%)	-1.7%	-7.7% to 4.2%
Not in mITT	362/452 (80.1%)	381/484 (78.7%)	1.4%	-4.0% to 6.8%
Clinically evaluable	621/779 (79.7%)	629/778 (80.8%)	-1.1%	-5.2% to 2.9%
Not in CE-SFU	56/81 (69.1%)	51/85 (60.0%)	9.1%	-6.5% to 24.8%
PORT Risk Class II	259/322 (80.4%)	257/324 (79.3%)	1.1%	-5.4% to 7.6%
PORT Risk Class III	302/383 (78.9%)	308/392 (78.6%)	0.3%	-5.7% to 6.3%
PORT Risk Class IV	116/155 (74.8%)	115/147 (78.2%)	-3.4%	-13.6% to 6.8%
Asthma or COPD	119/157 (75.8%)	119/156 (76.3%)	-0.5%	-10.4% to 9.5%
No asthma or COPD	558/703 (79.4%)	561/707 (79.3%)	0.0%	-4.2% to 4.3%

Subgroup	Solithromycin	Moxifloxacin	Difference	95% CI
Unilobar pneumonia	512/651 (78.6%)	504/641 (78.6%)	0.0%	-4.5% to 4.5%
Multilobar pneumonia	162/204 (79.4%)	174/217 (80.2%)	-0.8%	-8.9% to 7.4%
CrCl ≤50 mL/min	77/100 (77.0%)	76/104 (73.1%)	3.9%	-8.9% to 16.8%
CrCl >50 mL/min	598/758 (78.9%)	600/755 (79.5%)	-0.6%	-4.8% to 3.6%

In addition to the primary endpoint of early clinical response, additional endpoint assessments were conducted. The following tables show results for the individual phase 3 trials for the secondary endpoint of early clinical response with improvement in vital signs, the secondary endpoint of investigator-assessed clinical response at the EOT visit, investigator assessment of clinical response at the SFU visit, results at the ECR visit for individual CABP symptoms, and several other efficacy analyses. In this table, symptom response at SFU was a prespecified analysis that required chest pain and sputum production to be absent and for cough and dyspnea to be absent or improved since baseline. Early clinical response sustained at SFU was another prespecified analysis that required meeting both the early clinical response criteria used for the primary endpoint and this symptom response definition at the SFU visit. The response rates were similar between solithromycin and moxifloxacin for the additional endpoints considered. Confidence intervals for treatment effects on these endpoints generally ruled out losses of efficacy of more than 10%, and hence non-inferiority conclusions did not appear to strongly depend on the specific definition and timing of the primary efficacy endpoint.

Table 8.5: Analysis of Different Endpoints, ITT, CE01-300

Endpoint	Solithromycin	Moxifloxacin	Difference	95% CI
Early clinical response including vital signs				
Responder	207/426 (48.6%)	210/434 (48.4%)	0.2%	-6.7% to 7.1%
Nonresponder	207/426 (48.6%)	212/434 (48.8%)		
Indeterminate	12/426 (2.8%)	12/434 (2.8%)		
Symptom response at SFU				
Responder	315/426 (73.9%)	329/434 (75.8%)	-1.9%	-7.9% to 4.2%
Nonresponder	79/426 (18.5%)	76/434 (17.5%)		
Indeterminate	32/426 (7.5%)	29/434 (6.7%)		
Early clinical response sustained at SFU				
Responder	273/426 (64.1%)	277/434 (63.8%)	0.3%	-6.4% to 6.9%
Nonresponder	128/426 (30.0%)	133/434 (30.6%)		
Indeterminate	25/426 (5.9%)	24/434 (5.5%)		
Clinical response at EOT				
Clinical success	373/426 (87.6%)	392/434 (90.3%)	-2.8%	-7.2% to 1.7%
Clinical failure	43/426 (10.1%)	31/434 (7.1%)		
Indeterminate	10/426 (2.3%)	11/434 (2.5%)		
Clinical response at SFU				
Clinical success	360/426 (84.5%)	376/434 (86.6%)	-2.1%	-7.1% to 2.8%
Clinical failure	49/426 (11.5%)	38/434 (8.8%)		
Indeterminate	17/426 (4.0%)	20/434 (4.6%)		
Symptoms absent or improved at the ECR visit				
Cough	298/426 (70.0%)	301/434 (69.4%)	0.6%	-5.8% to 7.0%
Dyspnea	306/426 (71.8%)	335/434 (77.2%)	-5.4%	-11.4% to 0.7%

Endpoint	Solithromycin	Moxifloxacin	Difference	95% CI
Chest pain	344/426 (80.8%)	356/434 (82.0%)	-1.3%	-6.7% to 4.2%
Sputum production	284/426 (66.7%)	285/434 (65.7%)	1.0%	-5.6% to 7.6%
Survival	420/426 (98.6%)	428/434 (98.6%)	0.0%	-1.6% to 1.6%

Table 8.6: Analysis of Different Endpoints, ITT, Study CE01-301

Endpoint	Solithromycin	Moxifloxacin	Difference	95% CI
Early clinical response including vital signs				
Responder	185/434 (42.6%)	167/429 (38.9%)	3.7%	-3.1% to 10.5%
Nonresponder	235/434 (54.1%)	253/429 (59.0%)		
Indeterminate	14/434 (3.2%)	9/429 (2.1%)		
Symptom response at SFU				
Responder	346/434 (79.7%)	330/429 (76.9%)	2.8%	-2.9% to 8.5%
Nonresponder	59/434 (13.6%)	72/429 (16.8%)		
Indeterminate	29/434 (6.7%)	27/429 (6.3%)		
Early clinical response sustained at SFU				
Responder	297/434 (68.4%)	290/429 (67.6%)	0.8%	-5.6% to 7.3%
Nonresponder	117/434 (27.0%)	125/429 (29.1%)		
Indeterminate	20/434 (4.6%)	14/429 (3.3%)		
Clinical response at EOT				
Clinical success	381/434 (87.8%)	387/429 (90.2%)	-2.4%	-6.8% to 2.0%
Clinical failure	42/434 (9.7%)	31/429 (7.2%)		
Indeterminate	11/434 (2.5%)	11/429 (2.6%)		
Clinical response at SFU				
Clinical success	367/434 (84.6%)	380/429 (88.6%)	-4.0%	-8.8% to 0.8%
Clinical failure	54/434 (12.4%)	35/429 (8.2%)		
Indeterminate	13/434 (3.0%)	14/429 (3.3%)		
Symptoms absent or improved at the ECR visit				
Cough	298/434 (68.7%)	299/429 (69.7%)	-1.0%	-7.4% to 5.4%
Dyspnea	337/434 (77.6%)	335/429 (78.1%)	-0.4%	-6.2% to 5.3%
Chest pain	364/434 (83.9%)	367/429 (85.5%)	-1.7%	-6.7% to 3.4%
Sputum production	299/434 (68.9%)	280/429 (65.3%)	3.6%	-2.9% to 10.1%
Survival	429/434 (98.8%)	422/429 (98.4%)	0.5%	-1.3% to 2.3%

In the intravenous-to-oral Study CE01-301, the rate of investigator-assessed clinical failure at the SFU visit were higher for solithromycin than moxifloxacin by an amount meeting nominal statistical significance (54/434 [12.4%] for solithromycin versus 35/429 (8.2%) for moxifloxacin; difference = 4.3%; p = 0.05). The potential signal for reduced efficacy was examined in more detail. The numerically higher rate of clinical failure could not be explained by worse symptomatic improvement at the SFU for solithromycin, because as shown in the above table numerical trends favored solithromycin in this trial for the pre-specified endpoint of symptom response at the SFU visit. There was no evidence that solithromycin was less efficacious in severe pneumonia (higher PORT scores), elderly, or patients with impaired renal function.

Table 8.7: Clinical Success at the SFU visit in ITT Subgroups, CE01-301

Subgroup	Solithromycin	Moxifloxacin	Difference	95% CI
Age ≥65 years	160/188 (85.1%)	173/197 (87.8%)	-2.7%	-10.1% to 4.6%
Age <65 years	207/246 (84.1%)	207/232 (89.2%)	-5.1%	-11.6% to 1.4%
PORT Risk Class II	90/109 (82.6%)	97/107 (90.7%)	-8.1%	-18.0% to 1.8%
PORT Risk Class III	189/215 (87.9%)	194/215 (90.2%)	-2.3%	-8.7% to 4.0%
PORT Risk Class IV	88/110 (80.0%)	89/107 (83.2%)	-3.2%	-14.4% to 8.0%
CrCl ≤50 mL/min	49/59 (83.1%)	50/61 (82.0%)	1.1%	-13.6% to 15.8%
CrCl >50 mL/min	317/374 (84.8%)	327/364 (89.8%)	-5.1%	-10.1% to 0.0%

Results for ECR and investigator-assessed clinical response at the SFU visit for the pooled trials in subgroups of the mITT population defined by baseline pathogen are shown in Table 8.8. There were limited data on subjects with macrolide resistant bacterial pneumonia.

Table 8.8: Results for early clinical response at 72 (-12/+36) hours and investigator-assessed clinical response at the SFU visit by baseline pathogen, mITT, pooled CE01-300 and CE01-301

Pathogen subgroup	Early clinical response		Clinical response at SFU	
	Solithromycin	Moxifloxacin	Solithromycin	Moxifloxacin
S. pneumoniae	135/175 (77.1%)	149/178 (83.7%)	146/175 (83.4%)	155/178 (87.1%)
Macrolide resistant	17/24 (70.8%)	17/22 (77.3%)	22/24 (91.7%)	19/22 (86.4%)
S. aureus	31/43 (72.1%)	22/30 (73.3%)	32/43 (74.4%)	27/30 (90.0%)
Macrolide resistant	3/7 (42.9%)	3/3 (100%)	5/7 (71.4%)	3/3 (100%)
H. influenzae	78/98 (79.6%)	61/75 (81.3%)	79/98 (80.6%)	68/75 (90.7%)
M. catarrhalis	26/32 (81.2%)	20/26 (76.9%)	27/32 (84.4%)	23/26 (88.5%)
L. pneumophila	61/79 (77.2%)	64/80 (80.0%)	71/79 (89.9%)	75/80 (93.8%)
M. pneumoniae	65/76 (85.5%)	56/72 (77.8%)	65/76 (85.5%)	65/72 (90.3%)
Macrolide resistant	1/1 (100%)	2/2 (100%)	1/1 (100%)	2/2 (100%)

Efficacy Summary and Conclusions

The study populations in the phase 3 trials were appropriate for non-inferiority assessment in CABP and included a relatively large proportion of subjects with no prior antibacterial therapy, microbiologically confirmed pneumonia, and high PORT scores. Randomization balanced the solithromycin and moxifloxacin groups on key baseline factors. In both trials, solithromycin demonstrated non-inferiority with respect to the pre-specified primary analyses of early clinical response, and response rates were numerically similar to moxifloxacin. There was a low degree of missing or indeterminate outcome data. Subgroup analyses of ECR supported efficacy. Solithromycin and moxifloxacin also had similar response rates in most analyses of secondary endpoints or other efficacy endpoints. Although solithromycin led to a numerical increase in rates of investigator-assessed clinical failure in intravenous-to-oral Study CE01-301 and data on subjects with baseline isolates that were macrolide-resistant

were limited, the phase 3 trials provided evidence that oral and intravenous solithromycin are effective for the treatment of CABP.

9 Evaluation of Safety

9.1 Summary

A significant safety signal for hepatotoxicity was observed in the solithromycin development program. The rates of transaminase elevations were higher in solithromycin- treated patients than those treated with moxifloxacin and were related to solithromycin exposure. The high rate of infusion site-related reactions associated with solithromycin (31.3%) as compared to moxifloxacin (5.2%) is another safety concern.

Rates of deaths and serious adverse events observed in the solithromycin and moxifloxacin arms were similar. The most common treatment-emergent adverse events in both treatment arms were diarrhea, nausea, vomiting, headache and dizziness. In 856 solithromycin-treated patients in the phase 3 trials, approximately 95% completed treatment. The incidence of study drug discontinuation was similar for solithromycin and placebo in the oral study, CE01-300. Higher rates of discontinuation in the solithromycin arm (4.9%) compared to moxifloxacin (3.7%) occurred in the IV-to-oral trial CE01-301, largely due to infusion site reactions.

9.2 Methods

The safety analysis focuses on the results of the two Phase 3 trials, CE01-300 and CE01-301. The safety population includes randomized subjects who received at least one dose of solithromycin. The safety results were pooled across two studies, with the exception of infusion-related reactions that occurred only in CE01-301. Particular attention was paid to the major toxicities seen with telithromycin, i.e. hepatotoxicity, visual disturbances, and loss of consciousness. Patients with myasthenia gravis were excluded from the Phase 3 trials.

9.3 Overall Exposure to Solithromycin

A total of 1474 subjects have been exposed to solithromycin during its development (see Table 7.1). In phase 1, 554 healthy adult subjects received varying doses of solithromycin, while in phase 2, 64 patients with CABP received a therapeutic dose of solithromycin. In the two phase 3 trials, CE01-300 and CE01-301, a total of 856 patients received solithromycin, 424 subjects received oral drug and 432 subjects received IV and oral solithromycin. A total of 858 patients received moxifloxacin, 432 received oral, and 426 received IV and oral moxifloxacin. The key analysis populations are tabulated below.

Table 9.1: Key Study Populations in the Phase 3 Trials

Trial	Key Study Populations	Solithromycin Oral n (%)	Moxifloxacin Oral n (%)
CE01-300	ITT	426	434
	Safety	424 (99.5)	432 (99.5)
	Microbiological ITT (mITT)	235 (55.2)	226 (52.1)
CE01-301	ITT	434	429

Trial	Key Study Populations	Solithromycin Oral n (%)	Moxifloxacin Oral n (%)
	Safety	432 (99.5)	426 (99.5)
	Microbiological ITT (mITT)	173 (39.9)	153 (35.7)

In the phase 3 trials, 93.1% and 94.6% of patients in the pooled solithromycin and moxifloxacin arms, respectively received at least 5 days of IV or oral drug therapy. In CE01-301 (IV-to-oral), 11% and 12.5% in the solithromycin and moxifloxacin arms, respectively, received IV drug for the full 7-day duration. In patients who switched from IV to oral drug, most switched after 3 to 4 days.

9.4 Study Discontinuation

Most patients, 94.9% in the pooled solithromycin and 95.8% in the moxifloxacin arm, completed the study. In CE01-301, 6% of patients in the solithromycin arm and 4% of patients in the moxifloxacin arm discontinued from the study. The most frequent reason for discontinuation was withdrawal of consent, largely driven by infusion-related reactions in the solithromycin arm.

Table 9.2: Premature Withdrawal from Study in the Phase 3 Trials

	CE01-300		CE01-301		Total	
	Soli Oral (N=424)	Moxi Oral (N=432)	Soli IV to Oral (N=432)	Moxi IV to Oral (N=426)	Soli Pooled (N=856)	Moxi Pooled (N=858)
Premature Withdrawal from Study	18 (4.2)	19 (4.4)	26 (6.0)	17 (4.0)	44 (5.1)	36 (4.2)
Adverse Event	0	0	5 (1.2)	1 (0.2)	5 (0.6)	1 (0.1)
Lost to Follow-up	2 (0.5)	5 (1.2)	0	0	2 (0.2)	5 (0.6)
Withdrew consent	9 (2.1)	5 (1.2)	14 (3.2)	6 (1.4)	23 (2.7)	11 (1.3)
Non-compliance	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)
Death	6 (1.4)	6 (1.4)	5 (1.2)	7 (1.6)	11 (1.3)	13 (1.5)
Other	1 (0.2)	2 (0.5)	2 (0.5)	2 (0.5)	3 (0.4)	4 (0.5)

Source: Table 19, ISS

Most patients in the pooled phase 3 trials, 93.1% in the moxifloxacin arm and 91.6% in the solithromycin arm, completed study drug administration; Table 9.3 highlights the reasons for premature discontinuation of study drug. Overall, there were more patients who discontinued study drug in the pooled solithromycin arm compared with the pooled moxifloxacin arm, primarily due to infusion-related reactions in the solithromycin-treated patients in CE01-301.

Table 9.3: Discontinuation of Study Drug in the Safety Population of the Phase 3 Trials

	CE01-300		CE01-301		Pooled Phase 3 Population	
Reason for Discontinuation of Study Drug	Soli N=424 n (%)	Moxi N=432 n (%)	Soli N=432 n (%)	Moxi N=426 N (%)	Soli N=856 n (%)	Moxi N=858 n (%)
Adverse Event	16 (3.8)	13 (3.0)	21 (4.9)	17 (3.7)	36 (4.2)	28 (3.3)
Clinical failure	6 (1.4)	5 (1.2)	14 (3.2)	8 (1.9)	20 (2.3)	13 (1.5)
Clinically significant laboratory	0	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.1)	3 (0.3)

	CE01-300		CE01-301		Pooled Phase 3 Population	
Reason for Discontinuation of Study Drug	**Soli N=424 n (%)**	**Moxi N=432 n (%)**	**Soli N=432 n (%)**	**Moxi N=426 N (%)**	**Soli N=856 n (%)**	**Moxi N=858 n (%)**
abnormality						
Other*	6 (1.4)	7 (1.7)	10 (2.3)	10 (2.3)	16 (1.9)	17 (2.0)
Study drug not taken	2 (0.5)	1 (0.2)	1 (0.2)	2 (0.5)	3 (0.4)	3 (0.3)

Sixteen patients (3.8%) discontinued solithromycin due to adverse events (AEs) in CE01-300 and among these AEs, allergic dermatitis (1 patient), increase in hepatic enzymes (1 patient), nausea (2 patients) and vomiting (1 patient) were considered related to solithromycin; 13 patients (3%) discontinued moxifloxacin. The rest of the AEs resulting in discontinuation of solithromycin were related to worsening or complication of the underlying condition.

In CE01-301, there were 21 (4.9%) and 17 (3.7%) patients who prematurely discontinued solithromycin and moxifloxacin, respectively. Ten (2.3%) patients discontinued solithromycin due to an infusion-related reaction. One solithromycin-treated patient had anaphylaxis, and another had urticaria. In contrast, 5 patients (1.2%) in the moxifloxacin arm experienced anaphylaxis (1), urticaria (2), or pruritus/rash (3). No other noticeable imbalances in adverse events resulting in study drug discontinuation between the solithromycin and comparator arms were observed.

9.5 Deaths

There were 24 deaths in the phase 3 trials, 11 (1.3%) occurred in the solithromycin arm and 13 (1.5%) occurred in the moxifloxacin arm; 2 patients in the moxifloxacin arm died of complications of pulmonary malignancies several months after the end of the study period. In the phase 2 trial, there was one death in the levofloxacin arm. There were no deaths in the phase 1 trials.

All deaths in the phase 3 trials, regardless of cause, were categorized by the applicant as a clinical failure. Three of eleven deaths on solithromycin were considered unrelated to the study drug: 1 had an autopsy-proven acute MI on Day 3, 1 died presumably as a result of hyperkalemia and hypoglycemia on Day 5, and 1 had catastrophic respiratory deterioration and sepsis within hours of receiving her first dose of solithromycin.

Another patient, an 81 year old woman who was judged a clinical success at EOT upon completion of a 7-day course of IV to oral solithromycin, experienced sudden death at home on Day 8. She was chronically treated with rivaroxaban for atrial fibrillation, and during her hospitalization, progressive anemia without overt blood loss was noted. A possible drug-drug interaction between solithromycin, a CYP3A4 inhibitor and rivaroxaban, a CYP3A4 substrate could have increased rivaroxaban exposure and potentially contributed to anemia and death. A 67 year old man with cardiac and hepatic co-morbidities and diabetes, and an abnormal baseline ECG showing frequent PACs/PVCs, a single ventricular couplet and interventricular conduction delay was improving clinically on Day 3, but suffered sudden cardiac death that

same day. Ventricular fibrillation or torsades de pointes could have accounted for the death. No ECGs were done post baseline.

In 5 patients who died, there was concern for therapeutic failure of solithromycin contributing to death, and one patient might have experienced both failure of therapy and a solithromycin-related cardiac event. Of the 11 patients in the moxifloxacin arm who died during the study period, 1 was a definite treatment failure, and 2 were possible treatment failures, although complete clinical details were lacking.

9.6 Serious Adverse Events

In the pooled phase 3 trials, 58 (6.8%) patients in the solithromycin arm and 50 (5.8%) patients in the moxifloxacin arm experienced serious adverse events (SAEs).
In CE01-300, 1.4% (6/432) and 2.1% (9/424) of patients and 1.4% (6/426) and 2.8% (12/432) of patients in CE01-301 in the moxifloxacin and solithromycin arms, respectively were reported to have adverse events indicative of worsening bacterial pneumonia and its complications when the PTs (empyema/infectious pleural effusion, lung abscess, pneumonia/lobar pneumonia, respiratory tract infection and septic shock/sepsis) were combined.

Cardiac SAEs were slightly higher in both arms of CE01-301 compared to both arms of CE01-300, but comparable between treatment groups. One individual in the moxifloxacin arm had an SAE of hepatorenal syndrome, but no other liver-related SAEs were noted in either arm. Two patients in the solithromycin arm had cerebrovascular accidents. Anaphylaxis occurred in one patient in each treatment arm, and there was one episode of urticaria in the solithromycin arm.

9.7 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAE) are defined as any AE that started or worsened at, during the time of, or after the first dose of the study drug through the last study visit. The following table summarizes the occurrence of TEAEs in the phase 3 trials.

Table 9.4: Summary of TEAEs, Phase 3 Trials

	CE01-300		CE01-301		Pooled Phase 3 Studies	
	Solithromycin N=424 n (%)	Moxifloxacin N=432 n (%)	Solithromycin N=432 n (%)	Moxifloxacin N=426 n (%)	Solithromycin N=856 n (%)	Moxifloxacin N=858 n (%)
Subjects with TEAEs	155 (36.6)	154 (35.6)	223 (51.6)	148 (34.7)	378 (44.2)	302 (35.2)
TEAEs excluding IV infusion site reactions	155 (36.6)	154 (35.6)	149 (34.5)	140 (32.9)	304 (35.5)	294 (34.3)

As seen in Table 9.4, TEAEs occurred at a much higher rate in patients who received IV solithromycin compared to any other arm across both trials. This was largely driven by infusion-related reactions, and when these are excluded, the occurrence of TEAEs is comparable among both treatment arms in both trials. The following table shows TEAEs that occurred in ≥2% of patients in the pooled trials.

Table 9.2: Selected Treatment Emergent Adveres Events in ≥2% of Subjects, Phase 3 Safety Population

Preferred Term	CE01-300		CE01-301		Pooled Phase 3 Population	
	Soli N=424 n(%)	Moxi N=432 n(%)	Soli N=432 n(%)	Moxi N=426 n(%)	Soli N=856 n(%)	Moxi N=858, n(%)
Diarrhea	18 (4.2)	28 (6.5)	19 (4.4)	25 (5.9)	37 (4.3)	53 (6.2)
Nausea	15 (3.5)	17 (3.9)	14 (3.2)	7 (1.6)	29 (3.4)	24 (2.8)
Vomiting	10 (2.4)	10 (2.3)	4 (0.9)	3 (0.7)	14 (1.6)	13 (1.5)
Pneumonia	7 (1.7)	5 (1.2)	11 (2.5)	5 (1.2)	18 (2.1)	10 (1.2)
Hypokalemia	2 (0.5)	3 (0.7)	11 (2.5)	9 (2.1)	13 (1.5)	12 (1.4)
Headache	19 (4.5)	11 (2.5)	15 (3.5)	18 (4.2)	34 (4.0)	29 (3.4)
Dizziness	9 (2.1)	7 (1.6)	11 (2.5)	5 (1.2)	20 (2.3)	12 (1.4)
Insomnia	2 (0.5)	4 (0.9)	9 (2.1)	5 (1.2)	11 (1.3)	9 (1.0)
Hypertension	6 (1.4)	5 (1.6)	6 (1.4)	10 (2.3)	12 (1.4)	15 (1.7)
Abdominal Pain	9 (2.1)	10 (2.3)	3 (0.7)	4 (0.9)	12 (1.4)	14 (1.6)
Infusion Related Preferred Terms						
Infusion Site Erythema	0	0	19 (4.4)	2 (0.5)	-	-
Infusion Site Pain	0	0	45 (10.4)	6 (1.4)	-	-
Infusion Site Phlebitis	0	0	43 (10.0)	4 (0.9)	-	-
Infusion Site Thrombosis	0	0	9 (2.1)	7 (1.6)	-	-
Infusion Related Reaction	0	0	35 (8.1)	1 (0.2)	-	-

Infusion-related reactions were more common in the solithromycin-treated patients. Otherwise, the rates of TEAEs were balanced overall between the treatment groups.

