SOLITHROMYCIN FOR THE TREATMENT OF COMMUNITY ACQUIRED BACTERIAL PNEUMONIA

BRIEFING DOCUMENT FOR THE ANTIMICROBIAL DRUGS ADVISORY COMMITTEE

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AST	aspartate aminotransferase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ATS	American Thoracic Society
AUC	area under the plasma concentration time curve
AUC_{0-24}	AUC from time 0 to 24 hours after a dose
AUC_{0-tau}	AUC from time 0 to the last time point of collection
BCRP	breast cancer resistance protein
BMI	body mass index
bpm	beats per minute
BSEP	human bile salt export pump
CABP	community-acquired bacterial pneumonia
CDC	Centers for Disease Control and Prevention
CE	clinically evaluable
CFU	colony forming unit
CI	confidence interval
CL_{CR}	creatinine clearance
C_{max}	maximum plasma concentration
COPD	chronic obstructive pulmonary disease
CRP	C-Reactive Protein
CV	coefficient of variation
CVA	cerebrovascular accident
CYP	cytochrome P450

CYP3A4	cytochrome P450 3A4
DILI	drug-induced liver injury
ECG	electrocardiogram
ECR	early clinical response
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
ELF	epithelial lining fluid
EOT	end of treatment
erm	erythromycin ribosomal methylase
FDA	Food and Drug Administration
GAIN	Generating Antibiotics Incentives Now
HCV	hepatitis C virus
HBsAg	hepatitis B surface antigen
I	Intermediate
IC_{50}	concentration required for 50% inhibition in vitro
IDSA	Infectious Diseases Society of America
IND	Investigational New Drug Application
ITT	intent-to-treat
IV	intravenous
K_i	concentration required for half-maximal inactivation
K_{inact}	rate constant of maximal inactivation at saturation
L	liter
LFU	late follow-up
MDI	metabolism-dependent inhibition
MDRSP	multidrug resistant *S. pneumoniae*
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities

mef	macrolide efflux
MIC	minimum inhibitory concentration
MIC_{50}	minimum inhibitory concentration required to inhibit the growth of 50% of the isolates tested
MIC_{90}	minimum inhibitory concentration required to inhibit the growth of 90% of the isolates tested
mITT	microbiological intent-to-treat
mL	milliliter
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NASH	nonalcoholic steatohepatitis
NDA	New Drug Application
PCR	polymerase chain reaction
PCV7	7-valent pneumococcal conjugated vaccine
PD	pharmacodynamic(s)
PISP	penicillin intermediate *S. pneumoniae*
PK	pharmacokinetic(s)
PORT	Pneumonia Outcomes Research Team
PRSP	penicillin resistant *S. pneumoniae*
PSI	Pneumonia Severity Index
PSSP	penicillin susceptible *S. pneumoniae*
ΔΔQTcF	placebo-corrected QTcF change from baseline
QD	once daily
QIDP	Qualified Infectious Disease Product
R	Resistant
rRNA	ribosomal ribonucleic acid
S	Susceptible
SAE	serious adverse event

SD	standard deviation
SFU	short-term follow-up
SIRS	Systemic inflammatory response syndrome
SMQ	Standard MedDRA Query
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TK	thymidine kinase
T_{max}	time to maximum plasma concentration
TOC	test of cure
UAT	urinary antigen test
ULN	upper limit of normal
US	United States

1 EXECUTIVE SUMMARY

1.1 Introduction

This briefing document has been prepared by Cempra Pharmaceuticals, Inc. (Cempra), a pharmaceutical company dedicated to developing differentiated antibiotics for critical medical needs, including the ongoing public health crisis of antibiotic resistance. This document provides background information on solithromycin for the treatment of community-acquired bacterial pneumonia (CABP).

Solithromycin is a fourth generation macrolide antibiotic and the first fluoroketolide within the macrolide class.