There were 42 patients with uncategorized baseline hepatic impairment (HI) in the pooled solithromycin arm and 53 patients in the moxifloxacin arm; AST or ALT >3x ULN or total bilirubin >2x ULN were exclusion criteria. TEAEs occurred similarly in patients with and without HI in the solithromycin arm. More SAEs occurred in patients with HI than without HI in both treatment arms (11.9% with HI vs. 6.5% without HI in the solithromycin arm and 9.4% with HI and 5.6% without HI in the moxifloxacin arm).

Severe renal impairment was an exclusion criterion but there were 9 patients in the solithromycin arm and 6 patients in the moxifloxacin arm with a creatinine clearance (CrCl) <30 ml/min. Of note, these 15 patients received the full recommended therapeutic dose of solithromycin. Though the numbers are very small, the incidence of both TEAEs and SAEs in both treatment groups was noted to be increasing with decreasing CrCl as shown in the table below. In the solithromycin group hepatic enzyme elevations occurred in 3 (33%) different patients, of whom 2 had ALT elevations >3x ULN.

Table 9.6: Incidence of TEAEs (Excluding Infusion Site Events) and SAEs by Renal Impairment

	Solithromycin		Moxifloxacin	
	N	n (%)	N	n (%)
Any TEAEs				
>59 mL/min	671	222 (33.1)	671	216 (32.2)
30 mL/min to 59 mL/min	174	75 (43.1)	177	72 (40.7)
<30 mL/min	9	7 (77.8)	4	6 (66.7)
Any SAE				
>59 mL/min	671	35 (5.2)	671	36 (5.4)
30 mL/min to 59 mL/min	174	21 (12.1)	177	13 (7.3)
<30 mL/min	9	2 (22.2)	6	1 (16.7)

There were significant elevations in liver enzymes which will be discussed in Section 9.8.

9.8 Adverse Reactions of Special Interest and Submission Specific Safety Issues

9.8.1 Hepatotoxicity

For additional assessment of the liver toxicity profile of solithromycin, the reader is referred to the attached analysis by Dr. Mark Avigan.

Solithromycin is closely structurally related to telithromycin, an FDA-approved ketolide, and its history is germane to this discussion. Despite a low occurrence of hepatic events in the initial telithromycin NDA safety database of almost 3400 patients, the post-market phase was marked by the occurrence of more than 40 cases of severe telithromycin-related hepatotoxicity resulting in 4 deaths and a liver transplantation. Severe and sometimes fatal exacerbations of myasthenia gravis and occurrences of visual disturbance and loss of consciousness in patients treated with telithromycin were reported. Some of these events are thought to be mediated through binding of telithromycin to the nicotinic acetylcholine receptor (nACh).
The applicant had postulated that reduced binding of solithromycin to the nACh receptor relative to telithromycin would result in a reduction in hepatic adverse effects.

Nonclinical profile: Nonclinical studies in rats, monkeys and dogs point to the liver as a target organ of toxicity; single and repeat-dose solithromycin achieved high concentrations in the liver and lung, and with continued exposure, the drug and its metabolites accumulated in liver cells. Dose-dependent biliary inflammation, hepatocellular degeneration, and enzyme elevation were seen in 28-day toxicology studies in rats, and Kupffer cell hyperplasia suggestive of phospholipidosis were seen in cynomolgus monkeys.

Phase 1 studies: Among 550 healthy volunteers with systemic exposure to solithromycin, 7.5% (41 subjects) had ALT elevations above the upper limit of normal (ULN). Two subjects discontinued solithromycin due to ALT elevation >5x ULN.

Phase 2 trial: Among 64 patients treated with solithromycin, 1 (1.6%) had a peak ALT elevation to >3xULN, compared with 2/68 (2.9%) in the levofloxacin arm.

Phase 3 trials: In the phase 3 pooled safety database, overall ALT elevations of >3xULN, >5xULN, and >10xULN were seen in 7.2%, 2.4%, and 0.1% of patients in the solithromycin arm vs. 3.6%, 1% and 0.2% of patients in the moxifloxacin arm. This incidence was particularly marked in the IV-to-oral study where the incidences of peak ALT elevations >3xULN and >5xULN in the solithromycin arm were 9.1% and 3.1% vs. 3.6% and 0.7% in these categories respectively, in the moxifloxacin arm.

Table 9.3: Liver Function Test (LFT) Abnormalities at any Post-Baseline Visit, Phase 3 Safety Population

LFTs	Degree of Elevation	CE01-300 n (%)		CE01-301 n (%)	
		Solithromycin N=412	**Moxifloxacin N=423**	**Solithromycin N=418**	**Moxifloxacin N=415**
ALT	>ULN	172 (41.7)	141 (33.3)	198 (47.4)	122 (29.4)
	>3x ULN	22 (5.3)	15 (3.5)	38 (9.1)	15 (3.6)
	>5x ULN	7 (1.7)	5 (1.2)	13 (3.1)	3 (0.7)
	>10x ULN	1 (0.2)	2 (0.5)	0	0
	>20x ULN	1 (0.2)	1 (0.2)	0	0
AST		**Solithromycin N=406**	**Moxifloxacin N=416**	**Solithromycin N=416**	**Moxifloxacin N=409**
	>ULN	130 (32)	112 (26.9)	154 (37)	97 (23.7)
	>3x ULN	10 (2.5)	8 (1.9)	20 (4.8)	10 (2.4)
	>5x ULN	4 (1)	4 (1)	9 (2.2)	2 (0.5)
	>10x ULN	2 (0.5)	2 (0.5)	2 (0.5)	0
	>20x ULN	0	1 (0.2)	0	0
Bilirubin		**Solithromycin N=412**	**Moxifloxacin N=422**	**Solithromycin N=416**	**Moxifloxacin N=413**
	>ULN	15 (3.6)	16 (3.8)	21 (5.0)	17 (4.1)
	>2xULN	2 (0.5)	0	2 (0.5)	2 (0.5)
ALP		**Solithromycin N=411**	**Moxifloxacin N=423**	**Solithromycin N=417**	**Moxifloxacin N=415**
	>1.5xULN	22 (5.4)	17 (4)	21 (5)	7 (1.7)
	>3.0xULN	4 (0.9)	1 (0.2)	0	1 (0.2)
	>5.0xULN	3 (0.7)	1 (0.2)	0	0
	>10xULN	0	0	1 (0.2)	0

In CE01-301, the increased exposure with IV dosing of solithromycin, followed by an oral loading dose on the day of IV-oral switch, and the 7-day duration of treatment may all have contributed to the increased incidence of ALT elevation observed in these patients compared to patients in CE01-300.

Peak transaminase elevations with solithromycin occurred at different times in the oral and IV-to-oral trials. In CE01-300, the majority of peak transaminase elevations were seen approximately 4 days after initiation of treatment (though liver enzyme testing was not done between days 1 and 4), and almost 30% (6/22) were seen after completion of the treatment course (days 6-15). In contrast, in CE01-301, 50% (19/38) of patients in the solithromycin arm had peak ALT elevations within the first 5 days after initiation of treatment, but 50% (19/38) had peak elevations between days 6 and 15.

Solithromycin was discontinued prematurely in 2 patients due to hepatic enzyme elevations, but in general, transaminase elevations in the majority of patients appeared to be asymptomatic and generally transient. Liver adaptation was observed in a subset of patients with solithromycin-related hepatic enzyme elevations, i.e., AST and ALT levels decreased while patients were still on solithromycin; however, adaptation was not always observed or predictable.

Although no patient in the phase 3 trials fulfilled Hy's Law criteria, patterns of liver injury ranged from mild to more pronounced transaminase elevations with normal ALP and bilirubin levels in some cases, and with elevations of ALP in others. With fewer than 1000 CABP patients exposed to solithromycin for 5-7 days, the ability to detect a Hy's Law signal was limited by both the number of patients and short duration of exposure.

Early data from studies of solithromycin administration for 28 days and 13 weeks for reduction of airway inflammation in COPD (n=4) and for treatment of NASH (n=6) respectively, provides some safety information regarding longer exposure. To date, 3/4 patients (75%) in the COPD study have had significant hepatic enzyme elevations. These 3 patients each had a different pattern of hepatic injury as described below.

1. A 69-year-old male patient with COPD and benign prostatic hypertrophy on fluticasone-salmeterol and salbutamol inhalers and finasteride 5mg PO daily, was treated with solithromycin 400 mg once a day for a planned 28-day course. Liver enzymes were normal at baseline and Day 8, but elevated at Day 15; nonetheless, the study drug was continued and subsequent liver enzyme changes are shown in the table below:

Table 9.8: Patient 001 (COPD Study CE01-204)

Visit/ Day	ALT		AST		Bilirubin		ALP		WBC $\times 10^3/\mu L$	EOS $\times 10^3/\mu L$	Creat mg/dL	PT INR
	U/L	×ULN	U/L	×ULN	Total ULN:1.2 mg/dL	Direct ULN:0.4 mg/dL	U/L	×ULN				
Day 1	20	0.5	29	0.7	0.7	0.2	78	0.6	5.7	0.3	0.8	
Day 8	32	0.8	34	0.8	0.8	0.2	74	0.6	7.1	0.2	0.8	
Day 15	95	1.4	106	2.6	0.8	0.3	277	2.1	6.3	0.4	0.9	0.9
Day 23	476	11.9	368	9.0	4	2.2	1316	10.1	9.5	1.6	0.8	0.9
Day 24	427	10.7	322	7.9	2.9	1.5	1155	8.9	9.2	1.8	0.7	1
Day 28	269	6.7	144	3.5	1.2	0.5	969	7.5	6.8	1.2	0.7	
Day 34	92	2.3	59	1.4	0.8		471	3.6	6.1	0.7	0.7	0.9
Day 52	27	0.7	22	0.5	0.5	0.2	170	1.3	7.2	0.4	0.7	

By Day 23, the patient had become mildly icteric and developed pruritus, but was not hospitalized; significant eosinophilia was also noted. Solithromycin and finasteride were immediately discontinued, and additional workup found that ultrasound of the liver was normal, and a viral hepatitis screen was negative. The patient's liver enzymes started to decrease on Day 24 and were followed until Day 52 when all hepatic enzyme levels had returned to normal, and eosinophilia had resolved.

2. A 65-year-old woman with normal hepatic enzymes at baseline was noted to have elevation of ALT to 141 U/L (3.5xULN) and AST to 89 U/L (2.2xULN) on Day 26 at the end of

therapy. On Day 31, off therapy, ALT levels had increased to 7.3xULN with a mild ALP increase and a normal bilirubin. Enzyme levels subsequently started to decline but she refused further follow-up after Day 37.

3. A 73-year-old male with normal hepatic enzymes at baseline, had ALT elevation to 4.1xULN and AST elevation to 2.7xULN with a minor elevation of ALP on day 15. Solithromycin was continued, and a week later, a decline in ALT to 1.3xULN and a normal AST and ALP were documented.

Enrollment in the COPD study has been halted pending modification of the dosing regimen.

In the NASH study, 1 out of 6 subjects enrolled to date experienced a 4.5xULN ALT elevation on Day 29 of a planned 13-week course of solithromycin 400 mg daily. A protocol amendment changed the solithromycin dose to 200 mg once a day with the option to decrease the dose to 200 mg three times a week in the event of liver enzyme elevations.

Summary: In the solithromycin development program to date, a range of patterns of liver injury associated with exposure to solithromycin were observed. There was a spectrum of both hepatocellular and cholestatic signatures of hepatotoxicity, in one case accompanied by eosinophilia and suggesting hypersensitivity as a mechanism for liver injury. These findings were noted among a relatively small number of patients treated with solithromycin for CABP (n=920), normal healthy volunteers exposed to the drug in PK studies, and a small number of patients administered solithromycin in studies of other conditions. We conclude that these findings comprise a genuine liver injury signal.

Despite the differences in chemical structure, the hepatic adverse effects seen with solithromycin during its development program exceed the pre-marketing hepatic signal seen with telithromycin. Significant gaps in knowledge of the hepatic toxicity profile of solithromycin exist. For example, the likelihood of serious idiosyncratic liver injury in a larger population and the impact of prior sensitization to macrolides on solithromycin-induced liver injury are unknown.

The difference in peak ALT values between the treatment groups in CABP trials should be considered in the context of the established moxifloxacin safety profile. The WARNINGS AND PRECAUTIONS Section in the moxifloxacin product labeling describes “Other Serious and Sometimes Fatal Adverse Reactions” that include “hepatitis; jaundice; acute hepatic necrosis or failure”.

9.8.2 Infusion-related Reactions

Infusion-related adverse reactions occurred in 31.3% of patients who received IV solithromycin compared with 5.2% of moxifloxacin recipients, and led to discontinuation of solithromycin in 10 patients (2.3%) [See Sections 9.4 and 9.7]. None of these reactions were life-threatening, but limited the ability to continue IV solithromycin. Administration of parenteral solithromycin through a central line was not evaluated in the clinical program.

9.8.3 Visual Disorders

In the CABP development program, visual disorders were recorded in 11 patients, 9 of them in the solithromycin arm. Two patients in phase 1 studies had blurred vision, while 1 had asthenopia (“tired eyes”).

9.8.4 Loss of Consciousness

In the phase 3 trials, 1 (0.1%) patient in the solithromycin arm had syncope, and 1 (0.1%) developed hypotonia as compared to 1(0.1%) patient with syncope and 2 (0.2%) with hypotonia in the moxifloxacin arm.

10 Points for Advisory Committee Discussion

1. Has the Applicant provided substantial evidence of the efficacy of solithromycin for the treatment of community acquired bacterial pneumonia?

    - If yes, please provide any recommendations concerning labeling.
    - If no, what additional studies/analyses are needed?

2. Has the risk of hepatotoxicity with solithromycin been adequately characterized?
    - If yes, please provide any recommendations for labeling
    - If no, please discuss additional studies that are needed to further characterize the risk

3. Do the risks of solithromycin, including hepatotoxicity outweigh the potential benefits in the treatment of CABP?
    - If yes, please provide any recommendations for labeling
    - If no, what additional studies/analyses are needed?

Appendix 1: FDA Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment
Appendix 2: Hepatic Safety Review (Mark Avigan, MD, Hepatologist, Office of Surveillance and Epidemiology)

Guidance for Industry

Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Sumathi Nambiar, MD, MPH or Joseph Toerner, MD, MPH at 301-796-1300.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2014
Clinical/Antimicrobial

Revision 2

Guidance for Industry

Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Antimicrobial

Revision 2

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Guidance for Industry[1]
Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of community-acquired bacterial pneumonia (CABP). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for the treatment of CABP.[2] This draft guidance is intended to serve as a focus for continued comments and discussions among the Division of Anti-Infective Products, pharmaceutical sponsors, the academic community, and the public.[3]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[4]

[1] This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products regulated by CDER unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during drug development.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

This guidance revises the draft guidance for industry *Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment* that issued in March 2009. When final, this guidance will be considered the FDA's current thinking regarding the development of drugs for the treatment of CABP.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

This guidance provides information to assist sponsors developing drugs for the treatment of CABP. CABP is defined as an acute bacterial infection of the pulmonary parenchyma associated with chest pain, cough, sputum production, difficulty breathing, chills, rigors, fever, or hypotension, and is accompanied by the presence of a new lobar or multilobar infiltrate on a chest radiograph. Common typical bacterial pathogens that cause CABP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Moraxella catarrhalis.* Atypical bacterial pathogens such as *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* also cause CABP.

Changes from the 2009 draft CABP guidance, based on public discussions and comments to the docket, have been incorporated into the appropriate sections below.[5] These changes are intended to attain a greater degree of balance between the practicability of conducting CABP clinical trials and the trial procedures needed for a scientifically sound and interpretable trial.

[5] There have been several public discussions with the FDA regarding CABP. For example: (1) a 2008 Clinical Infectious Diseases supplement that summarized a workshop co-sponsored by the FDA and professional societies, titled "Workshop on Issues in the Design and Conduct of Clinical Trials of Antibacterial Drugs in the Treatment of Community-Acquired Pneumonia" (Clinical Infectious Diseases, December 1, 2008; volume 47 (supplement number 3)); (2) a 2008 Anti-Infective Drugs Advisory Committee (AIDAC) meeting on endpoints and clinical trial design issues for CABP at http://www.fda.gov/ohrms/dockets/ac/cder08 html#AntiInfective; (3) the December 9, 2009, AIDAC meeting on CABP issues at http://www fda.gov/AdvisoryCommittees/Calendar/ucm187911 htm; and (4) the November 3, 2011, AIDAC meeting on CABP clinical trials at http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm242307 htm (the November 3, 2011, AIDAC meeting information is at the bottom of the Web page). Notably, this revised guidance provides new efficacy endpoint recommendations (section III.B.8., Efficacy Endpoints), allows enrollment of up to 25 percent of the patient population who have received prior antibacterial drug therapy (section III.B.7., Choice of Comparators, Prior Antibacterial Drug Use, and Concomitant Therapy), and recommends the intent-to-treat population as the primary analysis population (section III.B.10., Statistical Considerations).

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Nonclinical Development Considerations

New antibacterial drugs being studied for CABP should have nonclinical data documenting activity against the commonly implicated pathogens for CABP.

2. Drug Development Population

The trial population should include individuals most likely to have CABP, as defined above, and who can therefore benefit from antibacterial therapy.

3. Efficacy Considerations

Noninferiority trials are interpretable and acceptable to support approval of a drug for an indication for the treatment of CABP. A showing of superiority to an effective control is also readily interpretable and would be acceptable.

Historical data show that antibacterial drugs demonstrate a considerable treatment effect compared to nonantibacterial therapies on clinical responses evaluated during the first 5 days of therapy.

Although it remains important for a trial to demonstrate sustained clinical responses, currently there is insufficient historical evidence to define the treatment effect on endpoints at or after therapy completion. There is adequate information to define a reliable treatment effect on all-cause mortality.

A single adequate and well-controlled trial in CABP supported by evidence of antibacterial activity accrued during a clinical development program (e.g., efficacy in another indication such as acute bacterial skin and skin structure infection; data from a phase 2 clinical trial in CABP) may provide evidence of effectiveness in CABP. Sponsors should discuss their proposed CABP development program with the FDA as well as the other independent evidence that would be used to support the findings from a single trial.[6]

4. Safety Considerations

If the same or greater dose and duration of the drug is used in clinical development for other infectious disease indications, safety data from the other infectious disease indications can be used in an overall safety database to support an indication for CABP. In general, a minimum of 700 patients should be included in the safety database. For new drugs that have an important clinical benefit over existing therapies, depending on the benefit demonstrated, a smaller

[6] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

premarketing safety database may be appropriate. Sponsors should discuss the appropriate size of the premarketing safety database with the FDA during clinical development.

B. Specific Efficacy Trial Considerations

1. Trial Design

CABP trials should be randomized, double-blind, and active-controlled using a noninferiority or superiority design. Placebo-controlled trials are not appropriate for this indication except when they are add-on superiority trials in which patients receive either placebo or investigational drug added to standard-of-care antibacterial drug treatment.

2. Trial Population

The trial population for efficacy trials should include patients with CABP based on the entry criteria described in section III.B.3., Entry Criteria. We recommend that at least 75 percent of patients in trials have Pneumonia Patient Outcomes Research Team (PORT) scores of III or higher (Fine, Auble, et al. 1997). For trials in which most patients would be treated as outpatients, sponsors should discuss the trial population and its level of baseline severity with the FDA in advance of a phase 3 trial (e.g., whether the trial may enroll patients with PORT scores of II or higher).

3. Entry Criteria

a. Clinical, radiographic, and microbiologic entry criteria

Sponsors should use entry criteria that select patients who have evidence of a diagnosis of CABP as outlined in Table 1.

Table 1. Summary of Entry Criteria for a CABP Trial

At Least Two Symptoms	**At Least Two Vital Sign Abnormalities**	**At Least One Finding of Other Clinical Signs and Laboratory Abnormalities**	**Chest Radiograph Findings**	**Microbiologic Criteria**
- Difficulty breathing - Cough - Production of purulent sputum - Chest pain	- Fever - Hypotension - Tachycardia - Tachypnea	- Hypoxemia - Clinical evidence of pulmonary consolidation - An elevated total white blood cell count or leukopenia	New infiltrates in a lobar or multilobar distribution	Appropriate sputum specimen: fewer than 10 squamous epithelial cells and more than 25 polymorphonuclear cells per low power field

An adequate specimen of respiratory secretions should be obtained in all patients and should be processed by the laboratory according to recognized methods for Gram stain, culture, and in vitro

antibacterial susceptibility testing performed on appropriate organisms isolated from the specimen.[7]

Bacterial detection methods other than culture may be used to define the microbiological intent-to-treat (micro-ITT) population (see section III.B.10.a., Analysis populations). Such methods may include the following: (1) use of rapid diagnostic tests (e.g., urinary antigen test for *S. pneumoniae*); and (2) nonculture methods of testing (e.g., serology, polymerase chain reaction). Use of rapid diagnostic tests may help to select a patient population with an identified bacterial etiology for CABP.

The clinical trial of an antibacterial drug also may provide an opportunity to contribute to the development and evaluation of a new diagnostic test. Sponsors interested in also using a clinical trial in patients with CABP as a means for the evaluation of a diagnostic test are encouraged to discuss this with the FDA.

b. Exclusion criteria

Exclusion criteria should include the following:

- Aspiration pneumonia
- Hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia
- Patients with known bronchial obstruction or a history of post-obstructive pneumonia (this criterion does not exclude patients who have chronic obstructive pulmonary disease)
- Patients with primary or metastatic lung cancer
- Patients with cystic fibrosis, known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis

4. Randomization and Blinding

Patients should be randomized to treatment groups at enrollment. All trials should be double-blind unless there is a compelling reason for not blinding treatment allocation. If trials are single-blind or open-label, sponsors should discuss potential biases with the FDA and how these biases will be addressed.

[7] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute; see also the American Society for Microbiology, 2011, Manual of Clinical Microbiology, 10th edition.

176 *5. Specific Populations*
177
178 The trials should include patients of both sexes and all races, as well as geriatric patients.[8]
179 Patients with renal or hepatic impairment may be enrolled, provided pharmacokinetics of the
180 drug have been evaluated in these patients and appropriate dosing regimens have been defined.
181
182 Sponsors should discuss drug development in the pediatric populations as early as is feasible.
183 The Pediatric Research Equity Act (PREA), as amended by the Food and Drug Administration
184 Safety and Innovation Act, states that initial plans for the conduct of pediatric studies (referred to
185 as an *initial pediatric study plan*) shall be submitted to the FDA before the date on which
186 required pediatric assessments are submitted under PREA and no later than (1) 60 days after the
187 end-of-phase 2 meeting or (2) such other time as may be agreed upon by the FDA and the
188 applicant.[9]
189
190 *6. Dose Selection*
191
192 To choose the dose or doses to be evaluated in phase 3 clinical trials, sponsors should integrate
193 the findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics,
194 safety and tolerability information from phase 1 clinical trials, and safety and efficacy
195 information from phase 2 dose-ranging clinical trials. Trials assessing drug penetration at the
196 site of action (e.g., epithelial lining fluid) may be helpful in defining doses that achieve
197 concentrations sufficient to exert an antibacterial effect. In addition, the pharmacokinetics of the
198 drug in specific populations (e.g., geriatric patients, patients with renal or hepatic impairment)
199 should be evaluated before initiation of phase 3 trials to determine whether dose adjustments are
200 necessary. This evaluation may prevent the exclusion of such patients from phase 3 clinical
201 trials.
202
203 *7. Choice of Comparators, Prior Antibacterial Drug Use, and Concomitant Therapy*
204
205 In general, the active comparator should be considered standard of care for this indication.
206 When evaluating the current standard of care, we consider recommendations by authoritative
207 scientific bodies (e.g., American Thoracic Society, Infectious Diseases Society of America)
208 based on clinical evidence and other reliable information that reflects current clinical practice.
209
210 Ideally, patients enrolled in a CABP clinical trial should not have received prior antibacterial
211 drug therapy because such therapy may have a number of potential consequences for a clinical
212 trial. Prior antibacterial drug therapy could:
213

[8] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*.