Cempra submitted New Drug Applications (NDAs) for solithromycin in the treatment of CABP in adults in April 2016. These applications are for oral administration with a 5-day regimen or intravenous (IV) administration with the option to transition to oral solithromycin during a 7-day regimen.

The proposed indication for CABP in patients ≥ 18 years of age is as follows:

> Solithromycin is indicated for treatment of CABP caused by susceptible isolates of the following Gram-positive and Gram-negative bacteria: *Streptococcus pneumoniae* (including penicillin-resistant isolates, macrolide-resistant isolates, multi-drug-resistant isolates, and cases with concurrent bacteremia), *Haemophilus influenzae* (including beta-lactamase producing isolates), *Moraxella catarrhalis*, *Staphylococcus aureus* (methicillin-susceptible [MSSA]), and the atypical bacterial pathogens *Legionella pneumophila* and *Mycoplasma pneumoniae.*

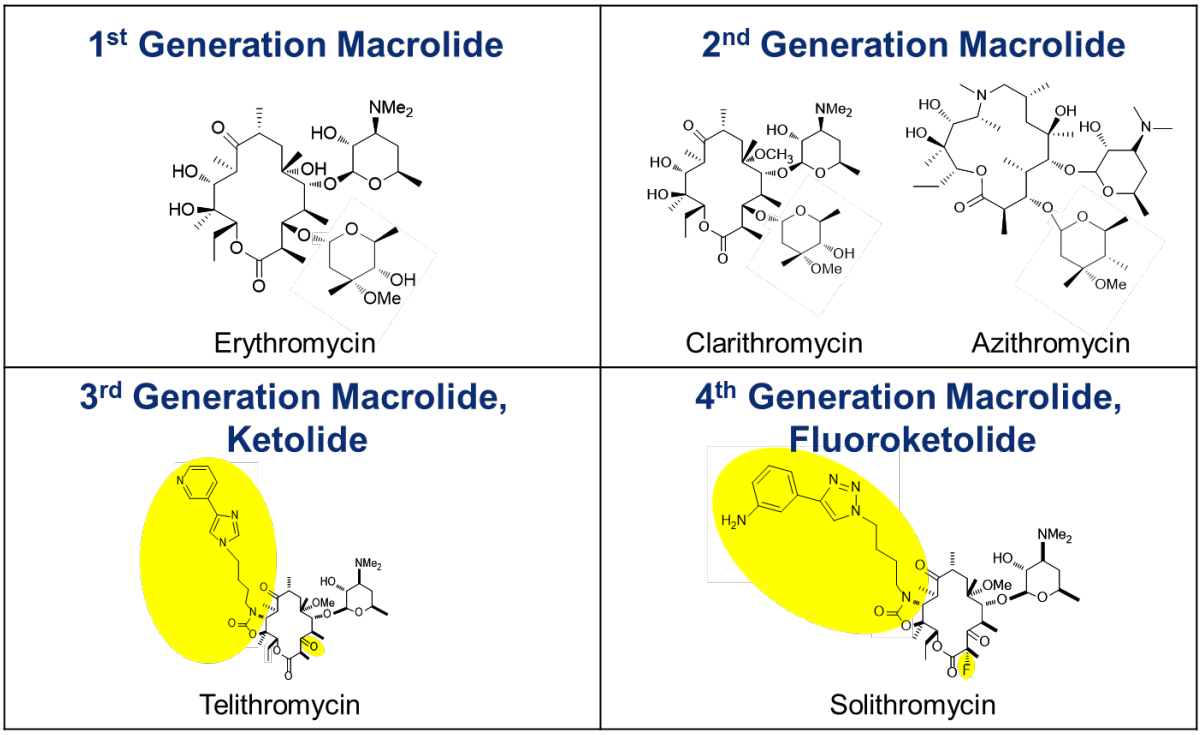
1.2 Unmet Need

Solithromycin addresses an important medical need for new antimicrobial treatments for CABP, a serious acute bacterial infection of the lungs. CABP is a significant cause of morbidity and mortality worldwide, and the most common cause of death from infectious disease in the United States (US). Macrolides played a central role in the treatment of CABP for decades, but pneumococcal macrolide resistance rates have now reached a critical threshold (approximately 50%) in the US and preclude most use of macrolides as monotherapy. In response to the problem of increasing resistance to macrolides and other classes of antibiotics, physicians now frequently prescribe respiratory fluoroquinolones or a combination of antibiotics (generally a macrolide + β-lactam, often a broad-spectrum IV cephalosporin). β-lactam monotherapy cannot be recommended because these agents do not provide coverage against important atypical CABP pathogens. Fluoroquinolones and combination therapies are effective, but these treatment strategies worsen the problem of antibiotic resistance, have deleterious effects on antibiotic stewardship, and have potential long-term safety consequences for patient health. Fluoroquinolones have established safety concerns (e.g. neuropathy, tendinopathies, QT prolongation), and commonly used cephalosporins for CABP are only available in IV formulations. Both fluoroquinolones and broad-spectrum cephalosporins can cause collateral damage in the bowel flora and increase the risk of *C. difficile* infection.

1.3 Chemical Structure, Mechanism of Action and Bacterial Susceptibility