[9] See PREA (Public Law 108-155; section 505B of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355c) as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (Public Law 112-144) and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

- Obscure true treatment differences between an investigational drug and the control drug introducing bias toward a finding of no difference between treatment groups (i.e., a bias toward noninferiority)[10]

- Particularly influence the efficacy findings based on an endpoint early in therapy (day 3 to day 5)

However, exclusion of all patients who have received prior antibacterial therapy also may pose problems, including:

- Excluding patients with greater disease severity (i.e., patients who received prompt administration of antibacterial drug therapy), which may result in a patient population with lesser severity of illness and greater potential for spontaneous recovery; this could bias trial results toward a finding of no difference between treatment groups (i.e., a bias toward noninferiority)

- Certain trial sites may not participate in the clinical trial because of concerns that trial treatment would not represent standard of care.

A pragmatic approach to these concerns is to: (1) encourage prompt enrollment procedures so that patients can receive the clinical trial treatment initially, with no need for other antibacterial drug therapy; and (2) allow enrollment of some patients who have received a single dose of a short-acting antibacterial drug within 24 hours of enrollment (ideally there would be few such patients but up to 25 percent of the patient population could be allowed). This would permit patients in the trial to receive prompt antibacterial drug therapy as clinically necessary, consistent with the standard of care. The results in the subgroup of patients (i.e., the majority of patients) who did not receive prior effective antibacterial drug therapy would be important to evaluate. The primary analysis should be stratified by prior therapy to assess the consistency of the results across the two subgroups (i.e., patients who received prior therapy and those who did not receive prior therapy).

In general, concomitant antibacterial therapy with an antimicrobial spectrum that overlaps with the spectrum of the investigational drug should not be administered during the trial. We recognize the need in certain circumstances for the empirical coverage against atypical pathogens (e.g., *Legionella* species). The additional antibacterial coverage for atypical pathogens should be discussed with the FDA before trial initiation. The additional antibacterial coverage for atypical pathogens should be promptly discontinued after a determination has been made that CABP is not caused by an atypical pathogen of concern (e.g., a negative test result on a *Legionella* antigen assay).

[10] For example, see Pertel, Bernardo, et al. 2008.

8. Efficacy Endpoints

a. Primary endpoint

The primary efficacy endpoint of clinical success is defined as improvement at day 3 to day 5 in at least two of the following symptoms: chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing.[11] Symptoms should be evaluated on a four-point scale (absent, mild, moderate, severe) with improvement defined as at least a one-point improvement from baseline to the assessment at day 3 to day 5 (e.g., from severe to moderate, from moderate to absent, or from mild to absent).[12]

An endpoint of all-cause mortality at 28 days after enrollment may be used as a primary efficacy endpoint in CABP clinical trials in certain patient populations. However, sponsors considering the use of all-cause mortality as the primary efficacy endpoint should discuss the trial design with the FDA.

b. Secondary endpoints

Sponsors should evaluate the following as secondary endpoints:

- Improvement at day 3 to day 5 in at least two of the following symptoms with no worsening in any of these symptoms of CABP compared to baseline: chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing; *and* improvement in vital signs (i.e., body temperature, blood pressure, heart rate, respiratory rate).[13]

- Clinical outcome at the end of therapy.

- Clinical outcome at a fixed time point after therapy completion. Patients with resolution of symptoms and signs attributable to CABP at 5 to 10 days following completion of treatment and who did not receive nontrial antibacterial drugs for treatment of CABP should be considered successes on this secondary endpoint.

Other examples of secondary endpoints for consideration are as follows:

- Changes in white blood cell counts from baseline to day 3 to day 5
- Changes in oxygenation from baseline to day 3 to day 5

[11] See Talbot, Powers, et al. 2012.

[12] See Toerner, Burke, et al. 2012. For information regarding the development of patient-reported outcome measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

[13] Improvement or stabilization of vital signs and other signs attributable to CABP should be defined in the protocol. For example, see table 10 in Mandel, Wunderink, et al. 2007.

c. IV and oral formulations

For drugs that have only an intravenous (IV) formulation available, sponsors should conduct trials with the IV formulation alone until the day 3 to day 5 efficacy endpoint assessment is complete, if feasible, to allow for assessment of both the efficacy and safety of the investigational drug. Assessment of the primary endpoint at day 3 to day 5 before switching to an oral antibacterial drug should ensure that the evaluation of efficacy reflects the effects of the investigational IV drug. The overall duration of antibacterial drug therapy (i.e., days of IV therapy plus days of oral drug therapy) should not involve an unnecessarily long course of oral switch therapy, so that the contribution of the IV investigational drug to overall efficacy on secondary endpoints at 5 to 10 days after completion of treatment can be assessed.

For drugs that have both an IV and oral formulation, the protocol should specify the criteria that allow for IV-to-oral switch. The sponsor should collect pharmacokinetic (PK) data for IV and oral formulations in earlier phase studies to select the appropriate oral dose for the IV-to-oral switch.

9. Trial Procedures and Timing of Assessments

a. Entry visit

The following information should be captured at the entry visit (see section III.B.3., Entry Criteria, and section III.B.8., Efficacy Endpoints):

- Appropriate demographic information
- History and physical examination findings
- Prior medication use
- Baseline assessments of symptoms
- Baseline assessments of clinical signs of CABP
- Baseline appropriate laboratory tests
- Chest radiographic findings
- Microbiological specimens
- Severity scores

b. On-therapy visits

Investigators should document findings from on-therapy clinical trial visits (e.g., history, physical examination, adverse effects, laboratory test results). Patients should be evaluated for the symptoms of chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing at day 3 to day 5. Patients also should be evaluated at the end of therapy.

c. After therapy visit

At this visit at 5 to 10 days after completion of treatment, sponsors should capture physical examination findings, assessments of symptoms, assessments of signs, assessments and

resolution of adverse effects, if any, and appropriate laboratory tests. Patients should be evaluated at day 28 for assessment of all-cause mortality.

10. Statistical Considerations

The trial hypotheses and the analysis methods should be prespecified in the protocol and in the statistical analysis plan, and should be finalized before trial initiation.[14]

a. Analysis populations

The following definitions apply to various analysis populations in CABP clinical trials:

- Safety population — All patients who received at least one dose of drug during the trial.
- Intent-to-treat (ITT) population — All patients who were randomized.
- Micro-ITT population — All randomized patients who have a baseline bacterial pathogen known to cause CABP against which the investigational drug has antibacterial activity. This includes bacterial pathogens identified by standard culture methods of an appropriate sputum specimen or blood. Recently conducted trials suggest that approximately 25 percent of the ITT population will have bacterial pathogens identified by standard culture methods. In addition, nonculture methods of detection of bacterial pathogens (e.g., urinary antigen test) may be used to identify patients for inclusion in a micro-ITT analysis population.
- Clinically evaluable or per-protocol populations — Patients who meet the definition for the ITT population and who follow important components of the trial as specified in the protocol.
- Microbiologically evaluable populations — Patients who meet the definition for the micro-ITT population and who follow important components of the trial as specified in the protocol.

Sponsors should discuss with the FDA the prespecified primary analysis population in advance of trial initiation. The ITT population may be considered as the primary analysis population when (1) the trial enrolls patients who are most likely to have a bacterial etiology for pneumonia and (2) the investigational antibacterial drug can be administered as monotherapy that has antibacterial activity against the typical bacterial pathogens that cause CABP.[15]

The ITT population is likely to have a substantial fraction of patients who do not have a bacterial pathogen identified on sputum culture. Nonetheless, the ITT population (i.e., patients who meet

[14] See ICH E9 and ICH E10, and the draft guidance for industry *Non-Inferiority Clinical Trials* (when final, this guidance will represent the FDA's current thinking on this topic).

[15] The micro-ITT population is an important analysis population, in particular if the investigational antibacterial drug has a narrow spectrum of activity (e.g., a drug active against a single genus and species of bacteria).

the inclusion criteria described in section III.B.3, Entry Criteria) may be informative based on observations from previously conducted trials and evaluations. For instance, among patients who did not receive prior therapy in a trial in which there was an observed treatment difference between two antibacterial drugs (Pertel, Bernardo, et al. 2008), the subgroup of patients who did not have a positive sputum culture for a bacterial pathogen showed a treatment difference similar to the treatment difference among the subgroup of patients with a positive culture. This indicates a strong likelihood that the patients enrolled in this trial without a positive sputum culture actually had bacterial disease (Rubin, Toerner, et al. 2012). In addition, extensive nonculture methods performed in a research setting from sputum specimens identified a possible bacterial etiology for pneumonia in some patients who did not have a bacterial pathogen identified on a sputum or blood culture (Johansson, Kalin, et al. 2010). Another evaluation of patients with pneumonia who did not have a bacterial pathogen identified on a sputum or blood culture found that a more invasive search can identify a bacterial etiology in a large proportion of patients (Ruiz-González, Falguera, et al. 1999).

However, sponsors planning to develop a drug for the sole indication of the treatment of CABP should consider conducting two adequate and well-controlled trials of identical design. Each of these trials could potentially be powered based on the ITT population of that trial. Further, a noninferiority efficacy analysis in a micro-ITT population could potentially use data pooled from both trials. Sponsors planning to conduct a single CABP trial, with other supportive data, to support approval for CABP should discuss this plan with the FDA in advance and are encouraged to submit a special protocol assessment.[16]

The micro-ITT population should allow a sufficient description of baseline microbiological findings for adequate labeling information.

b. Noninferiority margins

Historical experience indicates that there is a relatively large treatment effect of antibacterial therapy on clinical recovery at day 3 to day 5 (see the Appendix). In general, the selection of a noninferiority margin (M_2) of 12.5 percent is reasonable for CABP clinical trials using a clinical recovery endpoint at day 3 to day 5. In certain circumstances (e.g., a narrow spectrum drug for a limited population with unmet medical need), it may be reasonable to consider a noninferiority margin greater than 12.5 percent. Sponsors should discuss with the FDA a clinically appropriate noninferiority margin in advance of trial initiation.

c. Sample size considerations

A general framework is provided for sponsors to begin to discuss sample size considerations with the FDA during protocol development. In this illustrative sample size calculation, approximately 225 patients per group is estimated based on the following assumptions: (1) a rate of clinical success for the active-controlled therapy of 80 percent; (2) two-sided type I error (α) of 0.05; (3) type II error (β) of 0.10 (power 0.90); (4) a noninferiority margin of 12.5 percent (see the Appendix); and (5) an ITT analysis population.

[16] See the guidance for industry *Special Protocol Assessment*.

11. Risk-Benefit Considerations

Risk-benefit considerations may depend on the population being studied. For example, for an IV-administered antibacterial drug targeted for treatment of hospitalized patients seriously ill with CABP, certain types of adverse effects that can be monitored in a hospital setting might result in a risk-benefit consideration that is appropriate, while such adverse effects might result in a risk-benefit consideration that is not appropriate for an orally administered antibacterial drug targeted for treatment of mildly ill outpatients.

C. Other Considerations

1. Pharmacokinetic/Pharmacodynamic Evaluation

The PK/pharmacodynamic (PD) characteristics of the drug should be evaluated using in vitro methods and animal models of infection.

The limitations of *S. pneumoniae* pneumonia and *H. influenzae* pneumonia animal models, when considering their implications for humans, include the differences among the animal models in the mode of infection and in the reproducibility of infection (Tessier, Kim, et al. 2002; Gavalda, Capdevila, et al. 1997; Legget 1999; Miyazaki, Nunoya, et al. 1997), and differences in the effect of animal lung secretions versus human lung secretions on the activity of the antibacterial drug (Silverman, Mortin, et al. 2005). Animal studies are not a substitute for clinical trials in patients with CABP.[17]

The PK/PD characteristics of the drug (including the relationships to the minimum inhibitory concentrations) should be integrated with the findings from phase 1 PK clinical trials to help identify appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials. A dose-response trial may be considered as an option for clinical trials early in development to weigh risks and benefits when selecting doses and to ensure that suboptimal doses or excessive doses (beyond those that add to efficacy) are not used in the phase 3 trial, offering some protection against unexpected and unrecognized dose-related toxicity.[18]

Sponsors should consider obtaining blood samples from all patients in phase 2 and phase 3 clinical trials (*sparse sampling*) to allow for the estimation of drug exposure in each patient. A retrospective exposure-response analysis based on the population PK model should be performed to assess the relationship between exposure and observed clinical and microbiologic outcomes. The relationship between drug exposure and clinically relevant adverse events also should be explored to identify potential risks with different dosing regimens (if applicable) and specific patient populations.

[17] See 21 CFR 314.600 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.600)

[18] See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* and the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration*.

2. Labeling Considerations

Generally, the labeled indication should be the treatment of CABP caused by the specific bacteria identified in a sufficient number of patients in the clinical trials and should reflect the patient population enrolled in the clinical trials.

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APPENDIX:
NONINFERIORITY MARGIN JUSTIFICATION FOR CABP

Background

The selection of a noninferiority margin depends on a reliable estimate of the treatment effect of the active comparator (i.e., effect of the active comparator over placebo, referred to as M_1), usually based upon placebo-controlled trials, that can be assumed to hold for the noninferiority trial. After M_1 is established, clinical judgment determines how much of the estimated treatment effect (M_1) should be preserved in determining a clinically acceptable noninferiority margin, referred to as M_2.

Historical studies and clinical trials of antibacterial treatment of bacterial pneumonia provide evidence that antibacterial drugs have the following effects:

- Achievement of a greater proportion of patients with favorable clinical responses at time points earlier in the course of antibacterial drug therapy (i.e., at day 3 to day 5)

- Reduction of mortality in patients with pneumococcal or lobar pneumonia

An area of uncertainty in evaluating historical data is the spectrum of bacterial pathogens that cause CABP today. In most of the historical studies and historical-controlled clinical trials, CABP was considered synonymous with pneumococcal pneumonia because *S. pneumoniae* was regularly identified. A review of recently conducted trials showed that less than 20 percent of the total patient populations had documented *S. pneumoniae* (Higgins, Singer, et al. 2008). CABP is also caused by other pathogens such as *H. influenzae*, *H. parainfluenzae*, *S. aureus*, and *M. catarrhalis*, as well as atypical bacteria such as *M. pneumoniae*, *C. pneumoniae*, and *Legionella* species. Limited information is available on antibacterial treatment effect in CABP caused by *M. pneumoniae* (Kingston, Chanock, et al. 1961). A fundamental assumption is that historical response rates in infections such as *S. pneumoniae* CABP are relevant to response rates in modern infections with sensitive organisms.

We describe the steps taken to determine a noninferiority margin for two primary outcome measures: (1) an endpoint based on the outcome assessments of chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing; and (2) all-cause mortality endpoint.

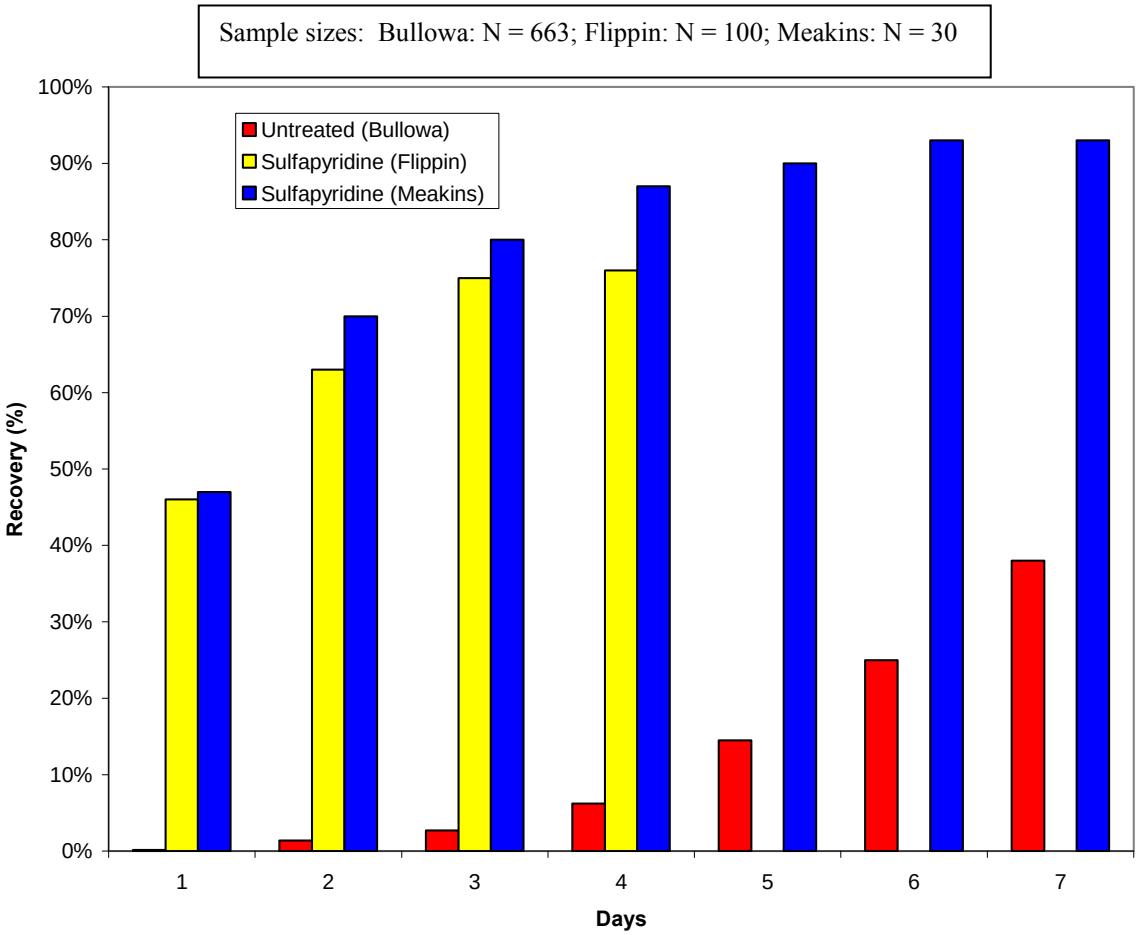
1. Endpoint Based on Clinical Outcome Assessments at Day 3 to Day 5 After Enrollment

Studies conducted around the time of the introduction of antibacterial drug therapy described clinical responses among untreated patients and patients treated with antibacterial drugs. These observational studies provide an estimate of the effect of antibacterial drugs on clinical response endpoints other than mortality.

Several papers described the clinical course of patients with pneumococcal pneumonia in a similar way; patients were recorded as having a successful clinical result by the demonstration of

fever resolution and accompanying improvement and resolution of other signs and symptoms of pneumonia. For example, a description in one of the papers stated, "This fall in temperature was in all cases accompanied by a conspicuous reduction in the pulse and respiratory rates, and the patients were improved subjectively" (Meakins and Hanson 1939). One study described the clinical course of 663 patients who did not receive antibacterial drug therapy (Bullowa 1937), while two other studies included patients who received antibacterial drug therapy. One study described the clinical course in 100 patients with pneumococcal pneumonia (Flippin, Lockwood, et al. 1939) and another study described the clinical course in 30 patients with pneumococcal pneumonia (Meakins and Hanson 1939). Figure A compares the three studies in the rates of clinical recovery, defined generally as the improvement in both clinical signs and symptoms.

Figure A. Rates of Clinical Recovery Recorded at Each Day

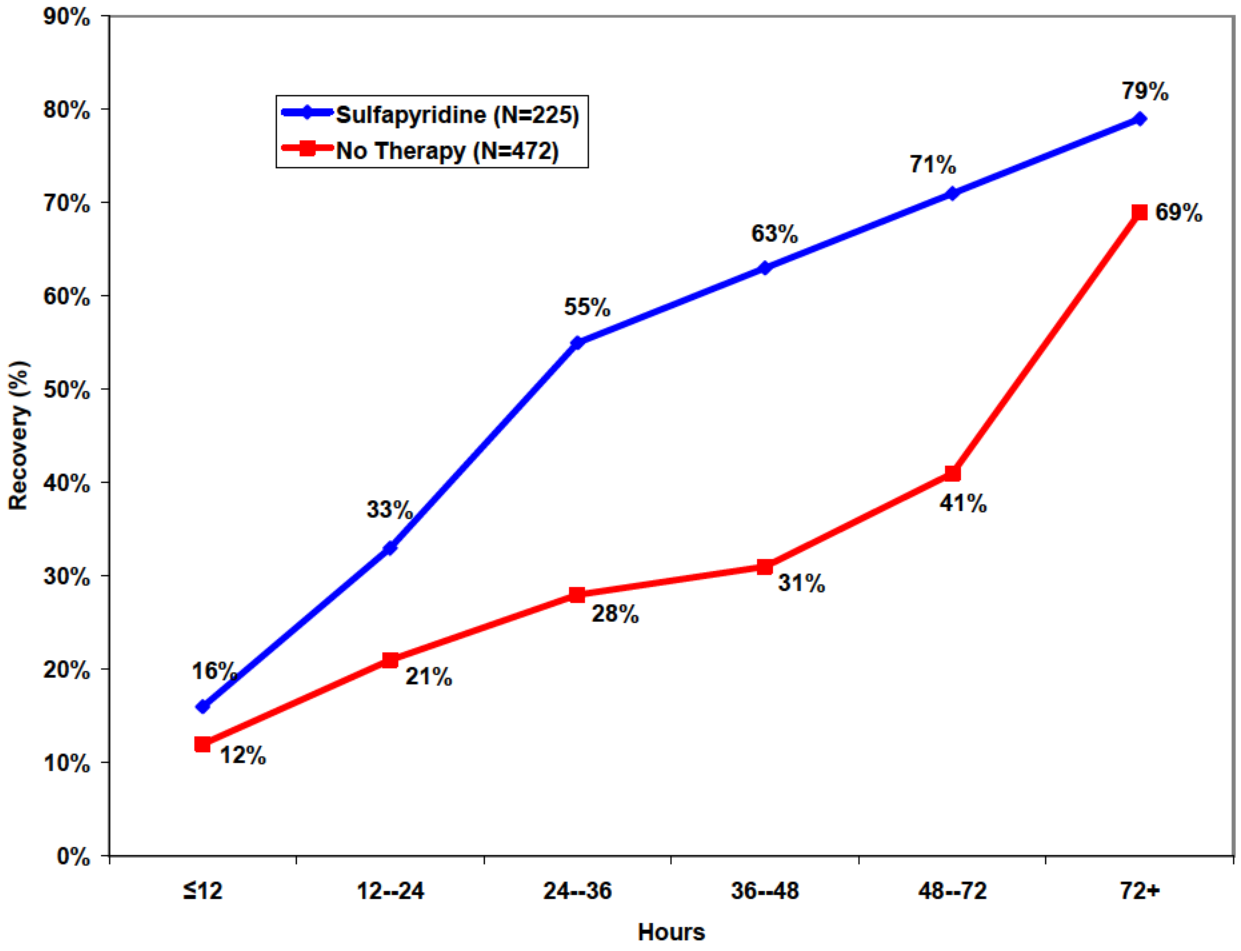


The difference in clinical recovery rates between patients in the two treatment studies and patients in the study without treatment were 72 percent and 77 percent.

Figure B shows the rates of clinical recovery in an observational study of patients with pneumococcal pneumonia who received antibacterial drug therapy (sulfapyridine) and a group of patients who received no specific therapy. Clinical recovery was defined as "permanent drop in

oral temperature below 100°F, with subsidence of other symptoms of acute infection" (Finland, Spring, et al. 1940). Time points at 36 to 48 hours and 48 to 72 hours after therapy initiation demonstrate the greatest treatment effect of clinical recovery. The treatment difference is approximately 30 percent (95 percent confidence interval: 22 percent, 37 percent) at the 48- to 72-hour time point. Clinical observations that were reported at any time after the 48- to 72-hour assessment are displayed as *72+* in Figure B. The time points after 72 hours (i.e., 72+) included recovery time points out to several weeks following therapy completion.

Figure B. Rates of Clinical Recovery of Acute Bacterial Pneumonia (Finland, Spring, et al. 1940)



Another paper described the outcomes among pediatric patients with pneumococcal pneumonia and provides additional support for a treatment effect of antibacterial drugs relatively early in therapy. The mean time to clinical recovery was 4.7 days among patients who received antibacterial drug therapy while patients who did not receive antibacterial drug therapy had a mean time to clinical recovery of 8.9 days (Wilson, Spreen, et al. 1939).