Figure 1 provides a comparison of the chemical structures of the four generations of macrolide antibiotics. Macrolides consist of a macrolactone ring with one or more deoxy sugars, such as cladinose, attached. Ketolides, which have several structural differences from the earlier macrolides, are formed from clarithromycin by substituting a keto-group for cladinose sugar and attaching a cyclic carbamate group to the lactone ring. Telithromycin includes a pyridine-imidazole group attached to the cyclic carbamate and the macrolactone ring. Solithromycin replaces the pyridine-imidazole group with an aminophenyl triazole group, which increases activity and stability. Solithromycin also includes a fluorine that protects the nearby keto group from the enolization seen with telithromycin.

Figure 1 Structural Comparison of the Four Generations of Macrolides



Importantly, solithromycin can be differentiated from telithromycin (Ketek®), a ketolide approved in 2004 for multiple indications, including CABP. Telithromycin has been associated with adverse reactions uncharacteristic of other macrolides, including severe exacerbation of myasthenia gravis, vision abnormalities, loss of consciousness, and rarely, idiosyncratic hepatic failure. In 2007, the telithromycin indication was limited to CABP.

Telithromycin contains a pyridine-imidazole side chain moiety that has been demonstrated to be a biochemical antagonist of nicotinic acetylcholine (nACh) receptors, both as part of the telithromycin molecule and as part of the metabolically cleaved side chain. The profile of telithromycin inhibition of nACh receptors in vitro was different from that of solithromycin and the older approved macrolides. The macrolide-atypical adverse reactions linked with telithromycin can largely be mechanistically explained by this antagonism.

Solithromycin and other macrolides selectively disrupt bacterial protein synthesis. All macrolides bind to bacterial 23S ribosomal ribonucleic acid, in the peptide tunnel, and interact with domain V. In addition, all ketolides interact with domain II. X-ray crystallographic analysis of solithromycin bound to the 70S *E. coli* ribosome confirms the primary binding site at domain V, the interaction at domain II by the side chain, and a third site of interaction between the fluorine at position C-2 of solithromycin and the peptide tunnel. These multiple interacting sites account for the low resistance rates and improved activity against macrolide-resistant isolates, including telithromycin-resistant *S. pneumoniae.* Consistent with this, solithromycin has been shown to bind to ribosomes prepared from cells carrying *erm* methyltransferase genes (the most common cause of macrolide resistance).