The clinical response endpoints that were evaluated in each of these studies were not well defined. The studies evaluated both signs and symptoms together. A large treatment effect was observed at the early time point in the course of therapy (i.e., day 3 to day 5 after therapy

initiation) for an endpoint that included improvement in both signs and symptoms. The studies show that the treatment differences become smaller at times beyond day 3 to day 5 of therapy. Aspects that support the use of these studies as an estimate of M_1 include the following:

- The studies documented bacterial pneumonia, all as *S. pneumoniae*.
- The estimate of the treatment difference appears to be large and is consistent across studies.
- Some patients included in the *no therapy* group in Figure B were patients who had signs and symptoms of milder pneumonia. Even after the availability of antibacterial drugs, the clinician chose not to treat such patients with antibacterial drug therapy because of the likelihood of spontaneous recovery. The inclusion of patients more likely to experience spontaneous recovery of pneumonia in the no therapy group leads to an underestimate of the true treatment difference among patients with more serious disease.
- The clinical response measurements are plausible consequences of treating an infection.

The limitations of these studies include the following:

- The studies were not randomized
- Historically controlled studies create a greater level of uncertainty in the estimate of treatment differences
- The clinical response evaluations were not defined
- The clinical response evaluations included improvement in both signs and symptoms together and did not separately evaluate improvement in chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing

The treatment difference appears to be large for an endpoint based on clinical outcome assessments earlier in the course of therapy for CABP. However, the results are variable, ranging from the point estimate of 30 percent treatment difference at a 48- to 72-hour time point noted in Figure B to a point estimate of 77 percent treatment difference at day 3 noted in Figure A.

It is difficult to provide a precise numerical value for the treatment effect of a proposed primary endpoint of symptom improvement at day 3 to day 5. However, an M_1 of at least 20 percent appears to be a reasonably appropriate and conservative estimate, accounting for the uncertainties with clinical recovery in the historical literature. A conservative estimate of M_1 at 20 percent is still large enough to support the selection of a noninferiority margin (M_2) of 12.5 percent for the endpoint of symptom improvement at day 3 to day 5. The selection of the noninferiority margin (M_2) is a matter of clinical judgment and should be justified by the sponsor.

2. All-Cause Mortality Endpoint

Table A provides an overview of the types of historical data used to support the identification of a treatment effect based on all-cause mortality.

Table A. Mortality in Observational Studies of Pneumococcal Pneumonia[1]

Publication	Population	Mortality (%) Untreated (Study Years)	Mortality (%) Antibacterial-Treated (Study Years)	Treatment Difference Untreated-Treated (95% Confidence Interval)
Finland (1943)[2]	≥ 12 years old bacteremic and nonbacteremic	N=2,832 (1929-1940)* 41%	N=1,220 (1939-1941) 17% (sulfonamides)	24% (21%, 27%)
Dowling and Lepper (1951)[3]	≥ 10 years old bacteremic and nonbacteremic	N=1,087 (1939, 1940)* 30.5%	N=1,274 (1938-1950) 12.3% (sulfonamides) N=920 (1938-1950) 5.1% (penicillins and tetracyclines)	18.2% (15%, 21%) 25.4% (22%, 28%)
Austrian and Gold (1964)[4]	≥ 12 years old bacteremic	N=17 (1952-1962) 82%	N=437 (1952-1962) 17%	65% (41%, 79%)

[1] Singer, Nambiar, et al. 2008
[2] Finland 1943
[3] Dowling and Lepper 1951
[4] Austrian and Gold 1964
* Historical controls

The lower bounds of the 95 percent confidence interval for the treatment effect varied from 15 to 41 percent in the observational studies in patients with pneumococcal pneumonia. Thus, a conservative estimate of M_1 for the endpoint of all-cause mortality in a CABP trial is at least 15 percent.

Summary

Based on data from historical studies and clinical trials, appropriate approaches to selecting noninferiority margins for CABP trials have been described. The available data support a noninferiority margin justification for two efficacy outcome assessments:

1. An endpoint based on symptom improvement at day 3 to day 5 compared to baseline

2. All-cause mortality endpoint

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	27 September 2016
To:	Sumathi Nambiar, MD, MPH, Director, Division of Anti-Infective Products (DAIP) Yuliya Yasinskaya, MD, Medical Officer, Team Leader Elizabeth O'Shaughnessy, MD, Medical Officer Ramya Gopinath, MD, Medical Officer
From:	Mark Avigan, MD, CM Associate Director, Critical Path Initiatives & Hepatologist Office of Pharmacoepidemiology (OPE) Office of Surveillance and Epidemiology (OSE)
CC:	Michael Blum, MD, Deputy Director, OPE John Senior, MD, Associate Director, OPE Ted Guo, PhD, Office of Biostatistics Robert Ball, MD, Deputy Director, OSE Gerald Dal Pan, MD, Director, OSE Edward Cox, MD, Director, Office of Microbial Products
Drug Name:	Solithromycin (CEM-101)
Formulations:	PO Capsules & IV formulation
NDA Numbers:	209006 & 209007
Applicant/sponsor:	Cempra Pharmaceuticals
Issue:	Assessment of liver toxicity profile of Solithromcyin in the clinical development program for Community – Acquired Bacterial Pneumonia (CABP)

INTRODUCTION

In a request dated 16 May 2016, DAIP has asked for consultation by a hepatologist to evaluate the hepatotoxic risk of solithromycin (CEM-101; 5-day administration with the oral formulation or 7-day administration with the sequentially administered IV & oral formulations) based on data

that has been collected in the clinical development program (Cempra Pharmaceuticals, Chapel Hill NC) for the treatment of community acquired bacterial pneumonia (CABP). Among 856 study subjects who were enrolled in two randomized Phase-3 clinical trial subjects, solithromycin administration (5 or 7-day treatment protocols) was associated with more frequent asymptomatic and transient serum hepatic aminotransferase (AT) elevations, when compared with moxifloxacin, the comparator agent that was tested. A range of increases of alkaline phosphatase (ALP) accompanied some but not all of the cases of solithromycin-associated increases of AT. There were no coinciding drug-related increases of bilirubin levels. Of concern, however, the sponsor has also reported that among only four study subjects who have so far been enrolled in a longer duration non-IND trial of solithromycin (3-week treatment protocol) to treat COPD that is being conducted in the UK, three individuals developed alanine amino transferase (ALT) elevations greater than 3X ULN, including one 69 year old male who developed clinically significant drug-related cholestatic hepatitis. In that case, the liver injury was marked by jaundice and pruritis, leading to the early discontinuation of the study drug on Day 23 of treatment.

Solithromycin is structurally highly related to telithromycin, another ketolide antibacterial drug marked by similar pre-approval clinical trial liver test abnormalities observed during its clinical development program. In 2007, after a number of post-market reports of telithromycin-associated clinically serious DILI that included some liver-related deaths were reported and evaluated by FDA, the agency removed approval of telithromycin use for the indications of acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis and instituted a product-label warning for hepatotoxicity. A 7-10 day treatment course of telithromycin for community acquired pneumonia [CAP (the indication now would be termed CABP)] of mild to moderate severity currently continues to be an approved indication.

With the findings of a liver injury signal associated with solithromycin, I have been asked to 1) evaluate the hepatic safety of this agent, based on current information, 2) address whether current data supports any claim that solithromycin is marked by a lower risk of hepatotoxicity, compared to telithromycin, and 3) consider specific concerns regarding a potential for hepatotoxicity and how this might be addressed in a regulatory manner.

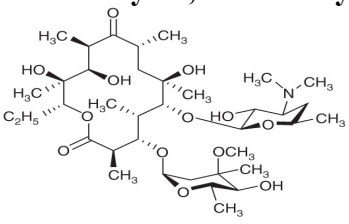
BACKGROUND

Solithromycin is a member of the ketolide group of antibiotics that includes telithromycin, cethromycin, modithromycin and solithromycin (1). Ketolides are third-generation macrolides that are derivatives of erythromycin A. As semisynthetic molecules, they all possess a 14-member lactone macrocycle ring. However, in the case of ketolides the cladinose sugar attached to the C-3 position in the macrocycle rings of erythromycin, azithromycin and clarithromycin has been removed and replaced with a keto group (See Fig. 1). In addition, most ketolides contain a cyclic carbamate group that forms a ring structure between C-11 with C-12 of the macrocyle that forms a bridge to an aryl-alkyl chain side-chain. These modifications have been introduced with a purpose to overcome certain categories of macrolide resistance conferred by a set of targeted bacterial mutations that are known to eliminate or reduce antibiotic suppression by earlier generation macrolides. Nonetheless, while less frequent, ketolide-resistant strains have been isolated and identified.

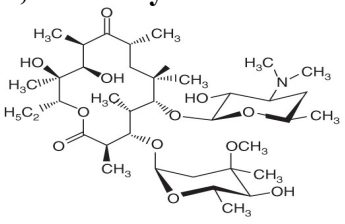
Generally, ketolides suppress bacterial growth by macrocycle-dependent contact with a few 50S ribosomal subunit proteins that play a central role in peptidyl tranferase activity in prokaryotic ribosomes, as well as interactions with at least three specific nucleotides within rRNA of the 23S subunit that are dependent on the C1-linked sugar moiety and the alkyl-aryl arm of this subclass of macrolides. These multiple site-specific physical interactions provide a strong-enough anchor to overcome loss of a single adenosine contact site (A2058) in the 23S subunit, due to methylation of the nucleotide. [This reaction is catalyzed by certain bacterial methyltransferases that are expressed in some isolates of streptococcus pneumoniae and confer resistance to the earlier generations of macrolides.] It is noteworthy that due to the similarities of their key structural elements, solithromycin and telithromycin molecules must be orientated in an identical fashion to effectively bind both to the peptidyl transferase component of the 50S ribosomal unit and the 23S rRNA contact sites.

There are a number of antibiotic drug classes that have a recognized role in the treatment of CABP. They include 1) β-lactams (e.g. amoxicillin-clavulanate), 2) Quinolones (e.g. moxifloxacin, levofloxacin, gemifloxacin), and 3) Second-generation macrolides (e.g. azithromycin, clarithromycin). Ketolides (e.g. telithromycin and solithromycin) are third-generation macrolides that were designed with the purpose of overcoming certain forms of respiratory pathogen resistance, as described above.

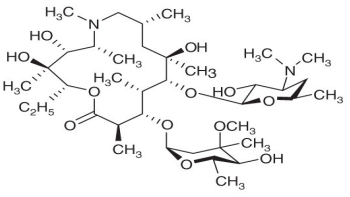
Figure 1. Structures of erythromycin, clarithromycin, azithromycin and the ketolides telithromycin, solithromycin, cethromycin and modithromycin[1]



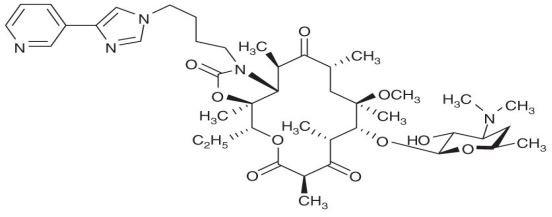
Erythromycin



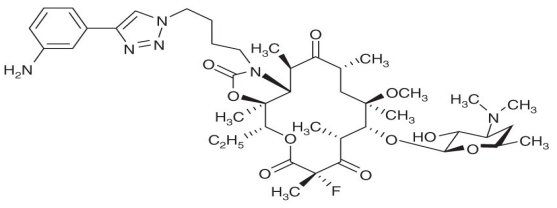
Clarithromycin



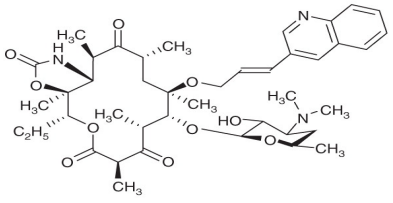
Azithromycin



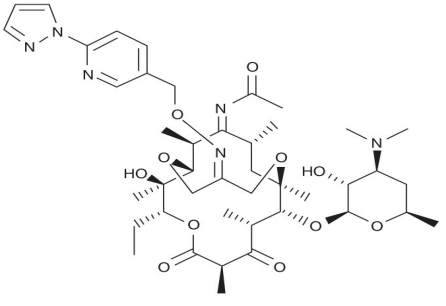
Telithromycin



Solithromycin



Cethromycin



Modithromycin

[1] Georgopapadakou, NH, Expert Opin Investig Drugs (2014) 23(10): 1313-1319

Hepatotoxic Profile of Macrolides

Macrolides have been associated with a number of distinct clinical signatures and levels of risk for hepatotoxicity (2). Among these, two forms of idiosyncratic liver injury or perturbation have been observed in association with exposure to each of the US-marketed orally absorbed macrolides (e.g. erythromycin, azithromycin, clarithromycin and telithromycin). These include: 1) transient asymptomatic elevations in the serum of liver aminotransferases (AT). Impacted to both by monitoring practices and durations of exposure, the measured rates of macrolide-associated asymptomatic AT elevations that have been reported range between 1% and 5% of treated subjects; 2) idiosyncratic hepatitis with jaundice. This rare form of macrolide-induced hepatotoxicity can develop between the first week and one month after initiation of treatment. Cholestatic hepatitis marked by elevations of serum ALT, ALP and bilirubin has been a characteristic signature in these cases, although cases of hyper-acute liver injury associated with rapid onset after initiation of macrolide treatment typically demonstrate a hepatocellular pattern of liver cell damage. Symptomatic cases of macrolide-induced hepatitis can be accompanied by fever and in some instances RUQ abdominal pain. The clinical course can be severe or prolonged; acute liver failure and even death have been observed in a fraction of these cases. In isolated cases, prolonged cholestasis and vanishing bile duct syndrome associated with erythromycin-induced liver injury has been reported.

Although not uniformly present in all cases of macrolide-induced hepatotoxicity, the presence of rash and eosinophilia in a subset of these cases suggest an immuno-allergic mechanism marked by hypersensitivity to the offending agent. Consistent with hypersensitivity as a likely mechanism, a number of cases of documented re-challenge marked by shortened latency after treatment initiation and heightened clinical severity, upon repeated macrolide exposure, have been reported. A concern that previous cross-sensitization between structurally-related macrolides in some cases of rapid-onset severe macrolide-induced DILI has been raised by some investigators. Whether such a mechanism is responsible for these adverse events will require more study.

Hepatotoxic Profile of Telithromycin

Currently, telithromycin is the only oral ketolide that has been approved in the US. As described above, it has a well-recognized hepatotoxic profile. Although overall, the percentages of study subjects with ALT levels >3X ULN in study subjects randomized to telithromycin in Phase III clinical trials for different indications were not substantially different than those in the comparator arms, in the subset of studies for the treatment of CAP a greater proportion of telithromycin-treated patients were found to have transient treatment-related low level elevations of ALT or aspartate aminotransferase (AST) relative to the comparators (3). Moreover, as stated in the product label, 0.07% of the study subjects receiving telithromycin in clinical trials developed reversible hepatitis with or without jaundice. In 2006, lingering concerns about a hepatotoxic risk tied to the agent, as well as a plausible potential to induce life-threatening weakness in myasthenia gravis (MG) and blurred vision in otherwise normal individuals through inhibition of acetylcholine receptors, led to an appraisal of these post-marketing adverse events associated with telithromycin. In this effort, a comprehensive assessment of 42 published and spontaneously reported post-marketing cases of clinically significant telithromycin-associated

liver injury was performed by an FDA expert panel [described in a peer-reviewed article (4)]. Among the 42 telithromycin-associated cases were five with a severe outcome of death (n=4) or liver transplantation (n=1); 32/42 cases were hospitalized; 25/42 developed acute hepatocellular injury associated with jaundice; 26 of the 42 cases were adjudicated by the panel as 'highly likely' or 'probable' in their causal association with telithromycin. Of note, distinct clinical features of these cases included some with a very short latency from initiation of treatment to onset of liver injury (median, 10 days; range 2 - 43 days; 4 cases had known previous telithromycin exposure) and rapid onset of fever (29%), abdominal pain (45%) and jaundice, with in some instances, reported eosinophilia (19%) and/or ascites (17%). These manifestations may suggest a mechanism of rapid-onset or previously acquired hypersensitivity to the drug or one of its metabolites, or cross-sensitization with a previously administered structurally-related macrolide.

Subsequent regulatory actions taken by the agency relevant to a risk for liver injury associated with telithromycin included: 1) institution of a Warning in the product label of hepatotoxicity marked by reports of 'acute hepatic failure and severe liver injury, in some cases fatal..', and 2) elimination of the previously approved indications to treat Acute Bacterial Sinusitis (ABS) and Acute Bacterial Exacerbation of Chronic Bronchitis (AECB), leaving only CAP of mild to moderate severity as an approved indication. [The regulatory removal of ABS and AECB as indications was prompted by analyses of both the hepatic and non-hepatic risks described above]. Parenthetically, for marketing reasons the innovator has recently altogether discontinued the domestic marketing of telithromycin.

Although they are highly related, selective differences of chemical structure between solithromycin and telithromycin that the sponsor has pointed out include: 1) the addition of a fluorine at Carbon-2 to inhibit enolization within the macrocycle and increase molecular stability, and 2) the replacement of the terminal pyridine – imidazole moiety (in telithromycin) with a terminal amino-phenyl triazole group in the aryl alkyl side chain [attached to the cyclic carbamate between C-11 and C-12 of the macrocycle] to reduce unintended inhibitory binding of the antibiotic to Ach receptors (5). A concern that such inhibition of vagal α7 nicotinic receptors by telithromycin would remove suppression of inflammatory cytokine release by hepatocytes / Kupffer cells, as well as induce cellular apoptosis, has provided the sponsor with a rationale for engineering this chemical substitution in solithromycin. Nonetheless, the impact of the elimination of the terminal pyridine-imidazole in solithromycin on risk for hepatotoxicity remains hypothetical, since the direct *in vivo* effects of this structural change on liver injury have yet to be determined.

Solithromycin Development Program with Reference to Liver Safety

Pre-clinical toxicological profile

Findings in a variety of animal species, as in humans, point to the liver as a target organ of toxicity. First, single dose and repeat dose oral solithromycin achieves high tissue concentrations in the liver and lung (~ 70% of the drug is metabolized and excreted by the liver). With increasing exposure through higher doses or longer duration of treatment, solithromcyin and its metabolites accumulate in liver cells. A number of important toxicological findings

connected to this process have been identified by the sponsor. These include the presence of: 1) dose-dependent biliary inflammation, hepatocellular degeneration and elevations of serum ALT, GGT and bilirubin (at doses ≥ 100 mg/kg/day, ~10-20X dose in humans) in pivotal 28-day toxicology studies in the rat; 2) dose-dependent hepatocyte vacuolation and Kupffer cell hyperplasia with elevations of serum ALT/AST attributable to phospholipidosis [phospholipid accumulates in hepatocyte lysosomes, presumably due to the inhibition of phospholipase A1 by solithromycin] (at doses of 100 & 200 mg/kg/day) in both 14-day and 13-week studies in the cynomolgus monkey. Although phospholipidosisis is not considered to represent a pathological process that is a direct precursor of serious DILI, the presence of cellular inflammatory and degenerative changes in the rat studies demonstrate that oral solithromycin, when it accumulates above a range of threshold concentrations in the liver, has the potential to cause a number of toxicological changes, in vivo, across these different preclinical models. Thus, if phospholipidosis also occurs in humans, its presence does not necessarily imply protection from the idiosyncratic activation of additional damage pathways that could be responsible for clinically significant hepatotoxicity.

Overview of Clinical Development Program

Approximately 2,000 human subjects have so far been exposed to solithromycin across all clinical studies that have been performed to date. Of these, in the integrated clinical trial dataset submitted by the sponsor there were a total of 1,474 study subjects who were exposed to the ketolide, including 920 adult individuals who were enrolled in the integrated Phase 2/3 CABP clinical trials and randomized to receive oral, IV, or IV (Day 1) followed by oral formulations of solithromycin for up to 7 days. In this study population, as well as in healthy volunteers in the integrated studies, and in participants in clinical studies to treat some other conditions, there was a robust signal of drug-induced liver test abnormalities or injury connected to the study drug.

As characterized both by the sponsor's expert Hepatic Safety Advisory Board (HSAB; Drs. Paul Watkins, James Freston, Leonard Seeff and Paul Tulkens) and the DAIP Clinical Review team, the protocol-driven clinical and biochemical monitoring of clinical study subjects has revealed a range of liver toxicities causally linked to solithromycin in normal volunteers and study subjects with CABP, COPD or NASH. These included 1) one case of symptomatic drug-induced cholestatic hepatitis in a patient with COPD who was treated for 23 days, until discontinuation of solithromycin due to the liver abnormalities; 2) higher percentages of solithromycin-treated individuals [most enrolled in the CABP trials] who developed asymptomatic drug-induced ALT/AST elevations relative to the randomized comparator groups [peaking at levels >3X ULN, >5-10X ULN, and one >20X ULN]. These ALT/AST abnormalities were accompanied by normal serum ALP and bilirubin levels in some instances, and increased ALP levels in others.

Solithromycin was discontinued by the study investigators due to the liver test abnormalities in a few cases. In many cases, beyond the characterization of liver test abnormalities and clinical findings, there was limited diagnostic or laboratory data that was provided in the integrated narratives. Because of a protocol rule to exclude enrollment of study subjects with a history of intolerance or hypersensitivity to any macrolide or fluoroquinolones, an assessment of DILI risk in individuals who had earlier toxic reactions to solithromycin, ketolide or macrolides before enrollment in the solithromycin trials is not achievable from this body of data. In addition to the aforementioned case of cholestatic hepatitis, 3/4 study subjects treated so far with solithromycin

Table 1 Number of Subjects and Patients in Pooled Studies in the ISS

Clinical Phase	Total Number of Subjects	Number of Subjects Administered Solithromycin	Number of Subjects Administered Comparator
Integrated Analysis Studies			
Phase 3 and Phase 2 Patients (All)	**1846**	**920**	**926**
Phase 3 Patients	1714	856	858
Phase 2 Patients	132	64	68
Phase 1 Subjects (All)	**671** [a]	**554**	**176**
Phase 1 Clinical Pharmacology Subjects	662	531	191
Oral Clinical Pharmacology Subjects	212	188	38 [b]
IV Clinical Pharmacology Subjects	363	270	138
Phase 1 Biopharmaceutics Oral Subjects	96	96	0
TOTAL			
Integrated Studies	**N=2517** [a]	**N=1474**	**N=1102**

Source: ISS Table 1.1
IV = intravenous.

a. The number of Phase 1 subjects administered solithromycin plus the number of subjects administered comparator does not equal the total number of subjects because some subjects received both study drugs in some studies.

b. Phase 1 subjects who received midazolam, ketoconazole, or rifampin were counted as receiving only solithromycin.

Table 2 Completed Phase 2 and 3 Studies in CABP

Study Number (Type of Study)	Design	Subjects (number) Sex Age Range	Solithromycin Administration	Comparator Administration
CE01-300 (Oral Efficacy and Safety in CABP)	Randomized, double-blind, multi-center	Adult patients (n=860 [ITT]; n=856 [Safety]) 456 M / 404 F 18-93 years	Solithromycin (n=424) 800 mg oral on Day 1, 400 mg oral on Days 2-5	Moxifloxacin (n=432) 400 mg Days 1-7
CE01-301 (IV to Oral Efficacy and Safety in CABP)	Randomized, double-blind, multi-center	Adult patients (n=863 [ITT]; n=858 [Safety]) 448 M / 415 F 18-94 years	Solithromycin (n=432) 400 mg IV on Day 1 400 mg daily After oral switch 800 mg oral first dose 400 mg oral daily Total of 7 doses	Moxifloxacin (n=426) 400 mg IV on Day 1 400 mg daily After oral switch 400 mg daily Total of 7 doses
Phase 3 Safety Subtotal		**n=1714**	**n=856**	**n=858**
CE01-200 (Oral Efficacy and Safety in CABP)	Randomized, double-blind, multi-center	Adult patients (n=132) 67 M / 65 F 18-87 years	Oral Solithromycin (n=64) 800 mg on Day 1; 400 mg on Days 2 to 5	Oral Levofloxacin (n=68) 750 mg on Days 1 to 5
Phase 2/3 Safety Subtotal		**n=1846**	**n=920**	**n=926**

Source: ISS Table 1.1
CABP=community-acquired bacterial pneumonia; F=female; ITT=Intent-to-Treat; IV=intravenous; M=male

Table 3 Non-Integrated Studies

Study Number Type of Study	Design	Subjects / Patients (number) Sex Age Range	Solithromycin Administration
CE01-113 PK in subjects with hepatic impairment (completed)	Open label, healthy control	Hepatically impaired subjects (n=24) 18 M / 6 F 42-68 years Healthy adult subjects (n=9) 6 M / 3 F 51-66 years	Solithromycin capsules (n=24 hepatically impaired subjects) (9 healthy subjects counted in integrated studies) 800 mg Day 1, 400 mg Days 2-5
CE01-115 PK in subjects with renal impairment (completed)	Open label, healthy control	Renally impaired subjects (n=16) 7 M / 9 F 48-82 years Healthy adult subjects (n=9) 4 M / 5 F 40-68 years	Solithromycin capsules (n=16 renally impaired subjects) (9 healthy subjects counted in integrated studies) 800 mg Day 1, 400 mg Days 2-5
CE01-204 Phase 2a Effect on airway inflammation in COPD (ongoing)	Randomized, double blind, placebo controlled, crossover	Patients with COPD ≥45 years (n=36 planned)	Solithromycin capsules 400 mg solithromycin or placebo 28 days, cross over to other drug for 28 days after 4-week washout (4 received solithromycin)
CE01-205 Phase 2a Treatment of NASH (Ongoing)	Open label	Patients 18 - 70 years with evidence of NASH (n=up to 15 planned)	Solithromycin capsules 200 mg for 91 days (n=4)
T4288-102 Multiple Dose PK (Toyama-sponsored) (Completed)	Randomized, double blind, placebo controlled	Healthy adult males (n=30) 30 M / 0 F 20 - 39 years	Solithromycin capsules 800 mg QD Day 1, 400 mg QD Days 2-7; or 600 mg QD Days 1-7 (n=24)
T4288-201 Phase 2 Treatment of CABP (Toyama-sponsored) (Ongoing)	Randomized, double blind, active controlled	Adults with CABP (n=115 as of January 3, 2016) (Enrollment Target=150) 70 M / 45 F 20 - 94 years of age	Solithromycin 800 mg Day 1 400 mg Days 2-5, or Solithromycin, 400 mg BID Day 1, 400 mg Days 2-5 or Levofloxacin, 500 mg QD

CABP=community acquired bacterial pneumonia, COPD=chronic obstructive pulmonary disease, NASH=non- alcoholic steatohepatitis, PK=pharmacokinetic

in the COPD trial (28-day active treatment protocol) for a period longer than 2 weeks developed serum liver enzyme abnormalities. In one of the few subjects enrolled in a NASH trial (90-day active treatment protocol) to date, the ketolide was temporarily discontinued and then restarted with lower frequency dosaging, due to rises of serum liver enzymes.

Summaries of the solithromycin clinical studies that were analyzed in the sponsor's Integrated Summary of Safety (ISS) are provided in Tables 1 & 2.

Table 4. Elevation of Hepatic Enzymes in the Phase 3 CABP study population

Parameter (unit)	Study CE01-300		Study CE01-301		Pooled Phase 3	
	Solithromycin Oral N=424 n (%)	Moxifloxacin Oral N=432 n (%)	Solithromycin IV to Oral N=432 n (%)	Moxifloxacin IV to Oral N=426 n (%)	Solithromycin N=856 n (%)	Moxifloxacin N=858 n (%)
ALT (U/L), n/N1						
>3×ULN	22/411 (5.4)	15/422 (3.6)	38/417 (9.1)	15/413 (3.6)	60/828 (7.2)	30/835 (3.6)
>5×ULN	7/411 (1.7)	5/422 (1.2)	13/417 (3.1)	3/413 (0.7)	20/828 (2.4)	8/835 (1.0)
>10×ULN	1/411 (0.2)	2/422 (0.5)	0/417	0/413	1/828 (0.1)	2/835 (0.2)

Table 5. Frequency of Hepatic Safety Laboratory Parameter Elevations and AEs at any Post-baseline study visit for Solithromycin and Comparators in the CABP Phase 3 Studies

Outcome Measure		CE01-300		CE01-301	
		Solithromycin n/N (%)	Moxifloxacin n/N (%)	Solithromycin n/N (%)	Moxifloxacin n/N (%)
ALT	>ULN	172/411 (41.8)	141/422 (33.4)	198/417 (47.5)	122/413 (29.5)
	>3×ULN	22/411 (5.4)	15/422 (3.6)	38/417 (9.1)	15/413 (3.6)
	>5×ULN	7/411 (1.7)	5/422 (1.2)	13/417 (3.1)	3/413 (0.7)
	>10×ULN	1/411 (0.2)	2/422 (0.5)	0/417	0/413
	>20×ULN	1/411 (0.2)	1/422 (0.2)	0/417	0/413
AST	>ULN	130/406 (32)	112/416 (26.9)	154/416 (37.0)	97/409 (23.7)
	>3×ULN	10/406 (2.5)	8/416 (1.9)	20/416 (4.8)	10/409 (2.4)
	>5×ULN	4/406 (1.0)	4/416 (1.0)	9/416 (2.2)	2/49 (0.5)
	>10×ULN	2/406 (0.5)	2/416 (0.5)	2/416 (0.5)	0/409
	>20×ULN	0/406	1/416 (0.2)	0/416	0/409
ALP	>1.5×ULN	22/411 (5.4)	17/423 (4.0)	21/417 (5.0)	7/415 (1.7)
	>3.0×ULN	7/411 (1.7)	2/423 (0.5)	1/417 (0.2)	1/415 (0.2)
ALT or AST >3×ULN	& with Total Bilirubin >1.5×ULN	1/412 (0.2)	1/422 (0.2)	1/416 (0.2)	1/413 (0.2)
	& with Total Bilirubin >2.0×ULN	0/412	0/422	1/416 (0.2)	1/413 (0.2)
	& with ALP >1.5×ULN	10/411 (2.4)	5/422 (1.2)	11/416 (2.6)	3/413 (0.7)

To augment the analysis of liver safety data, the sponsor also provided some data acquired from a set of additional studies (some not completed) that have not been integrated into the ISS (Table 3). With reference to the characterization of risk of DILI associated with solithromycin, an assessment of these data is important. In particular, two of the non-integrated studies have protocols in which solithromycin administration is intended for either 28 days (COPD trial) or 3 months (NASH trial). The detection of a compelling signal for liver hepatotoxicity in their small

emerging study populations treated with the study drug provides crucial information about the impact that the duration of treatment and/or total treatment exposure with solithromycin may have on DILI risk (see below).

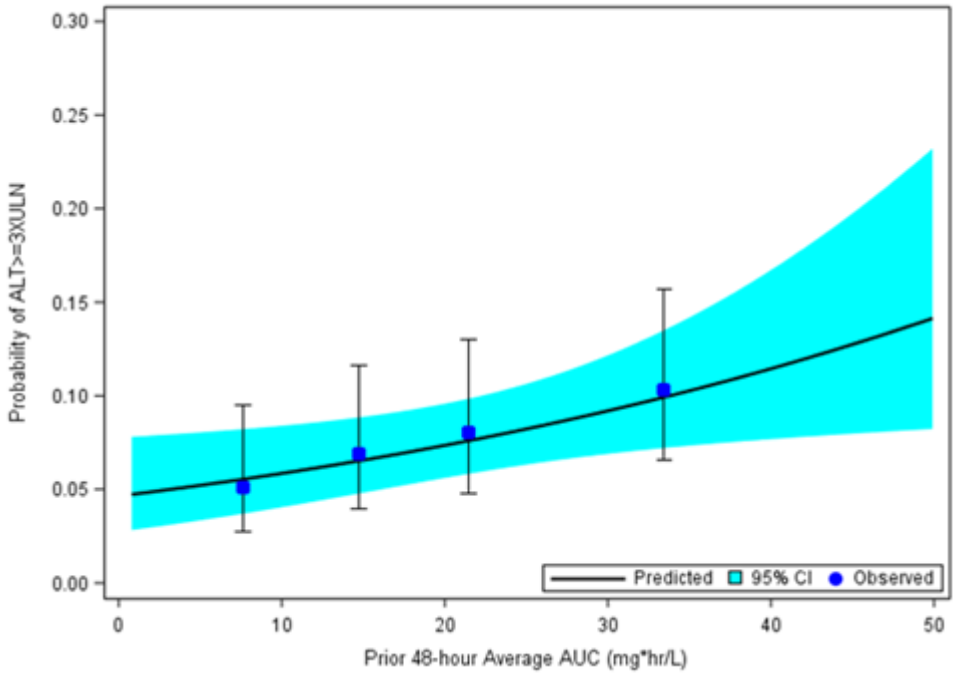
A finding across many of the randomized clinical trials within the solithromycin development program is the presence of higher percentages of isolated liver serum enzyme elevations (accompanied by normal bilirubin levels) in subjects treated with the ketolide, relative to the comparator treatment groups. These elevations have typically been observed to peak during treatment in serum samples collected on Day 4 – 11. Study subjects with these abnormalities have often been asymptomatic with rapidly resolving liver test abnormalities after cessation of solithromycin treatment. In some cases, adaptation marked by biochemical test improvement despite continued treatment with solithromycin was documented, whereas in others the drug was discontinued before improvement was observed. Of note, the range of peak levels, even with short-term treatment for CABP was broad (see Tables 4 & 5) and because of the high multiples of the AT upper limits of normal in at least one case the antibiotic was discontinued before completion of the dosaging schedule. Finally, in some, but not all instances associated with a rise of aminotransferases (in which the bilirubin levels remained within normal limits), the alkaline phosphatase levels (ALP) also increased to levels above 2X ULN (see below) to yield a 'mixed hepatocellular - cholestatic injury' picture with R values slightly less than 5. Nonetheless, there were also cases that were entirely hepatocellular in which the ALP levels did not rise and the R values exceeded 5.

Both preclinical and Phase I dose escalation studies in healthy subjects have identified liver toxicity manifested as elevations of serum ALT as an important dose and overall drug exposure limiting factor. In the CABP Phase 3 studies there were higher rates of ALT elevations >3X ULN and >5X ULN in CE01-301 compared to CE01-300. This difference is attributable to the overall higher drug exposure in CE0-301 due to protocol differences of formulations (IV vs PO), dosaging and durations of treatment. When average AUC over a 48hr period was measured as an indicator of solithromycin exposure, individual PK data derived from study subjects of the two Phase 3 studies revealed a positive correlative relationship between drug exposure levels and the probability of increased ALT levels (see Figure 1).

Because solithromycin accumulates in liver cells at much higher concentrations than in serum, the use of AUC to reflect increasing hepatic exposure may underestimate dosaging-driven accumulating shifts in the liver tissue concentrations of the ketolide and/or its metabolites that probably directly drive the observed ALT effects. Nonetheless, exogenous or endogenous factors that increase AUC would still be likely connected to ALT elevations and an increasing risk for hepatotoxicity. These include a) increasing the number of days in which the IV formulation is administered, b) increasing the oral dose (from 400 mg to 800 mg) on the day of switch from the initial IV formulation, and/or c) extending the duration of treatment (e.g. from 5 days to 7 days, or longer). Analyses performed by the sponsor / OCP have shown that increasing the number of days of IV dose administration beyond one dose on the first day of treatment was connected to a substantial rise in the percentage of treated subjects who developed serum ALT > 3X ULN (8.3% vs 2.8%). With reference to endogenous factors, certain drug – drug interactions (DDI) affecting shared transporters or metabolizing enzymes have a strong potential to increase AUC levels. In addition, a reduced Creatinine Clearance of solithromycin

has been found to increase values of the antibiotic's AUC. Dose adjustment may be required to offset increased exposure to solithromycin causing liver toxicity in patients with DDI or moderate or severe renal insufficiency.

Figure 1. Relationship between the Probability of Patients with ALT > 3xULN in Study CE01-300 and CE01-301 and the Prior 48-hour Average AUC[1]

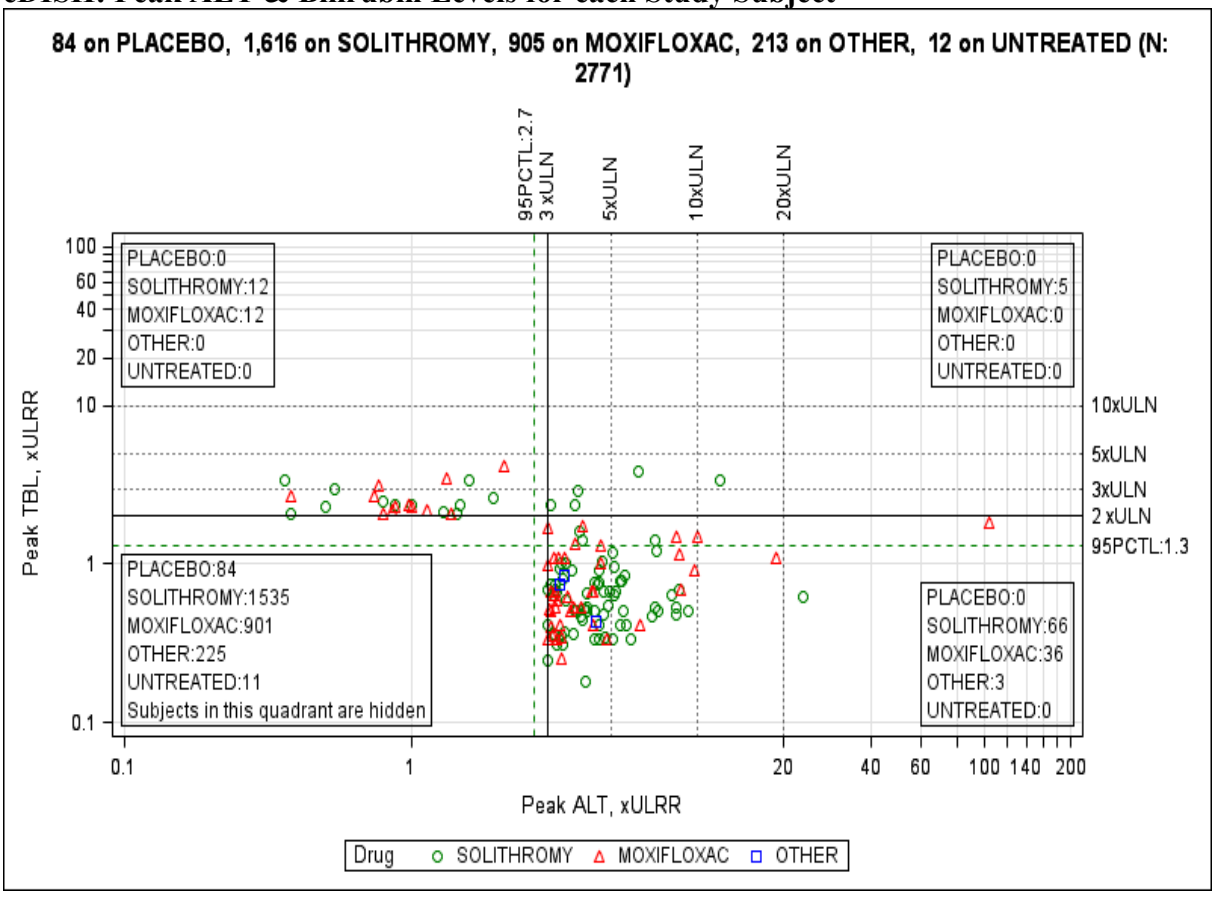


[1]From FDA's Clinical Pharmacology Review

eDISH ANALYSIS OF SOLITHROMYCIN CLINICAL TRIALS

Brief study subject-level narratives of cases of acute liver injury across all the integrated studies were compiled in the sponsor's ISS, as well as a separate submission entitled the 'Solithromycin Hepatic Safety Review'. The narratives with liver abnormalities were only provided for cases marked by the following characteristics: a) Patients discontinuing solithromycin due to liver-related AEs or events, b) ALT >3×ULN and bilirubin >2×ULN post-baseline, c) ALT >3×ULN and bilirubin ≥ 1.5×ULN post-baseline, d) total bilirubin >2×ULN post-baseline, e) Phase 1 studies with an ALT or AST >5×ULN, f) Phase 3 CABP trials with an ALT >5×ULN, g) Phase 3 CABP trials with an AST >5×ULN or ALP >5×ULN, without an ALT >5×ULN, h) non-integrated study cases with notable liver findings. In response to an Information Request from FDA, the sponsor has also submitted the integrated and non-integrated clinical study population liver test data in an e-DISH format, with links to the clinical narratives of the cases with the liver abnormalities listed above. Dr. Ted Guo, PhD, a Mathematical Statistician in the Office of Biostatistics has expertly supervised this data transfer and integration with eDISH.

eDISH: Peak ALT & Bilirubin Levels for each Study Subject[1]



[1]Pooled Data from Integrated and Select Non-Integrated Solithromycin Clinical Trials

CASE ASSESSMENTS

Below, based on liver test result criteria, I have listed some of the solithromycin-associated cases of interest and the sponsor's assessments of causal relatedness with the antibiotic across the clinical trials for CABP, a Phase 1 study in normal volunteers and for the treatment of COPD and NASH. With the clinical and lab information that was provided, cases of liver injury that were more likely attributable to an alternate cause have been excluded from the list. Therefore, based on the information that has been provided and using a categorical scale widely employed by experts at FDA and the NIH Drug-induced Liver Injury Network (DILIN) (see Appendix), I have assessed the hepatotoxic events identified in the cases that have been listed below as greater than 50% likelihood ['Probable', 'Highly Likely', or 'Definite'] in their causal association with solithromycin. Representative cases among these are followed by their eDISH narratives, graphs and/or tables; these are indicated with an asterix. In a few of the listed cases, solithromycin may have 'Possibly' contributed to the worsening of an underlying liver biochemical abnormality that was present at baseline. These are summarized and indicated with a 'bw'.

A. Cases with Peak ALT and/or AST >5X ULN, or who discontinued Solithromycin due to Liver Test Results & Sponsor's Assessment of Causal Relatedness

CE01-300 (CABP Phase-3 Trial; n=426 treated with solithromycin)

054-0629*
124-0028
309-0406
509-0320 [bw] Legionella infection, Baseline ALT 2.7X ULN increased to 8.1X ULN
608-0060
805-0082*
805-0397
708-0089
210-0163

CE01-301 (CABP Phase-3 III Trial; n=434 treated with IV & PO solithromycin)
1075-003
2007-001 [bw] Mycoplasma infection, Baseline ALT 1.9X ULN increased to 5.1X ULN
2013-001
2311-007*
2418-003
2616-010*
3206-001
3306-012
3309-007*
3309-009* [bw] Baseline ALT 2.0X ULN increased to 5.1X ULN
3606-015* [bw] Baseline ALT 2.0X ULN increased to 5.1X ULN
3606-020
3804-004

CE01-200 (CABP Phase-2 Trial; n=65 treated with solithromycin)
0149-0008 [bw] HCV infection, Baseline ALT 2.0X ULN increased to 4.9X ULN

CE01-116 (PK study; Single & Multiple IV or IV/PO Doses; Normal Volunteers, n=62)
Subject 5003*

CE01-204 (Randomized COPD Trial; n=3 treated with solithromycin)
Subject 0001*
Subject 0005*
Subject 0006*

CE01-205 (Open Label NASH Trial; n=4 treated with solithromycin)
Subject 0005*

B. List of Cholestatic Cases with Peak ALP >5X ULN & Sponsor's Assessment of Causal Relatedness

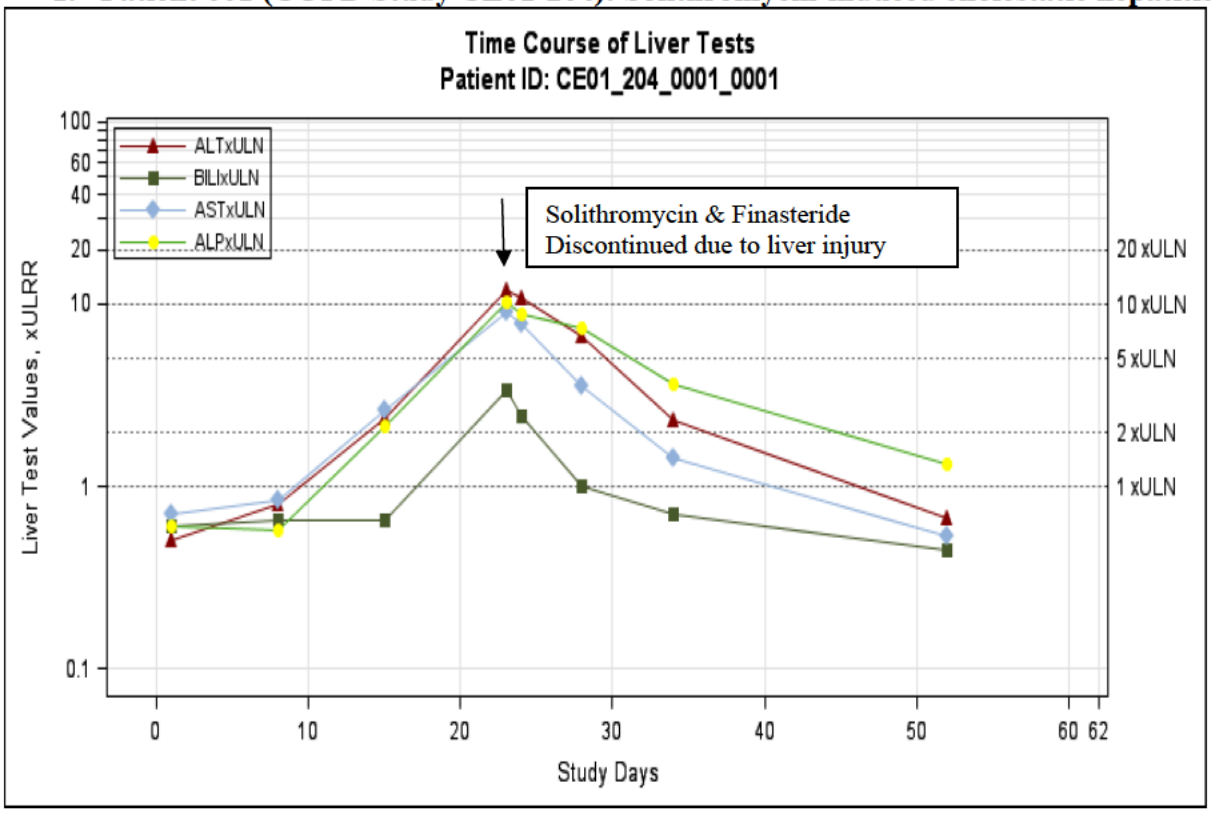
CE0-300 (CABP Phase-3 Trial; n=426 treated with solithromycin)
271-0202*
904-0120

CE0-301 (CABP Phase-3 III Trial; n=434 treated with IV & PO solithromycin)
2307-016 [bw] Hepatosplenomegally, Baseline ALP 4.2X ULN increased to 11.3X ULN

EVALUATION OF REPRESENTATIVE CASES

Among the cases listed above, I have selected a subset that represents a range of Solithromycin-associated hepatotoxicity injuries that has so far been observed in the drug development program. Narratives provided by the sponsor follow the graphically displayed time course of ALT, AST, ALP and total bilirubin measurements in these cases (using e-DISH), as well as extractions from the narratives and relevant lab data that have been provided by the sponsor. These cases are asterixed in the list, above. My brief clinical and causality assessments with a categorical assessment scale widely used by FDA and NIH DILIN expert analysts (see Appendix) are italicized.

1. Patient 001 (COPD Study CE01-204): Solithromycin-induced cholestatic hepatitis



Narrative: This 69-year-old male with a history of COPD and benign prostatic hypertrophy received 400 mg oral solithromycin for 23 days (of a planned 28 day course). Concomitant medications at the time of enrollment included fluticasone/salmeterol and salbutamol metered-dose inhalers and oral finasteride 5 mg QD. Hepatic safety labs were normal at baseline and Day 8. At Day 15, elevations of ALT, AST, and ALP values without associated bilirubin change were noted. Study drug dosing continued, with a follow up evaluation at Day 23. At that time, further increases in ALT (to 476 U/L, 11.9×ULN), AST (to 368 U/L, 9.0×ULN) and ALP (to 1316 U/L, 10.1×ULN) were noted, as well as elevation of total bilirubin to 4.0 mg/dL (2.2×ULN), accompanied by the new onset of eosinophilia [The eosinophil count increased from 300/µL (Day 1) to 1,600/µL]. Administration of solithromycin and finasteride was

discontinued. The patient was mildly icteric, with pruritus. An ultrasound of the liver and biliary tract was normal, and viral hepatitis screens were negative. On Day 24, the following day, hepatic aminotransferase tests and bilirubin had improved somewhat although the eosinophil count remained high (1,800/μL). On a follow-up visit on Day 28, steady improvement in liver chemistries was observed, and itching had resolved. The patient continued in follow-up until Day 52 (29 days after study drug was stopped) when all of the liver test results, as well as the eosinophil count, had returned to the normal range. The patient did not require hospitalization for this event. Liver function as measured by prothrombin time (INR) remained normal throughout. Plasma concentrations of solithromycin and finasteride were measured at Day 7, Day 14 and Day 23 at about 4 hours post dose (predicted C_{max} timepoint). Solithromycin concentrations were 718, 993, and 750 ng/mL (these values were within the expected range). Finasteride concentrations were elevated 3- to 4-fold above the reported values for a 5 mg dose.