Solithromycin has activity against the most common CABP pathogens, including strains resistant to β-lactams, fluoroquinolones, and macrolides. It also has potent activity against atypical bacterial pathogens including *M. pneumoniae, L. pneumophila* and *Chlamydophila pneumoniae*. It is bactericidal against most isolates of *S. pneumoniae, H. influenzae, Streptococcus pyogenes,* and *Francisella tularensis* while older macrolides have been considered bacteriostatic against these species. Solithromycin is mostly bacteriostatic against *S. aureus*. Solithromycin also concentrates in cells to a significantly greater extent than other macrolides, and is more active intracellularly against *L. pneumophila, Listeria monocytogenes* and phagocytosed *S. aureus* than azithromycin.

Importantly, solithromycin has minimal effect on *Bacteroides* species, which suggests a low potential for *C. difficile* overgrowth. In the Phase 2 and 3 CABP studies, no patients receiving solithromycin developed a recognized *C. difficile*-associated diarrhea or enterocolitis. In a Phase 1 fecal flora study that demonstrated minimal impact on gut *Bacteroides*, stool samples were negative for *C. difficile* by both culture and toxin detection diagnostic methods following 7 days of drug administration to healthy subjects.

The most common mechanism for development of macrolide resistance is ribosomal methylation due to expression of the *erm* methyltransferase gene. Additional mechanisms that have been observed include expression of macrolide efflux pumps encoded by the *mef* gene and mutations to L4 or L22 in ribosomal proteins. Solithromycin has been demonstrated to retain potent antibacterial activity against pneumococcal strains that express both *erm* and *mef* and against ribosomal protein mutants (Table 1).

Table 1 Comparative Susceptibility of Solithromycin against Pneumococcal Strains with Defined Mechanisms of Macrolide Resistance

Resistance Mechanism	N	Solithromycin (µg/mL)		Azithromycin (µg/mL)	
		Range	MIC_{90}	Range	MIC_{90}
Macrolide S	50	0.002 - 0.015	0.015	0.06 - 0.25	0.125
Macrolide R (*ermB*)	54	0.004 - 1	0.5	>64 - >64	>64
Macrolide R (*mefA*)	51	0.008 - 0.25	0.125	1 - >64	8
Macrolide R (*ermA*)	4	0.008 - 0.015	-	2 - 8	-
Macrolide R (*ermB* and *mefA*)	31	0.015 - 1	0.25	2 - >64	>64
Macrolide R (L4 mutations)	27	0.03 - 0.125	0.125	2 - >64	>64
Macrolide R (23S rRNA mutations)	4	0.002 - 0.03	-	32 - >64	-

S=Susceptible, R=Resistant; MIC=minimum inhibitory concentration; MIC_{90}= MIC required to inhibit growth of 90% of isolates tested; rRNA=ribosomal ribonucleic acid

Solithromycin had a low rate of spontaneous mutations in single-step mutation analyses, and serial passage analysis confirmed a low rate of resistance development. In an investigation of the potential for resistance selection in strains that already possess macrolide-resistance determinates, only 1 of 8 *S. pneumoniae* strains evaluated had an increase in minimum inhibitory concentration (MIC) exceeding 1 µg/mL (the proposed susceptible breakpoint). At this time, solithromycin resistance has not been observed in isolates collected as part of the global surveillance program despite the high rates of macrolide resistance (Table 2).

Table 2 Comparative Susceptibility of Solithromycin against CABP Pathogens in Global Surveillance Data from 2014

Organism group (no. tested)	Solithromycin MIC (µg/mL)			Azithromycin MIC (µg/mL)		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
S. pneumoniae (1713)	0.008	0.12	0.002 - 1	0.12	>32	0.015 - >32
S. aureus, MSSA (667)	0.06	0.06	0.03 - >32	1	>32	0.008 - >32
S. aureus, MRSA[a] (357)	0.06	>32	0.008 - >32	>32	>32	0.25 - >32
H. influenzae (1308)	1	2	≤ 0.06 - >8	0.5	1	≤ 0.03 - >4
M. catarrhalis (577)	0.06	0.12	0.002 - 2	0.03	0.06	0.002 - 0.5

MIC=minimum inhibitory concentration; MIC_{50}=MIC required to inhibit growth of 50% of isolates tested; MIC_{90}= MIC required to inhibit growth of 90% of isolates tested; MSSA=methicillin-susceptible *S. aureus*; MRSA=methicillin-resistant *S. aureus*

a. Solithromycin is active against community-associated MRSA, but has reduced activity against hospital-associated MRSA.

Solithromycin also has potent activity against the atypical CABP pathogens *M. pneumoniae*, including macrolide-resistant strains, *L. pneumophila*, and *C. pneumoniae* (Table 3).

Table 3 Comparative Susceptibility of Solithromycin against Atypical Bacterial Pathogens

Organism Group (no. tested)	Solithromycin MIC (µg/mL)			Azithromycin MIC (µg/mL)		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
M. pneumoniae (36)	0.000032	0.000125	≤ 0.000000063 - 0.5	0.00025	0.0005	≤ 0.000016 - >32
L. pneumophila (300)	0.008	0.016	≤ 0.004 - 0.06	0.06	0.25	0.008 - 1
C. pneumoniae (10)	0.25	0.25	0.25 - 1	0.125	0.125	0.015 - 0.125

MIC=minimum inhibitory concentration; MIC_{50}=MIC required to inhibit growth of 50% of isolates tested; MIC_{90}= MIC required to inhibit growth of 90% of isolates tested

1.4 Clinical Pharmacological Characteristics

Solithromycin exhibits nonlinear pharmacokinetic (PK) characteristics after oral and IV administration. Exposure is greater than dose proportional at doses less than 400 mg but approximately dose proportional at higher doses, due to auto-inhibition of metabolism via cytochrome P450 3A4 (CYP3A4).

Oral bioavailability of solithromycin is approximately 67% at the 400 mg dose and is not influenced by food. Oral solithromycin has a plasma half-life of approximately 10 hours and demonstrates approximately 2-fold accumulation with repeat dosing. Based on this observation and results from PK/pharmacodynamic (PD) target attainment analyses, a loading dose and maintenance dose schedule was selected for oral solithromycin that achieves concentrations near steady state on the first day of dosing and maintains target plasma concentrations over the dosing period. Area under the plasma concentration time curve (AUC) and maximum plasma concentration (C_{max}) with 800 mg orally on Day 1 followed with 400 mg daily resulted in drug concentrations with high probability of effective bacterial control both in lung and plasma throughout the treatment course.

The IV solithromycin dose is 400 mg once daily (QD) and may be administered for up to 7 days. The first oral dose in transition from IV to oral is 800 mg, maintaining high epithelial lining fluid (ELF) and plasma exposures through the transition period. Subsequent oral doses are 400 mg per day.