Patient 001 (COPD Study CE01-204): Tabulated Lab Data[1]

Visit/ Day	ALT		AST		Bilirubin		ALP		WBC	EOS	Creat	PT
	U/L	×ULN	U/L	×ULN	Total ULN:1.2 mg/dL	Direct ULN:0.4 mg/dL	U/L	×ULN	×10³/μL	×10³/μL	mg/dL	INR
Day 1	20	0.5	29	0.7	0.7	0.2	78	0.6	5.7	0.3	0.8	
Day 8	32	0.8	34	0.8	0.8	0.2	74	0.6	7.1	0.2	0.8	
Day 15	95	1.4	106	2.6	0.8	0.3	277	2.1	6.3	0.4	0.9	0.9
Day 23	476	11.9	368	9.0	4	2.2	1316	10.1	9.5	1.6	0.8	0.9
Day 24	427	10.7	322	7.9	2.9	1.5	1155	8.9	9.2	1.8	0.7	1
Day 28	269	6.7	144	3.5	1.2	0.5	969	7.5	6.8	1.2	0.7	
Day 34	92	2.3	59	1.4	0.8		471	3.6	6.1	0.7	0.7	0.9
Day 52	27	0.7	22	0.5	0.5	0.2	170	1.3	7.2	0.4	0.7	

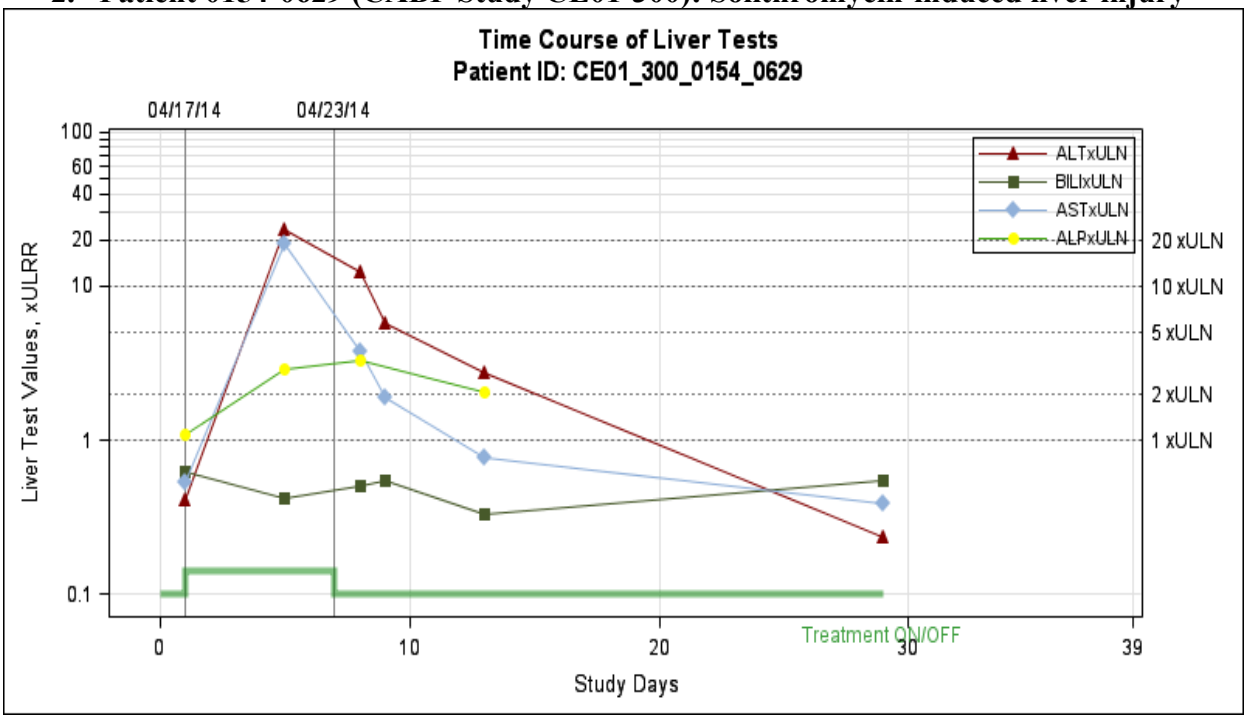
[1] Sponsor's Hepatic Safety Review, Table 57

Asse***ssment:*** *The case represents a clinically significant episode of solithromycin-induced hepatotoxicity (Severity Level 2) marked by jaundice and pruritis, in which a causal association with the study drug in my view is 'Highly Likely'. I agree with the sponsor's assessment that the ..' concomitant elevations of ALP, ALT, and bilirubin characterize this event as an episode of cholestatic hepatitis, a clinically significant event…' and… 'a well-recognized' adverse event tied to macrolides. Nonetheless, in contextualizing this point, it should be noted that macrolide-induced cholestatic hepatitis is a rare idiosyncratic event. Compared with the small overall exposure of solithromycin in the drug development program, the other macrolides have had a much higher overall usage in the post-market. The accompanying eosinophilia in this case is consistent with hypersensitivity as a possible basis for the solithromycin-associated liver injury. Together with the clinical manifestations of cholestatic liver injury, the systemic eosinophilic response represents a compounded mechanism of injury when compared with cases with isolated and asymptomatic ALT elevations tied to increasing solithromycin exposure (see above). Of concern is that among the 3 patients who had been enrolled into the COPD study [28-day solithromycin treatment trial (CE01-204)] and randomized to receive solithromycin at the time of the sponsor's last NDA submission, all three developed various levels of acute solithromycin-induced liver injury (see other cases below). In addition, in the NASH study [3-month solithromycin treatment trial (CE01-205)] which had only enrolled four patients, at least one study subject developed solithromycin-induced hepatocellular liver injury on Day 29, prompting*

a 16-day suspension of treatment until treatment with the drug was reinstituted to complete the planned course of therapy (see below).

The sponsor is correct in pointing out that in the face of its extensive post-marketing use finasteride has NOT been identified as an agent that causes idiosyncratic liver injury. The observation that circulating finasteride levels had increased at the time of the liver injury suggests that common pathways of clearance (Cyp 3A4, BSEP) were driven by solithromycin exposure or the liver injury itself. Nonetheless, there is no evidence that the increases in finasteride levels, per se, would have been responsible for the cholestatic liver injury in this case. As the sponsor has pointed out, four other individuals in the CABP trials who were receiving finasteride, when treated with solithromycin, did not develop liver injury.

2. Patient 0154-0629 (CABP Study CE01-300): Solithromycin-induced liver injury

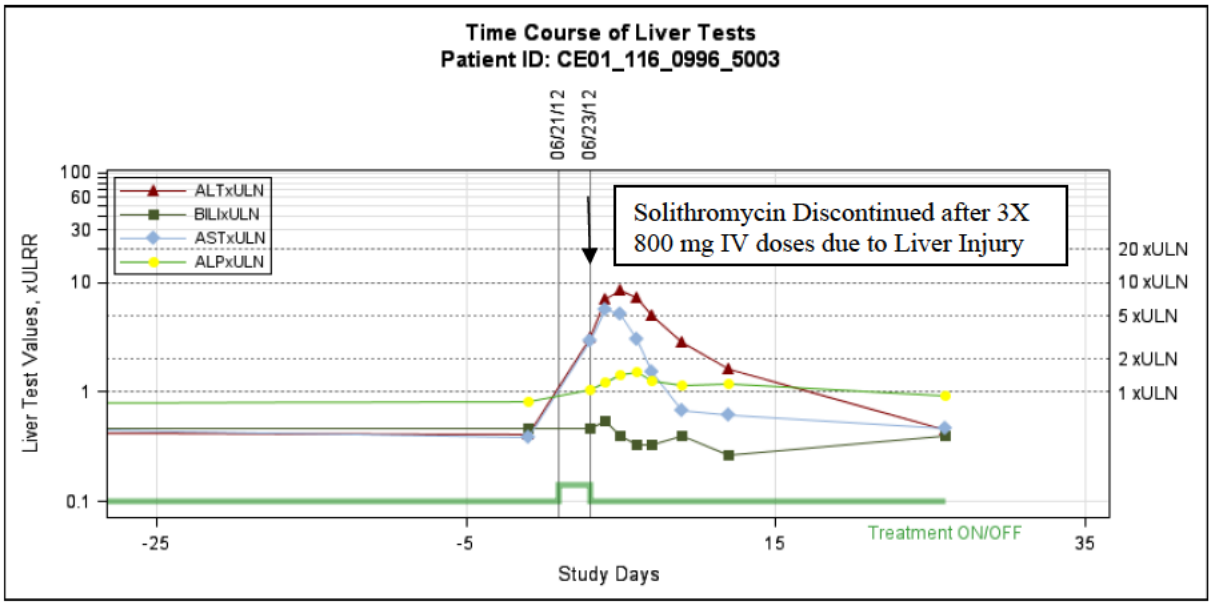


Narrative: This 65 year old female with CABP received 5 oral doses solithromycin (Days 1-5) and 2 doses of placebo (Days 6 and 7). She had a medical history of hypertension, type 2 diabetes, and hyperlipidemia and was receiving valsartan, rosuvastatin, hydrochlorothiazide, and metformin prior to enrollment in the study. Rosuvastatin was stopped on Day 1 (the CPK values were consistently WNL). A microbiological diagnosis of Legionella infection was established by acute and convalescent serologic testing. The liver test results were normal or near normal at baseline: Prior to treatment with solithromycin, the baseline measures included: serum ALT 14 U/L, AST 18 U/L, total bilirubin 0.4 mg/dL, and ALP 132 U/L (1.1xULN), absolute eosinophil count 690/microliter (ULN 570/microliter) and eosinophil percentage 10.6% (ULN 6.8%). The elevated eosinophil parameters improved following study drug dosing. Baseline HBSAg and HCV RNA tests were negative, and there was no medical history of liver disease. The patient developed asymptomatic hepatic enzyme elevations during treatment. ALT values on Days 5, 8, 9, 13 and 29 were 790 U/L (23.2xULN), 416 U/L (12.2xULN), 315 U/L (9.3xULN), 93 U/L

(2.7x ULN), and 13 U/L, respectively. AST values followed a similar course, with values on Days 5, 8, 9, 13 and 29 of 636 U/L (18.7xULN), 129 U/L (3.8xULN), 65 U/L (1.9xULN), 26 U/L and 13 U/L, respectively. Total bilirubin did not exceed the ULN with values of 0.4, 0.5, 0.6, 0.7, 0.4, and 0.7 mg/dL on Days 1, 5, 8, 9, 13, and 29, respectively. ALP rose from 132 U/L at baseline on Day-1, to values of 350 U/L (2.8xULN), 405 U/L (3.3xULN), and 252 U/L (2.0xULN) on Days 5, 8, and 13, respectively. Gamma glutamyl transferase (GGT) was tested in a local laboratory and was elevated at 753 U/L (15.1xULN of 50 U/L) on Day 8, with a subsequent decline to 475 U/L (9.5xULN) on Day 13. At baseline, the lactate dehydrogenase (LDH) was normal, with a value of 153 U/L (ULN is 234 U/L). At Days 5, 8, and 13, the corresponding LDH values were 687 (2.9x ULN), 180, and 162 U/L, respectively. An abdominal ultrasound was recommended by the sponsor, but was declined by the investigator who noted the absence of symptoms of liver injury. The INR at baseline was 1.0 and in follow up on Day 8 was 0.9, suggesting that hepatic synthetic function was not compromised during this episode. The R-value (ALT fold ULN/Alkaline phosphatase fold ULN) at Day 5 was 8.3, consistent with the pattern of a predominantly hepatocellular injury, despite the fact that the concomitant alkaline phosphatase had risen to 2.8 XULN. The sponsor concluded that the liver injury test abnormalities were related to solithromycin, contravening an interpretation by the site investigator that they were not related.

Assessment: *I agree with the sponsor's assessment that this case of liver toxicity is related to solithromycin treatment. In my view, a causal association of the hepatotoxic event with this agent is 'Probable'. The case represents an episode of asymptomatic solithromycin-induced liver toxicity that occurred within five days of initiating the oral antibiotic. With an ALT level peaking at 23X ULN (Day 5) and an ALP at 3.3X ULN (Day 8) (Severity Category: Level-1) and reversal of the liver abnormalities only after the 5-day planned treatment course of solithromycin was completed, it is not discernable whether liver injury would have progressed had there been continuation of solithromycin treatment or a history of prior sensitization to the ketolide or another macrolide.*

3. **Healthy Volunteer 0996-5003 (PK study CE01-116): Solithromycin-induced liver injury**



Narrative: This 36-year-old healthy male volunteer on no chronic medications only received three 800 mg IV doses of solithromycin over approximately 48 hours (Days 1, 2, and 3). Baseline hepatic safety laboratory tests were normal (ALT 26 U/L, AST 16 U/L). On Day 3 the ALT was 3.1xULN (196 U/L) with a similarly elevated AST (118 U/L, 2.8xULN), and the study drug dosing was discontinued. On Day 4, the ALT was 6.9xULN (436 U/L) and the AST elevations peaked at 5.7xULN (234 U/L). The ALT elevations peaked at 8.4xULN (532 U/L on Day 5, with an AST value of 5.1xULN (210 U/L). Thereafter, the ALT values on Days 6, 7, 9, 12 and 26 were 448 U/L, 316U/L, 178 U/L, 102 U/L and 28 U/L, respectively (7.1xULN, 5xULN, 2.8xULN, 1.6xULN, and within normal range). At Days 6, 7, 9, 12 and 26, the AST values were: 124 U/L (3x ULN), 62 U/L (1.5xULN), 28 U/L (normal), 25 U/L (normal), and 19 U/L (normal), respectively. ALP rose from normal at baseline (102 U/L), to 132 U/L on Day 3, to 154 U/L on Day 4 (1.2xULN), to 177 U/L on Day 5 (1.4xULN), peaking on Day 6 at 194 U/L (1.5xULN), and then dropping to 146 U/L (1.1xULN) on Day 9, before returning to a normal value (117 U/L) on Day 26. Direct and total bilirubin values were normal at all time points, and the patient remained asymptomatic. All the liver parameters had returned to normal by Day 26. Note that 400 mg, rather than 800 mg intravenous doses have been utilized in the subsequent CABP phase 3 trials.

Assessment: *The liver acute liver injury in this normal healthy volunteer in a Phase I PK study of solithromycin in my view is 'Definite' or, at the very least, 'Highly Likely' in its causal association with the ketolide. The injury which occurred only after 3 daily 800 mg IV doses of the antibiotic was hepatocellular by biochemical profile. Although it did not progress to serious liver injury, the ALT levels continued to ascent for 2 more days after discontinuation of the study drug until reversing course, suggesting that the cessation of solithromycin administration itself, rather than adaptation, was the key determinant of the pathway to hepatocellular recovery. Problematically, this case may reflect a steep dose – liver injury response curve for solithromycin, such that a mere doubling of daily dosing (from 400 mg to 800 mg) may reduce the latency from initiation of treatment, as well as increase the rate at which even healthy volunteers may develop hepatotoxicity. Dosing limits of both the IV and oral formulations for outlier individuals who may have an increased susceptibility to solithromycin-induced DILI remain to be determined.*

4. Patient 805-0082 (CABP Study CE01-300): Solithromycin-induced liver injury

This 82-year-old male with a past medical history of hypertension and coronary artery disease treated with perindopril, isosorbide and dalteparin, who developed CABP, received 5 daily doses of oral solithromycin. Other concomitant medications received during the study included acetylcysteine and metamizole. No microbiological diagnosis was established. At baseline, the ALT (18 U/L), AST (23 U/L), total bilirubin (0.5 mg/dL) and ALP (61 U/L) were all normal. On Day 4, the ALT was 36 U/L (ULN is 32 U/L), AST was 48 U/L (1.3xULN), total bilirubin was normal (0.6 mg/dL), and ALP was normal (75 U/L). On Day 7, the ALT was 94 U/L (2.7xULN), AST was 54 U/L (1.5xULN), while the total bilirubin and ALP remained normal. On Day 12, while he remained asymptomatic, the ALT had increased to 178 U/L (5.1xULN), AST was 121 U/L (3.4xULN), with normal bilirubin (0.6 mg/dL) and ALP (104 U/L). Baseline tests for HCV RNA and HBV Surface Antigen were negative. INR was minimally elevated at baseline (1.3) and normal on Day 7 (1.2). The patient was seen on Day 146 at which time ALT was 9 U/L, and AST was 11 U/L.

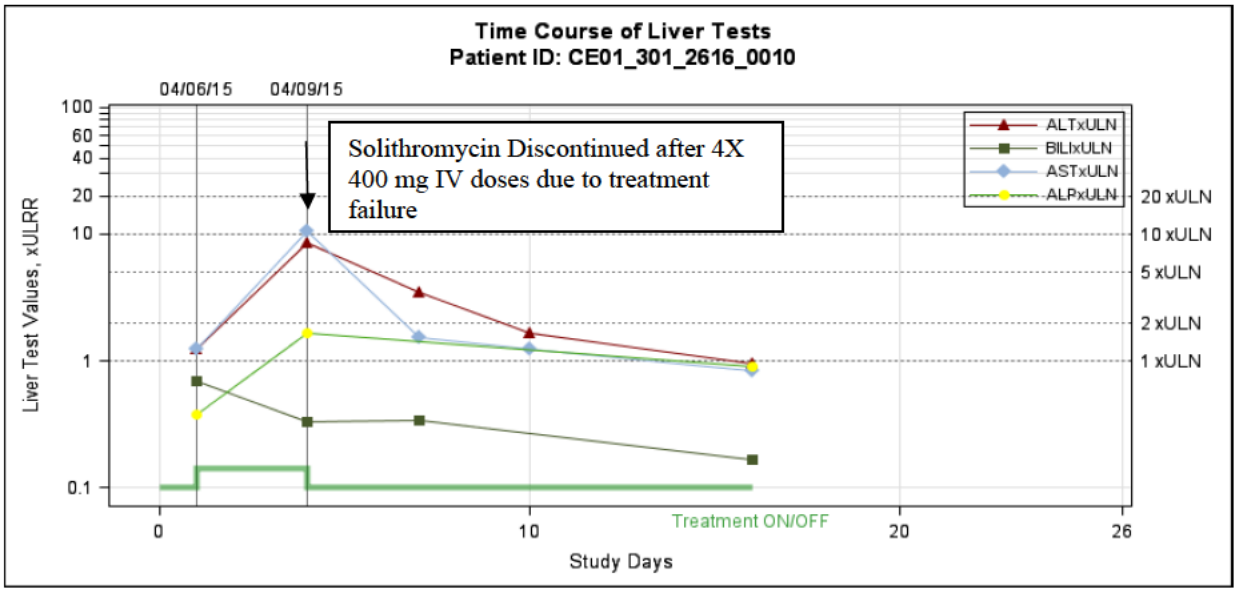
Patient 805-0082 (CABP Study CE01-300): Tabulated Lab Data[1]

Visit/Day	ALT		AST		Bilirubin		ALP	WBC	EOS	Creat	PT
	U/L	×ULN	U/L	×ULN	Total ULN: 1.2 mg/dL	Direct ULN: 0.4 mg/dL	U/L	x10³/µL	x10³/µL	mg/dL	INR
Baseline Day 1	18		23		0.5	0.2	61	4.2	0.05	0.8	1.3
ECR Day 4	36	1	48	1.3	0.6	0.2	75	5.7	0.31	0.6	
EOT Day 7	94	2.7	54	1.5	0.6	0.2	107	7.4	0.36	0.6	1.2
SFU Day 12	178	5.1	121	3.4	0.6	0.2	104	5.6	0.13	0.7	
Unsched Day 146	9		11								

[1]Sponsor's Hepatic Safety Review, Table 37

Assessment: *The sponsor's assessment that the liver injury is attributable to the study drug is correct in my view. In my judgement the causal association of the acute rise in ALT which began on Day 7 and progressed on Day 12 is 'Probable' in its causal association with Solithromycin. This case is marked by a Level 1 category of clinical severity. Compared to some of the other listed cases characterized by transient dose-related amino transferase elevations that occurred within a few days of starting treatment with the study drug, this case is one of a number that have a delayed signature of solithromycin-associated liver injury in which the serum enzyme elevations only occurred after the 5-day treatment period had been completed. The post-treatment phenomenon of hepatotoxicity is not consistent with immediate effects of high circulating levels of solithromycin. Moreover, adaptation was not a feature of this event.*

5. Patient 2616-0010 (CABP Study CE01-301): Solithromycin-induced liver injury

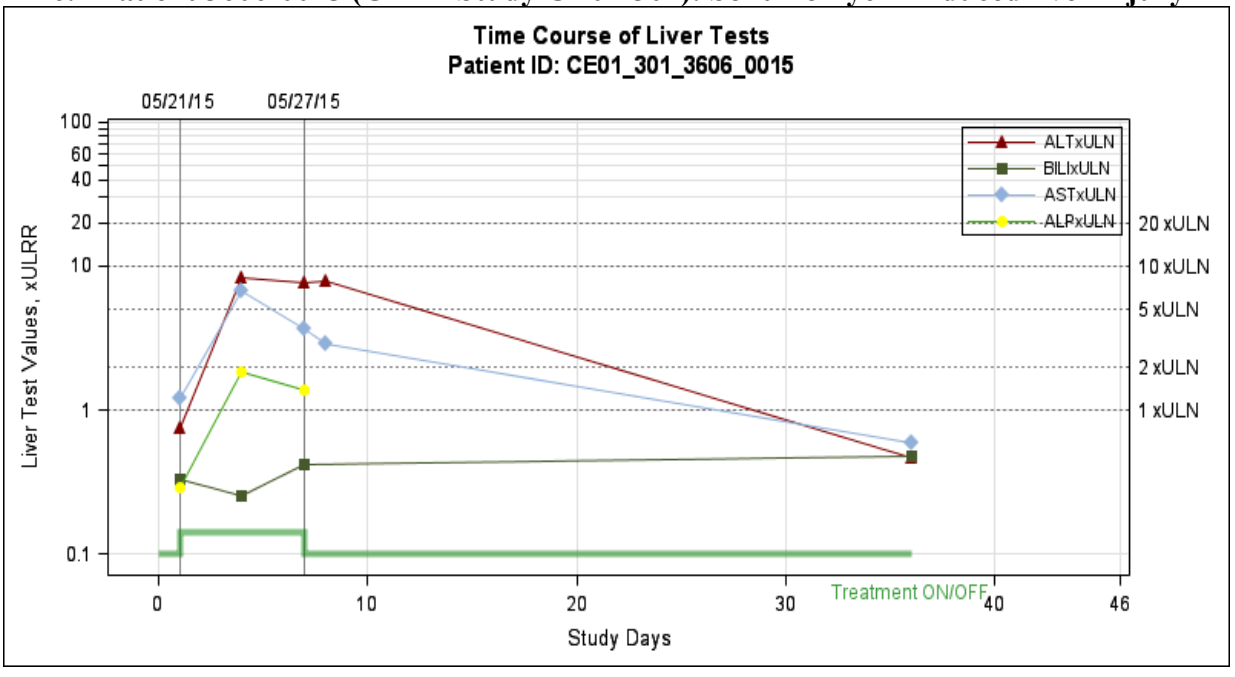


Narrative: This 43 year old male with CABP and no significant past medical history received 4 daily IV doses of Solithromycin (400 mg/dose, Days 1-4). Staphylococcus aureus was grown from sputum and pneumococcus was detected by quantitative nasopharyngeal PCR. Concomitant medications during study drug dosing included acetaminophen and mucolytics (bromhexine and ambroxol). Due to persistent cough and dyspnea, treatment was considered unsuccessful at Day

5, and therapy was switched to doripenem and vancomycin. At baseline, the ALT was 41 U/L, AST 38 U/L, ALP 48 U/L and total bilirubin 0.6 mg/dL. On Day 4, the ALT was 370 U/L (8.6xULN), AST was 376 U/L (10.4xULN), ALP was 215 U/L (1.6xULN), with a normal total bilirubin of 0.4 mg/dL. Somewhat improved by Day 7, the ALT was 138 U/L (3.4xULN) and AST was 54 U/L (1.5xULN). On Day 10, the ALT was 66 U/L (1.6xULN) and AST was 43 U/L (1.2xULN); ALP was not measured on Day 7 or 10. By Day 16, these values had returned to normal with ALT 41 U/L, AST 30 U/L, and ALP 117 U/L. Bilirubin levels remained normal at all the time points that were tested. The patient reported no AEs. This patient was a treatment failure, with the white blood cell count rising from 7.0 thousand/µL at baseline to 11.7 thousand/µL on Day 4.