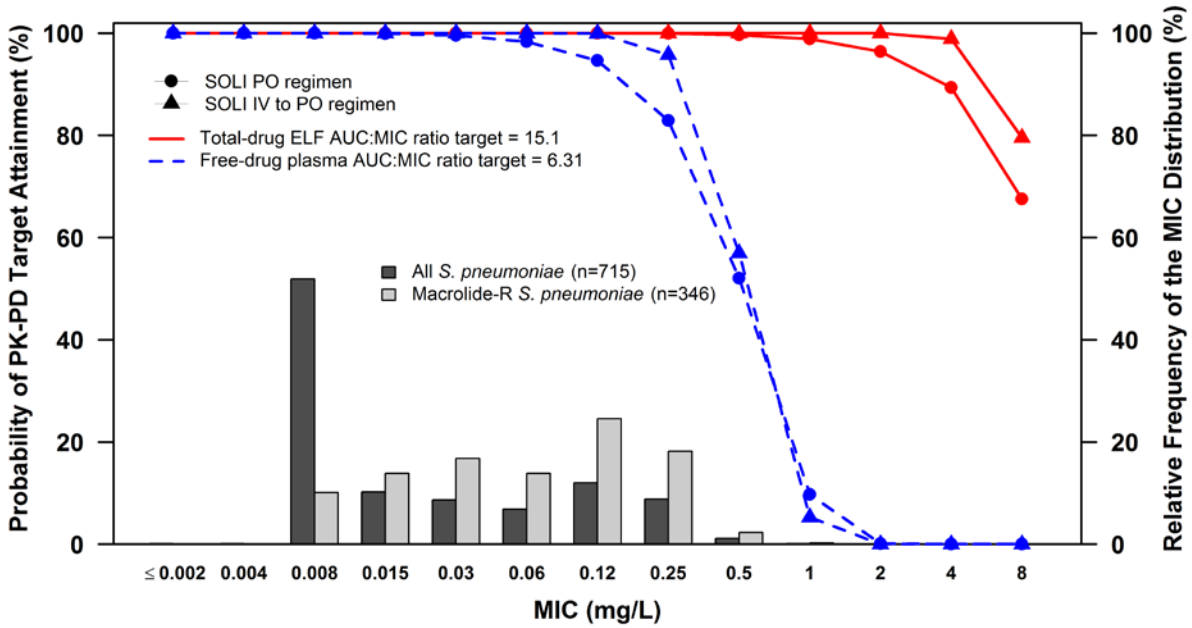
Solithromycin is excreted primarily by the liver, but no dose adjustment is needed in patients with hepatic impairment. In patients with severe renal impairment (creatinine clearance [CL_{CR}] <30 mL/min), plasma exposure could be increased 2-fold, therefore a dose adjustment is recommended.

Solithromycin is the major component in plasma with two minor metabolites (<5% of parent each). Approximately 19% of an oral dose is metabolized via first pass (liver and gastrointestinal tract). Similar to other macrolides, solithromycin is metabolized by CYP3A4, with minimal contribution from other cytochromes P450 (CYPs).

The drug-drug interaction profile of solithromycin is consistent with that of previously approved macrolides. Solithromycin should not be administered to patients who are receiving strong or moderate CYP3A/P-gp inducers because of the risk of subtherapeutic exposure and loss of efficacy. Concomitant administration of solithromycin with sensitive CYP3A and/or P-gp substrates that have potential adverse effects due to increased plasma concentrations (e.g. digoxin) may require monitoring and/or dose adjustment of the concomitantly administered drug.

Figure 2 shows the PK/PD target attainment over the first 48 hours of therapy for the planned oral and IV to oral solithromycin regimens for patients with CABP. As shown, these oral and IV dosing regimens are expected to provide high probabilities of PK/PD target attainment for both the total-drug ELF AUC:MIC ratio target associated with a 1-log colony forming unit (CFU) reduction from baseline (the most relevant exposure for CABP given that ELF represents effect site exposure) and the free-drug plasma AUC:MIC ratio target associated with the same endpoint. For the total-drug ELF AUC:MIC ratio target associated with a 1-log CFU reduction from baseline, percent probabilities of PK/PD target attainment approached or exceeded 90% up to an MIC value of 4 µg/mL across dosing regimens. For an MIC value of 0.12 µg/mL, which is the MIC_{90} value for *S. pneumoniae* based on global surveillance data, the percent probabilities of PK/PD target attainment over the first 48 hours of therapy for the free-drug plasma AUC:MIC ratio target associated with a 1-log CFU reduction from baseline were 94.6% and 99.9% for the oral and IV to oral dosing regimens, respectively.