Assessment: *In my view the sponsor's conclusion that the elevations of liver test values on Day 4 were likely study drug-related is correct. In my view the causal association with solithromycin is 'Highly Likely'. The case was distinguished by exposure to only 4 daily doses of IV Solithromycin (400 mg) before switching to another antibiotic regimen due to treatment failure. With ALT and ALP levels peaking on Day 4 at 8.6X ULN and 1.6X ULN, respectively, the R value was >5. These values in a Severity Level 1 injury point to a predominantly hepatocellular pattern of toxicity. It is not discernable whether liver injury would have progressed had there been continuation of solithromycin treatment.*

6. Patient 3606-0015 (CABP Study CE01-301): Solithromycin-induced liver injury

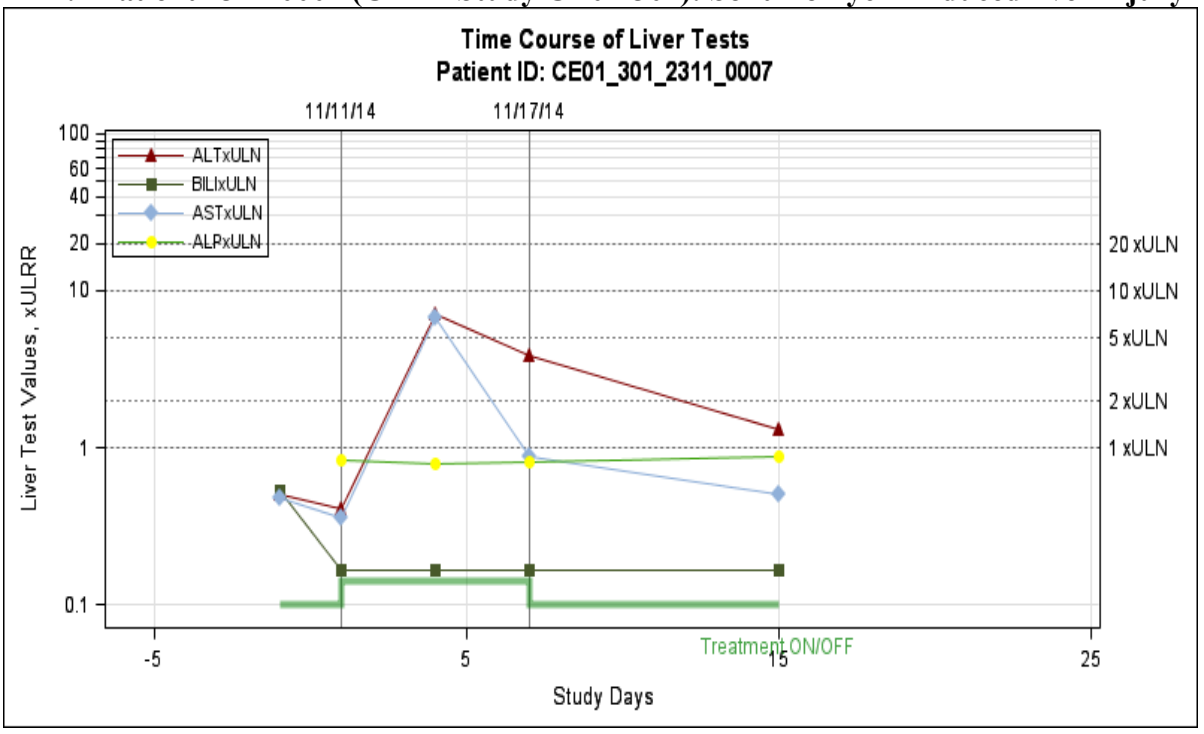


Narrative: This 58 year old male with CABP and no significant past medical history received 7 daily doses of IV solithromycin (400 mg/dose (Days 1-7). No microbiological diagnosis was established. Concomitant medications included metamizole for fever and pain. His baseline liver tests were normal, with the ALT 32 U/L, AST 35 U/L, ALP 38 U/L, and total bilirubin 0.4 mg/dL. On Day 4, the ALT was 360 U/L (8.4xULN), AST was 242 U/L(6.7x ULN), ALP was

238 U/L (1.8xULN), with a normal total bilirubin of 0.3 mg/dL. On Day 7, the ALT was 331 U/L (7.7xULN), AST was 131 U/L (3.6xULN), ALP was 179 U/L (1.3xULN) with a normal total bilirubin of 0.5 mg/dL. On Day 8, the ALT was 319 U/L (7.4xULN) and AST was 107 U/L (2.9xULN). At the Long-term Follow-up Visit on Day 36, the ALT was 19 U/L and AST 22 U/L with a normal total bilirubin of 0.6 mg/dL. A coincidental finding of a pheochromocytoma was reported on Day 14. It was considered unrelated to the elevated liver test results.

Assessment: *I agree with the sponsor's conclusion that the aminotransferase elevations on Day 4 appear to be related to the study drug. In my judgement this liver injury is 'Probable' in its causal association with Solithromycin and fits a Level-1 Category of Severity. With an R value of 4.6 the hepatotoxic profile has the characteristics of a 'Mixed' hepatocellular and cholestatic components. Although the ALT elevation slightly improved on Day 7 at the end of the treatment phase, the liver test abnormalities completely recovered only when solithromycin exposure had ended. Nonetheless, with no evidence of progression of the liver injury after Day 4, it is possible that an adaptive hepatic response to the daily IV exposure with the ketolide was in its early phase.*

7. Patient 2311-0007 (CABP Study CE01-301): Solithromycin-induced liver injury

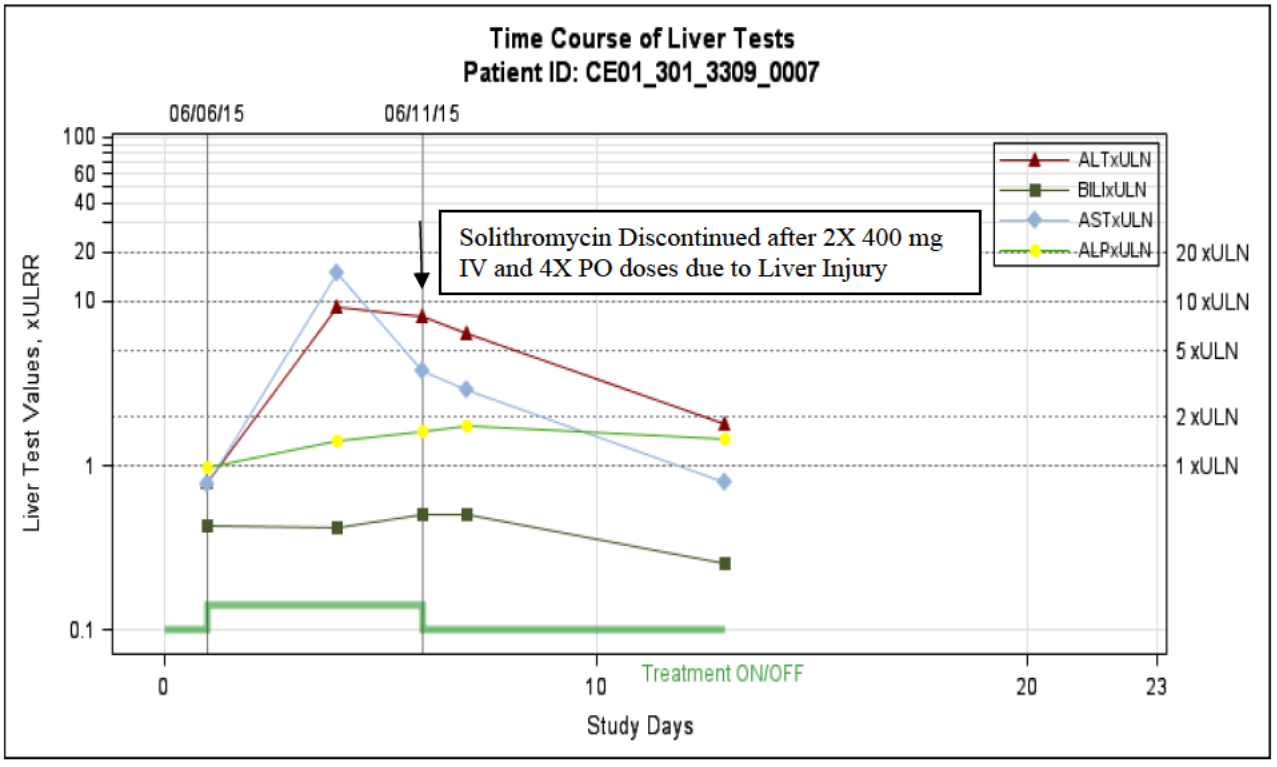


Narrative: This 52 year old female with CABP and with a past medical history of asthma who was on no chronic medications received 6 daily IV doses (400 mg, Days 1-6) followed by 1 oral dose (Day 7) of solithromycin. No microbiological diagnosis was established. She also received aminophylline and methylprednisolone as concomitant medications. At baseline, the ALT was 14 U/L and AST was 12 U/L. On Day 4, the ALT was 240 U/L (7.0xULN) and AST was 228 (6.7xULN). By Day 7, while still on solithromycin, the ALT had decreased to 130 U/L

(3.8xULN) with an AST of 30 U/L. On Day 15, the ALT was 44 (1.2xULN) and AST 17 U/L. The ALP and bilirubin values remained normal throughout.

Assessment: *The sponsor's assessment that the acute aminotransferase elevations on Day 4 appear to be related to the study drug appears to be correct. In my view the causal association of this Severity Level-1 case with solithromycin is 'Probable'. With no substantial changes of ALP levels from baseline the hepatoxic profile was predominantly hepatocellular. As in the previous case, there was some improvement of the ALT levels by the last day of solithromycin treatment. This documented halt in the progression of the liver injury may be reflective of an early phase of hepatic adaptation to the ketolide.*

8. Patient 3309-007 (CABP Study CE01-301): Solithromycin-induced liver injury



Narrative: This 61-year-old female with CABP and a history of preexisting anemia, thrombocytopenia, hyponatremia, and pre-renal azotemia received only 6 doses of solithromycin, comprised of two IV doses (400 mg, Days 1-2) and 4 oral doses (Days 3-6). No microbiological diagnosis was established. Concomitant medications included acetaminophen, diphenhydramine, salbutamol by inhalation, acetylcysteine and iron and potassium supplements. At baseline, the ALT was 21 U/L, AST 26 U/L, ALP 121 U/L, and total bilirubin 0.3 mg/dL. On Day 4 there were asymptomatic increases of ALT to 315 U/L (9.2xULN), AST to 500 U/L (14.7xULN), and ALP to 173 U/L (1.4xULN) with a total bilirubin of 0.5 mg/dL. The study drug was discontinued after the 6th dose on Day 6 due to these aminotransferase elevations. During continued study drug dosing on Day 6 the ALT was 272 (8xULN), AST 126 (3.7xULN), and ALP 196 (1.5xULN). On Day 7, ALT was 218 (6.4xULN), AST was 99 (2.9xULN), and ALP 215

(1.7xULN). By Day 13, the ALT was 61 U/L (1.7xULN), AST was 27 U/L, and ALP was 177 U/L (1.4xULN). Bilirubin levels remained normal at all time points.

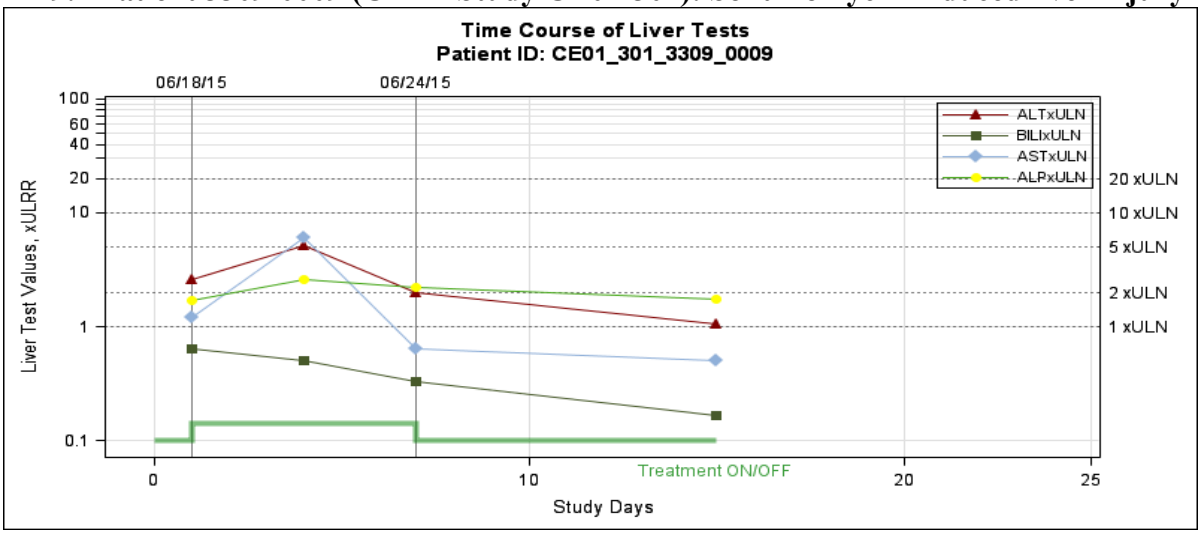
Patient 3309-007 (CABP Study CE01-301): Tabulated Lab Data[1]

Visit/Day	ALT		AST		Bilirubin		ALP		WBC	EOS	Creat
	U/L	×ULN	U/L	×ULN	Total mg/dL	Direct mg/dL	U/L	×ULN	×10³/µL	×10³/µL	mg/dL
Baseline Day 1	21		26		0.3	0.1	121		16.9	0.04	2.7
ECR Day 4	315	9.2	500	14.7	0.5	0.2	173	1.4	23.0	0.11	1.3
Unsched Day 6	272	8	126	3.7	0.6	0.3	196	1.5	17.5	0.06	1.4
EOT Day 7	218	6.4	99	2.9	0.6	0.3	215	1.7	14.0	0.20	1.3
SFU Day 13	61	1.7	27		0.3	0.2	177	1.4	11.1	0.02	1.2

[1]Sponsor's Hepatic Safety Review, Table 47

Assessment: *I agree with the sponsor that the acute aminotransferase elevations in this case are related to the study drug. In my judgement, the causal association of this acute Severity Level-1 hepatotoxic event is 'Probable'. The decision to discontinue solithromycin treatment after the 6th dose on Day 6 (the protocol for CE01-301 specified a 7-day treatment course) was determined by the high levels of the acutely elevated ALT levels on Days 4 and 6 that were measured. Although a matter of speculation, it is likely that these elevations would have been self-limited, irrespective of whether a 7th dose of solithromycin would have been given as an oral formulation on Day 7. Questions are nonetheless raised a) whether 'real-world' outpatients with CABP should have routine liver tests performed at baseline, during and after solithromycin treatment for CABP, b) whether there should be 'Stop-rules' with switching to a non-solithromycin regimen prompted by specified cut-off values of serum ALT, AST, ALP and/or bilirubin, and c) whether there is justification and practicality for the performance of such routine testing.*

9. Patient 3309-0009 (CABP Study CE01-301): Solithromycin-induced liver injury



Narrative: This 56 year old female with CABP and with a past medical history of diabetes and dyslipidemia treated chronically with gliclazide, metformin, and atorvastatin, received 2 daily IV doses (400 mg, Days 1-2) followed by 5 daily oral doses (Days 3-7) of solithromycin. No microbiological diagnosis was established. Other concomitant medications included

acetaminophen, acetylcysteine, and salbutamol. The baseline ALT was 68 U/L (2xULN), AST 38 U/L (1.1xULN), and ALP 210 (1.7xULN), with total bilirubin 0.6 mg/dL. On Day 4, the ALT was 174 U/L (5.1xULN), AST was 206 U/L (6xULN) and ALP was 318 U/L (2.5xULN), with a total bilirubin of 0.6 mg/dL. By Day 7, during continued study drug dosing, each of these parameters had improved, with an ALT of 67 U/L (1.9xULN), AST of 22 U/L, and ALP of 272 U/L (2.2xULN). The bilirubin remained normal at all time points. On Day 15, the ALT was 36 U/L, AST was 17 U/L, and ALP was 213 (1.7xULN).

Assessment: *The sponsor's conclusion that the aminotransferase and ALP elevations appear to be related to the study drug is correct in my view. In my judgement the causal association with Solithromycin is 'Probable'. With an R value between 2 and 5 this liver injury fits a 'Mixed' picture of hepatocellular and cholestatic toxicity and conforms to a Level-1 Severity category. Improvement of the biochemical abnormalities by the last day of solithromycin treatment suggests that an adaptive hepatic response to solithromycin exposure was underway. The mild abnormalities of liver tests at baseline may reflect either effects of an atypical bacterial pneumonia (e.g. Mycoplasma, Legionella, etc.), a chronic underlying condition such as NASH or HCV, or drug-related perturbations associated with one of the subject's chronically administered medications.*

10. Patient 005 (COPD Study CE01-204): Solithromycin-induced liver injury

Narrative: This 65-year-old female with a history of COPD, hypothyroidism, hyperlipidemia and coronary artery disease received 400 mg oral solithromycin daily for 26 days. She was treated with triotropium, atorvastatin (20 mg QD), levothyroxine, seretide and salbutamol metered-dose inhaler for her other medical conditions. The liver tests were normal through Day 14. On Day 26, at the completion of the dosing period, elevations of ALT (to 141 U/L, 3.5×ULN) and AST (to 89 U/L, 2.2×ULN) were noted. The bilirubin was not elevated, and ALP was below baseline values at this time. On return at Day 31, off study drug, ALT had increased to 7.3×ULN, with a mild increase in ALP and a normal bilirubin level. These parameters were improved at Day 36 and Day 37, after which the patient refused further evaluation. She remained asymptomatic throughout this episode of ALT elevations. Plasma samples obtained at the one-week visit and on Day 26 at the time of early elevation of ALT levels revealed anticipated steady-state concentrations of solithromycin and atorvastatin.

Patient 005 (COPD Study CE01-204): Tabulated Lab Data[1]

Visit/ Day	ALT		AST		Bilirubin		ALP		WBC	EOS	Creat	PT
	ULN:40		LN:41		Total ULN:1.2	Direct ULN:0.4	ULN:130		×10³/µL	×10³/µL	mg/dL	INR
	U/L	×ULN	U/L	×ULN	mg/dL	mg/dL	U/L	×ULN				
Baseline	24	0.6	27	0.7	0.5	0.1	133	1.0	7.4	0.2	0.8	
Day 8	24	0.6	25	0,6	0.4	0.1	137	1.1	7.3	0.2	0.7	1.0
Day 14	29	0.7	27	0.7	0.4	0.1	139	1.1	8.8	0.2	0.6	1.0
Day 26	141	3.5	89	2.2	0.5	0.1	128	1.0	8.5	0.4	0.8	1.0
Day 31	292	7.3	126	3.1	0.4	0.1	190	1.5	6.7	0.3	0.7	0.9
Day 36	100	2.5	37		0.4	0.1	171	1.3		0.3	0.7	
Day 37	78		n/a		0.6		168					

[1]Sponsor's Hepatic Safety Review, Table 58

Assessment: *In my view the causal association between the liver toxicity event and solithromycin exposure is 'Probable'. As in a previous case, after the last oral dose of the ketolide on Day 26, the ALT continued to rise from 141 U/L to 292 U/L five days later. This suggests that adaptation was not taking place and that the improvement in liver test results that was later observed occurred because of discontinuation of the study drug.*

11. Patient 006 (COPD Study CE01-204): Solithromycin-induced liver injury

Narrative: This 73-year-old male with a history of COPD received oral solithromycin, 400 mg QD, for 28 days. He was treated for his other medical conditions with tiotropium, seretide and salbutamol. On Day 15, an elevation of ALT to 165 U/L (4.1×ULN) was noted, with a parallel AST elevation to 2.7×ULN and ALP elevation to 1.3×ULN. The bilirubin was not elevated, and the patient was asymptomatic. Study drug dosing continued, and on repeat evaluation at Day 23, ALT, AST, and ALP had improved significantly. On Day 28, the last day of study drug dosing, ALT, AST, and ALP were all normal. Solithromycin concentrations on days 8, 14 and 26 at 4 hours post drug administration were 840, 797 and 802 ng/mL, respectively, within the range of expected values for the 400 mg oral QD dose.

Patient 006 (COPD Study CE01-204): Tabulated Lab Data[1]

Visit/ Day	ALT		AST		Bilirubin		ALP		EOS ×10³/µL	Creat mg/dL
	ULN:40		ULN:41		Total ULN:1.2	Direct ULN:0.4	ULN:130			
	U/L	×ULN	U/L	×ULN	mg/dL	mg/dL	U/L	×ULN		
Baseline	17		21		0.6	0.1	109		0.1	0.9
Day 9	17		20		0.7	0.1	99		0.2	0.9
Day 15	165	4.1	108	2.7	0.8	0.2	174	1.3	0.4	1.0
Day 23	53	1.3	26		0.5	0.1	144	1.1	0.2	0.9
Day 28	30		25		0.5	0.1	129		0.2	1.0

[1]Sponsor's Hepatic Safety Review, Table 59

Assessment: *The ALT rise to 4.1X ULN was completely resolved on the last day of treatment with the ketolide (Day 28). I agree with an interpretation by the sponsor that this case of solithromycin-induced liver toxicity resolved as a manifestation of adaptation to solithromycin. This is in contrast to Patients 001 and 005 in the COPD study for whom reversal of hepatotoxicity only occurred after cessation of treatment with the ketolide (In Patient 005, the ALT elevations continued to rise for an additional 5 days after study drug discontinuation before improvement began to occur).*

12. Patient 005 (NASH Study CE01-205): Solithromycin-induced liver injury

Narrative: This 47-year-old male with a history of NASH, obesity, dyslipidemia, reactive airway disease, and angioedema was enrolled in the proof-of-concept NASH protocol with a planned 13-week study drug administration. Concomitant medications for his other conditions included rosuvastatin (10 mg QD), albuterol and epinephrine. The patient initiated study drug dosing with 200 mg of oral solithromycin daily. ALT and AST were mildly elevated at baseline, consistent with his underlying disease (note that this site's laboratory considers the ULN for ALT to be 65 U/L). Through Day 22, modest improvement in ALT and AST values were noted. At Day 29, elevations of ALT to 290 U/L (4.5×ULN) and AST to 242 U/L (6.5×ULN) were

observed, without a significant change in ALP or bilirubin. CPK did not increase above the baseline value of 145 U/L during this period (ULN=199 U/L). The new ALT and AST increases were considered a study drug related AE, and dosing of both solithromycin and rosuvastatin was suspended for 16 days until ALT and AST values returned to baseline levels. Upon resumption on Day 45, Solithromycin dosing was reduced in frequency at 200 mg TIW. The patient tolerated this dosing schedule without a liver toxic adverse event and at Day 89, the final day of study drug dosing, ALT, AST, and GGT levels were at or below baseline values.

Patient 005 (NASH Study CE01-205): Tabulated Lab Data[1]

Visit/ Day	ALT		AST		Bilirubin		ALP	GGT	WBC	EOS	Creat	PT
	ULN: 65 U/L		ULN:37 U/L		Total ULN: 1.2	Direct ULN:0.4	ULN: 117 U/L	(15-85)	x10³ µL	x10³/µL	mg/ dL	INR
	U/L	×ULN	U/L	×ULN	mg dL	mg/dL	U/L	U/L				
Screen	64		51	1.4	0.6	0.2	83	27	11.5	0.18	0.91	1.0
Patient initiates oral solithromycin dosing, 200 mg QD, on Day 1												
1	61		51	1.4	0.5	0.2	81	28	11.9	0.23	0.86	1.0
4	60		47	1.3	0.4	0.1	96					
8	62		62	1.7	0.7	0.1	77	26	10.8	0.23	0.84	
15	53		47	1.3	0.7	0.2	78	28			0.97	
22	54		51	1.4	0.5	0.1	83					
29	290	4.5	242	6.5	0.8	0.2	103	274	9.9	0.28	0.81	1.0
Solithromycin dosing placed on hold, after Day 29 dose, for ALT elevation												
32	158	2.4	78	2.1	0.4	0.1	98					
36	84	1.3	48	1.3	0.5	0.1	91					
45	68		53	1.4	0.7	0.2	84	76			0.78	
Solithromycin dosing resumed on Day 45, 200 mg TIW (Mon/Wed/Fri)												
50	90	1.4	59	1.6	0.5	0.1	87	110				
54	79	1.2	49	1.3	0.7	0.2	78		12.1	0.15	0.86	1.0
64	53		39	1.1	0.5	0.1	86	41				
72	46		37		0.5	0.1	86					
78	48		43	1.2	0.9	0.2	75					
85	48		47	1.3	0.5	0.1	77					
89	47		36		0.6	0.1	81	29	12.0	0.17	0.97	1.0
Solithromycin dosing completed on Day 89.												

[1]Sponsor's Hepatic Safety Review, Table 60

Assessment: *I agree with the sponsor's conclusion that the new onset of ALT elevations on Day 29 of the study was related to the study drug. With the observed biochemical improvement emanating from the 16 day suspension of solithromycin treatment and the lower frequency dosing schedule that was adopted subsequently, in my view the causal association of the hepatotoxic event with the ketolide is 'Probable'. It is difficult to predict the degree or tempo at which the liver injury would have progressed had there been no treatment pause and subsequent adjustment of solithromycin dosaging when the AT elevations occurred.*

13. Patient 271-0202 (CABP Study CE01-300): Solithromycin-induced liver injury

This 61-year-old female with CABP and a past medical history of hypertension and diabetes treated with insulin received 5 doses of oral solithromycin. The other concomitant medications included paracetamol and irbesartan. The baseline hepatic aminotransferase values were normal except for ALP which was mildly elevated. On Day 4, an ALT elevation to 78 U/L (2.3×ULN) was noted, with mild rise to 85 U/L at Day 8, and return to normal by Day 15. ALP increased to 562 U/L (4.6×ULN) at Day 4, with further elevation to 614 U/L at Day 8 (5.0×ULN), and was persistently elevated at Day 15 (316 U/L, 2.6×ULN). At the next evaluation at Day 29, the ALP had returned to below baseline values. The bilirubin remained normal throughout. AEs of lower limb edema (unrelated) and right hypochondium pain (considered study drug related by the site investigator) were reported. An abdominal ultrasound done on Day 4 showed "a low grade fatty liver" and a cholangiopancreatography done on Day 15 was normal.

Patient 271-0202 (CE01-300): Tabulated Lab Data[1]

Visit/ Day	ALT		AST		Bilirubin		ALP		WBC	EOS	Creat	PT
	U/L	×ULN	U/L	×ULN	Total ULN:1.2 mg/dL	Direct ULN:0.4 mg/dL	U/L	×ULN	×10³/µL	×10³/µL	mg/dL	INR
Baseline Day 1	27		31		0.5	0.2	141	1.2	10.3	0.09	1.3	1.2
ECR Day 4	78	2.3	59	1.74	0.5	0.2	562	4.6	8.3	0.13	1.1	
EOT Day 8	85	2.5	40	1.18	0.4	0.1	614	5.0	9.1	0.15	1.6	0.9
SFU Day 15	26		13		0.4	0.1	316	2.6	8.0	0.07	1.6	
Day 29	20		18				117	1.1				

[1]Sponsor's Hepatic Safety Review, Table 52

Assessment: *In my view, this case of acute mild cholestatic liver injury is 'Probable' in its causal association with solithromycin. In contrast to other solithromycin-associated cases in which the most pronounced liver injury enzyme abnormalities that were observed were elevated aminotransferases, a rise in ALP that peaked (5X ULN) on Day 8 predominated. An alternative diagnosis to consider is transient extra-hepatic biliary cholestasis associated with choledocholithiasis. With the US and cholangiopancreatographic findings described in the narrative this possibility is less likely. Characteristic of cases of mild drug-induced cholestasis, the observed biochemical resolution was not immediate, taking a few weeks until the elevated ALP normalized.*

Risk for DILI associated with Solithromycin: Current Information & Assessment

In the Solithromycin Development Program to date a range of liver injuries causally associated with exposure to the ketolide has been observed. The findings of a spectrum of both hepatocellular and cholestatic signatures of hepatotoxicity among a relatively small number of human study subjects treated with solithromycin for CABP (n=920), normal healthy volunteers exposed to the ketolide in PK studies as well as a handful of patients administered the antibiotic in studies of other conditions comprise a genuine liver injury signal. This signal raises an important question of what the actual risk for serious or life-threatening DILI would be in a much larger 'real-world' post-market exposure population.

In the pooled Phase 3 clinical trials of solithromycin (CE01-300 and CE01-301) for CABP there was a substantially higher percentage of study subjects receiving the ketolide who developed ALT elevations greater than 3X ULN compared with subjects randomized to receive moxifloxacin, the comparator drug [7.2% vs 3.6%]. Although often asymptomatic and self-limited the ALT peaks that were causally related to solithromycin exposure included subsets that were >3X and >5X ULN, and included one individual who developed hepatocellular injury with ALT increases that exceeded 20X ULN.

Acute liver toxic effects were also observed in other solithromycin-treated populations, including at least one healthy PK study volunteer who developed a peak ALT of 8.4X ULN after receiving only 3 daily 800 mg doses of the IV formulation and in a substantial proportion of the few study subjects who were treated for COPD and NASH. In the COPD trial, among the only 4 patients who were randomized to a 28-day solithromycin treatment arm, one study subject developed symptomatic cholestatic hepatitis with jaundice, pruritis, and eosinophilia [peak ALT: 11.9X ULN, ALP: 10.1X ULN, total bilirubin: 2.2X ULN] that only resolved after early discontinuation of the drug after Day 23.

Increased Solithromycin Exposure and DILI risk

Different protocol modifications that can lead to an increase of exposure to solithromycin appear to be tied to an increase in the risk to develop liver toxicity. These include a) increasing the loading and/or maintenance daily dose, b) shifting from a daily oral to the IV formulation, and c) increasing the duration of treatment. However, because of apparent variability in individual susceptibility to these solithromycin-induced liver test abnormalities, an absolute dosing threshold within the therapeutic dosing range that was tested (400 mg – 800 mg, PO and/or IV formulations) below which these events were entirely avoidable in all treated individuals has not been identified.

The observation that the mean peak ALT levels rose as the average 48hr integrated AUC measures increased in datasets collected from Phase 3 study subjects with CABP treated for 5-7 days demonstrates that increasing concentrations of solithromycin might have a toxic effect on human hepatocytes, *in vivo*, even when these reflect a range in which there were small dosaging differences between study subjects and relatively short durations of treatments. In an analysis of the frequencies of ALT elevations by quartiles of *peak* levels of plasma solithromycin exposure in CE01-300 and CE01-301 that the sponsor performed only small incremental enzyme changes were evident as this measure of drug exposure increased. This finding suggests the importance of using AUC measures integrated over the entire solithromycin exposure period, rather than peak levels alone. It also fortifies the point that there is significant inter-individual variation regards the threshold plasma concentrations that drive the toxic effect.

As shown in rats and cynomolgus monkeys, solithromycin readily distributes into the liver and lung with tissue concentrations that may be manifold greater than plasma concentrations. If liver tissue concentrations that increase over multiple doses of the antibiotic were available, these might have been used to more accurately predict thresholds for liver toxicity compared to the plasma measures. In line with this concept, the sponsor has clearly demonstrated that systemic exposure in rats and monkeys increased with duration of dosing in repeat-dose oral toxicity studies. In the 28-day rat and 14-day monkey studies, tissue concentrations in liver (and lung)

exceeded Cmax plasma concentrations by up to 33-fold in rats and up to 711-fold in monkeys. The high proportion of patients who developed liver toxicity after 2-3 weeks of solithromycin treatment in the COPD and NASH studies likely reflects the toxic potential of this kind of a 'build-up' effect of liver tissue solithromycin concentrations and activation of cellular toxic pathways over repeat dosaging. Although a number of the enrolled study subjects in these studies appear to have experienced adaptation, the presence of the symptomatic case of solithromycin-induced cholestatic hepatitis described above raises a significant concern that there is a subset of susceptible individuals in whom solithromycin may also trigger an idiosyncratic inflammatory reaction with significant clinical consequences.

Adaptation - Observed Range of Responses to Solithromycin-induced liver injury

Using a time-to-event analysis, the sponsor has pointed out that most of the CABP study subjects with oral solithromycin-induced serum ALT elevations developed peak enzyme levels within 1-5 days, during the treatment phase and then demonstrated improvement of these abnormalities with complete resolution in some instances at the time when they received their last study drug dose, or at the short-term follow-up visit. Of note, blood for enzyme testing was drawn on Days 1, 4, 7 and then at the short-term follow-up visit (5-10 days after the last dose of study drug). This finding supports an interpretation that adaptation occurs in many subjects who develop solithromycin-induced asymptomatic liver test abnormalities, *during* the 5-7 day treatment phase for CABP. 72.7% and 71.4% of individuals in CE0-300 with asymptomatic ALT rises >3X ULN (group 1) and >5X ULN (group 2) fit this pattern of liver injury, respectively. On the other hand, the peak elevations of ALT only occurred *after* solithromycin was discontinued in 27.2% (group 1) and 28.6% (group 2) of the CE01-300 study population with these drug-related abnormalities. Among these individuals it is notable that the peak serum enzyme elevations occurred 6-10 days *after* the drug course had been completed (Day 11-15) in 4.5% (group 1) and 5.3% (group 2). Moreover, only 50% of patients in the IV-to-oral study, CE01-301, with drug-induced liver enzyme abnormalities manifested these increases in the first 5 days after initiation of the 7-day solithromycin treatment course, while 50% reached their peak enzyme levels between Days 6 and 15. Whether these individuals would have developed an adaptive hepatic response had they continued solithromycin treatment cannot be conclusively determined.

Telithromycin Safety Data & DILI Risk: Lessons Learned

As mentioned above, solithromycin is structurally highly related to telithromycin, a ketolide relative with a hepatotoxic profile that includes a documented risk for life-threatening DILI. To determine whether solithromycin is associated with the same or a qualitatively different degree of risk for clinically severe hepatotoxicity than telithromycin, it is important to review how the telithromycin DILI signal was characterized during different phases of that drug's life-cycle. Importantly, in the pre-approval Phase III controlled studies of telithromycin for CAP, among the study subjects treated with the ketolide (n=320) an association only with mild increases in hepatic transaminases was identified, whereas in the Phase III non-CAP controlled trials study this liver injury signal was absent in subjects treated with the ketolide (n=1,132) (3). It should be noted that in these studies there were no observed cases with biochemical changes that were consistent with Hy's Law (concomitant increases of ALT/AST >3X ULN and total bilirubin >2X ULN). Based on the product label, only 1.6% of study subjects treated with telithromycin in the Phase III program developed elevations of ALT> 3X ULN. Prompted by concerns surrounding a telithromycin-treated study subject with CAP who was found to have recurrent episodes of

hepatitis and eosinophilia after the study treatment period ended (whose etiology was not clear) and another subject with CAP who developed asymptomatic transient elevations of serum ALT levels peaking at 13X ULN on Day 5 of treatment, telithromycin continued to receive further scrutiny. As described in the Background section, it is notable that a causal connection between the antibiotic and serious idiosyncratic DILI was only strongly fortified in the post-market period of that product when published reports, as well as spontaneous FAERS reports, documented both the causal association, as well as rapid-onset clinical signatures associated with telithromycin-induced DILI. In the published case series of 42 telithromcyin-associated cases of DILI [included 4 deaths and one liver transplant outcome] (4), the associated findings of severe hepatocellular injury, short latency (median, 10 days), fever, eosinophilia, abdominal pain and/or ascites, and the presence of four cases of severe liver injury marked by very short latency from treatment initiation after documented previous exposures to the antibiotic, raised a concern that acquired hypersensitivity to the ketolide or one of its metabolites, or cross-sensitization to a structurally related macrolide may put patients at higher risk for developing serious hepatotoxicity.

Computational Modeling of Solithromycin Associated Risk: Analysis Issues & Limitations

To support a view that liver injury caused by solithromycin is predicted to be associated with a range of hepatocyte loss that for all the treated individuals is entirely below a critical threshold that would lead to compromised liver function, the sponsor has recently submitted an analysis of computational simulations performed by DILIsym Services. These simulations are based on a proprietary model that assumes ranges of certain physiological or cellular conditions that may impact hepatotoxic outlier susceptibility in a population of virtual patients. Hepatic functions incorporated into the model that could impact drug toxicity effects include aspects of mitochondrial function, glutathione homeostasis, caspase activation, bile acid concentrations and oxidative stress susceptibility. These are superimposed on a physiologically-based pharmacokinetic (mathematical) model which quantitatively predicts the kinetic partitioning of drug and metabolite concentrations between plasma, individual tissues and different cell types, etc. Applying assumptions of study drug ADME and information on the impact of cellular transporters on distribution of the drug, etc., the modeling then calculates predicted levels of the drug, based on the clinical trial dosaging protocol(s). It is then further refined using empirical pharmacokinetic measurements of the drug and its metabolites.

Testing how bile acid transport inhibition, mitochondrial toxicity or oxidative stress would impact population-level profiles of liver test results in a simulated CABP patient population, and matching these predictions for a 'best fit' to empirical liver test data derived from sets of individuals treated with the study drug in clinical trials, DILIsym Services has concluded that in the case of solithromycin, the main driver of hepatocyte loss causing the range of ALT and ALP abnormalities that were observed in the clinical study program is likely to be most strongly connected to drug-induced mitochondrial toxicity, through a mechanism of electron transport chain inhibition. In contrast, in the case of erythromycin test results measured in other studies that were not connected to the Solithromycin Development Program, the mechanistic contributions to hepatotoxicity that best fit the observed liver test data were bile acid transporter inhibition and reactive oxygen species generation.

Although predictions from this modeling approach may become more valuable in the long-term as more information accrues, with the limited power of study subject liver test data that has been

used, a firm conclusion that solithromycin is not associated with a risk for clinically serious idiosyncratic hepatotoxicity cannot be drawn [A negative predictive value using this model to reliably predict the absence of risk for severe DILI (a rare event) would need to be virtually 100%]. Separately, in the simulation of solithromycin dosing to treat CABP, known mechanisms and pathways that appear to contribute to severe liver injury associated with macrolides and ketolides are not addressed by the model. Among these, immuno-allergic reactions and hypersensitivity pathways tied to DILI that have been identified with members of these drug groups have not been incorporated into the simulation analysis. A somewhat surprising additional unexplained gap in the analysis submitted by DILISym Services is the absence of the parallel testing of telithromycin hepatotoxicity in a simulated CAP population. The sponsor has put forth a so far unproven argument that despite their pharmacological and structural similarities as ketolides, solithromycin is marked by a substantially lower potential to cause severe hepatotoxicity than telithromycin. Thus, the use of telithromycin as a 'positive control' in the model with comparative liver test data would be highly relevant and might support the utility of the model.

Predicting DILI Risk in a Large Post-marketing Population Treated with Solithromycin

In large exposure populations of those individual drugs that cause idiosyncratic liver injury, the proportions of individuals destined to develop adaptive responses vs those who would otherwise develop progression of organ injury with continuation of treatment depends on the particular drug, the mechanism(s) that underlie the hepatotoxic reactions, the range of individual susceptibilities for the development of drug-specific DILI and other factors such as dosaging effects, disease-drug interactions, drug-drug interactions, genomic and/or epigenenetic marker influences, etc. Importantly, in clinical studies, drugs associated with idiosyncratic acute liver failure, such as troglitazone, INH, ximelagatran, etc. have been observed to induce a broad range of liver injuries, including Hy's Law cases as well as asymptomatic mild increases of ALT followed by adaptation and resolution of these liver test abnormalities, despite continued treatment (6). Even among the drugs known to cause severe idiosyncratic hepatocellular injury and acute liver failure, most cases of their associated hepatotoxicity are only marked by mild transient ALT rises, due to hepatic adaptation. Empirically, other drugs, such as acetaminophen and tacrine have a more uniformly benign population-level signature of DILI. When dosed as recommended, drug-specific idiosyncratic hepatocellular toxicity that is commonly associated with these agents almost never progresses to serious life-threatening outcomes, because of robust hepatocellular adaptation which virtually is never deficient. In the face of the liver signal associated with solithromycin in the clinical studies described above, it is important to determine where the ketolide fits in this spectrum of risk for severe liver injury in a large treatment population. A complete evaluation of this question would require the study of a sufficiently powered solithromycin exposure population that employs a protocol to identify and characterize all the serious liver safety events that occur. As described in the ISS, 920 study subjects in the CABP Phase II and III study safety population were administered multiple doses of the PO and/or IV formulations of solithromycin for 5-7 days. Although the 24 Phase I studies listed in the ISS enrolled an additional 554 study subjects who were administered solithromycin, many of these individuals (normal volunteers and special populations) either received a single or just a few doses of the drug, or took part in brief dose escalating schedules. Such very limited drug exposures in many of the individuals enrolled in Phase I protocols do not justify their inclusion in

a tally of the number of solithromycin-treated study subjects to assess the powering and boundaries of idiosyncratic DILI risk associated with the drug. On the other hand, in the non-integrated studies, relatively small numbers of additional patients with COPD and NASH have received multiple doses of solithromycin in clinical studies and these should be included in assessing the powering for safety outcomes.

Gaps in Clinical Data to Determine Risk for Serious DILI Associated with Solithromycin

The sponsor has pointed out that in the case of macrolides, drug-induced cholestatic hepatitis occurs at approximate rates of 3.6/100,000 prescriptions for erythromycin, 3.8/100,000 for clarithromycin, and 5.5/100,000 for telithromycin. With the robust solithromcyin-associated liver injury signal that has been described, there are a number of gaps in the Solithromycin Development Program database that must be overcome to conclude with confidence whether solithromycin has a similar, improved or worse risk profile, compared with telithromycin and/or the other macrolides. First, with approximately only 1,000 study subjects treated by the sponsor with the antibiotic in a therapeutic framework so far, a lower boundary for risk for clinically serious hepatocellular liver injury or Hy's Law cases causally linked to the antibiotic that can be excluded by the rule-of-three is only approximately 1/330 (7). The presence of one case of clinically significant cholestatic hepatitis with jaundice in the relatively small exposure population of the Solithromycin Development Program that required early discontinuation of the study drug together with the robust ALT signal seen in the CABP trials leaves an open question concerning the actual 'real-world' population-level risk for serious DILI associated with solithromycin, even with short duration therapeutic use. Expanding the size of the ketolide-treated CABP study population size being tracked for safety outcomes would provide data to ensure that DILI risk connected to this antibiotic is not especially high.

In addition, because of concerns surrounding the association of telithromycin has with severe rapid-onset idiosyncratic hepatocellular DILI in patients receiving short duration therapy, a determination whether the lower boundary of risk for Hy's Law cases (and/or other forms of clinically significant hepatocellular injury) is at least above 1/4,000 (using a rule-of-three calculation) would be more reassuring. Second, because the clinical study protocols excluded patients with known hypersensitivity to any macrolide (including ketolides) it is not possible to assess whether prior sensitization with one of the ketolides or any of the macrolides is problematic and would play a critical role to precipitate severe and/or rapid-onset solithromycin-induced DILI. Although this cannot be directly studied, the possibility that such patients might be at higher risk when treated with the ketolide must be carefully weighed.

RECOMMENDATIONS

There are two avenues to consider regarding regulatory action when taking into account the uncertainties and significant gaps in current clinical study data that prevent an accurate prediction of the level of risk that solithromycin treatment has for clinically serious idiosyncratic DILI in a large post-market exposure population with CABP or other conditions. Which of these avenues should be followed depends on whether the benefits of solithromycin treatment have convincingly been shown to have 1) a substantial advantage in effectiveness for a segment of CABP patients over existing approved treatments, 2) a therapeutic role in the treatment of

CABP by organisms that are resistant to other macrolides, and 3) a demonstrated safety advantage for non-liver serious AEs. In the absence of any of these, to strengthen confidence that the risk for serious DILI with this ketolide is well below ~1/330 (as can be determined from current data), and to elevate the statistical power for evaluating DILI risk of these events in CABP patients, the number of study subjects treated with solithromycin should be increased from 924 to approximately 12,000 and carefully assessed for liver safety events, either in expanded Phase III randomized trials or in a large clinical safety study, *in advance* of making a regulatory decision regarding approval for CABP. An exclusion of Hy's Law cases, or cases of clinically severe solithromycin-induced hepatitis in this larger database will offer reassurance that under similar therapeutic conditions and in the patient population for whom the antibiotic will be indicated, despite the high frequency of elevated aminotransferases caused by the drug and the presence of a case of cholestatic hepatitis in a COPD study subject with longer term use, the risk for clinically serious hepatocellular DILI is likely to be less than 1/4,000 and for acute liver failure with death and/or liver transplant, less than 1/40,000.

Alternatively, if solithromycin treatment has been found to convincingly offer a clinically substantial benefit over other currently approved treatments a second avenue might be considered. To strengthen the underpinning of this option it will be critical to avoid or reduce conditions of solithromycin usage that may without proven benefit increase drug exposure levels that have been demonstrated to be associated with higher rates of hepatocellular toxicity and possibly an increased risk for serious liver injury. In my judgement, as part of a risk mitigation strategy the following elements should be strongly considered: 1) Indicate IV and PO solithromycin for CABP only, accompanied by a labeled warning, boxed warning or contraindication stating that because of concerns about a heightened risk for clinically significant hepatotoxicity these products should NOT be used for longer than 7-days and that they should NOT be used to treat other conditions such as acute exacerbation of chronic bronchitis or acute bacterial sinusitis for which efficacy has not been tested and which may require longer periods of treatment, 2) Contraindicate or Warn against use of these products in individuals with a history of hypersensitivity and/or DILI associated with an earlier exposure to any macrolide or ketolide (e.g erythromycin, clarithromycin, azithromycin, fidaxomicin and telithromycin), 3) Limit the recommended daily doses of IV and PO solithromycin formulations to 400mg, 4) Limit use of the IV formulation to the smallest number of daily doses of treatment that are required to effectively treat CABP before completing treatment with the oral formulation, 5) Contraindicate or recommend against use of solithromcyin in patients with severe renal insufficiency because of reduced clearance effects of the drug and rising exposure levels that may be toxic, 6) List common concomitant drugs that are known or likely to alter solithromycin metabolism or clearance, leading to substantial changes in circulating levels of the antibiotic, 7) Establish a post-marketing requirement that the sponsor perform a CABP safety study to measure liver outcomes in a significantly large cohort of patients with CABP, 8) Establish a post-marketing requirement that the sponsor follow-up on all reports it receives about solithromycin associated liver AEs and perform an active structured query with the reporter to define the clinical characteristics and etiology of each of these events. These should be analyzed by individuals with clinical expertise in the evaluation of DILI and reported to the FDA for regulatory review.

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Appendix

Assessment of potential drug-induced liver injury of the present cases uses the grading system for likelihood of attribution and liver disease severity developed by the National Institutes of Health's Drug-Induced Liver Injury Network (DILIN) Study Group.*

Likelihood of Causality

Score	Causality	Likelihood (%)	Textual Definition
1	Definite	≥95	Causality is "beyond a reasonable doubt"
2	Highly Likely	75-94	Causality supported by "clear and convincing evidence"
3	Probable	50-74	Causality supported by the "preponderance of the evidence"
4	Possible	25-49	Less than the preponderance of evidence but still possible
5	Unlikely	<25	Causality unlikely or excluded

Disease Severity Scale

Score	Grade	Definitions
1	Mild	Elevated ALT and/or Alk P but serum bilirubin <2.5 mg/dL and INR <1.5
2	Moderate	Elevated ALT and/or Alk P and serum bilirubin ≥2.5 mg/dl or INR ≥1.5
3	Moderate-Severe	Elevated ALT and/or Alk P and bilirubin or INR and new or prolonged hospitalization due to dili
4	Severe	Elevated ALT and/or Alk P and serum bilirubin ≥2.5 mg/dl and there is one of the following: -Hepatic failure (INR ≥1.5, ascites or encephalopathy -Other organ failure (renal/pulmonary) d/t dili
5	Fatal	Death or liver transplant from dili

*Fontana RJ, Seeff LB, Andrade RJ, Bjornsonn E, DayCP, Serrano J, Hoofnagle HJ. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology 2010;52:73-742

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