Figure 2 Percent Probabilities of PK/PD Target Attainment for Solithromycin Oral and IV to Oral CABP Dosing Regimens



PK=pharmacokinetic; PD=pharmacodynamic; ELF=epithelial lining fluid; AUC:MIC=area under the plasma concentration time curve; MIC=minimum inhibitory concentration; R=resistant

Note: MIC distribution is of *S. pneumoniae* isolates collected from the US during a 2014 surveillance study

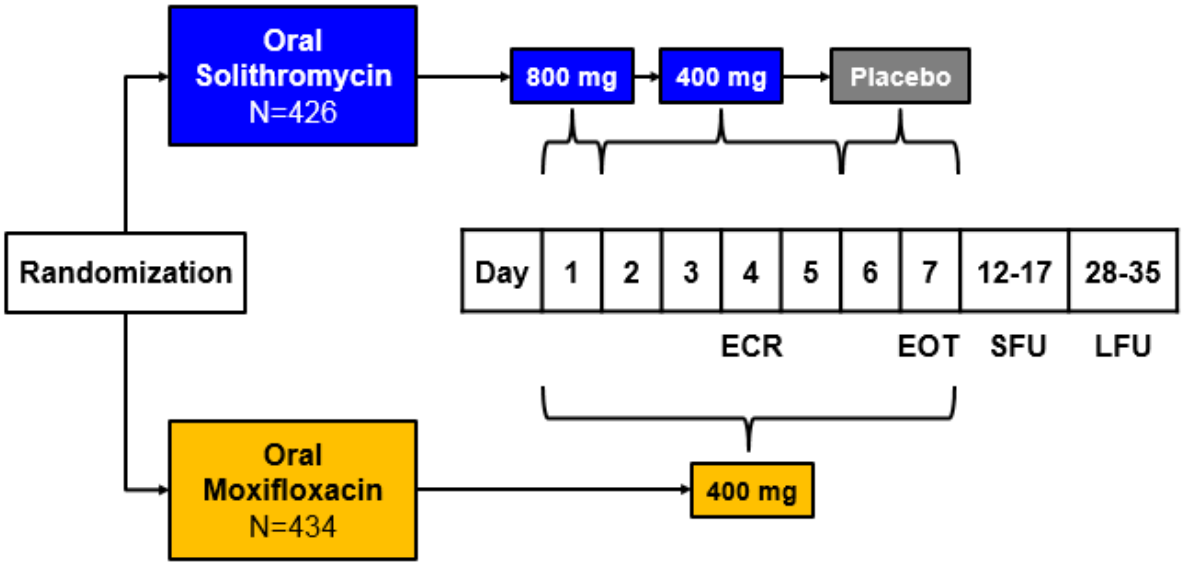
1.5 Clinical Studies in CABP

The efficacy and safety of solithromycin in CABP were established in two large Phase 3 studies, with supporting data from a Phase 2 study. The Phase 2 Study 200 was a randomized, double-blind, multicenter trial that compared the safety and efficacy of oral solithromycin with oral levofloxacin in 132 CABP patients. In this study, solithromycin demonstrated comparable efficacy outcomes to levofloxacin based on an investigator assessment at a test-of-cure (TOC) visit 4 to 11 days after the last dose (primary endpoint), and based on a programmatic, symptom-based assessment of early response on Day 3.

The pivotal Phase 3 Studies 300 and 301 were randomized, double-blind, multicenter, global studies that evaluated the non-inferiority of solithromycin to moxifloxacin. Moxifloxacin was chosen as the active comparator due to its established efficacy in the treatment of CABP, its potent activity against key typical and atypical CABP pathogens, and its availability in oral and IV formulations at the same recommended dose worldwide.

Figure 3 and Figure 4 illustrate the design of each study. Study 300 evaluated 5 treatment days with oral solithromycin compared with 7 treatment days with oral moxifloxacin, with an additional 2 placebo days in the solithromycin regimen to maintain blinding. The initial dose for solithromycin was 800 mg followed by 400 mg daily. Moxifloxacin patients received 400 mg on each dosing day. All doses were administered QD.

Figure 3 Study 300 Design: Oral Dosing

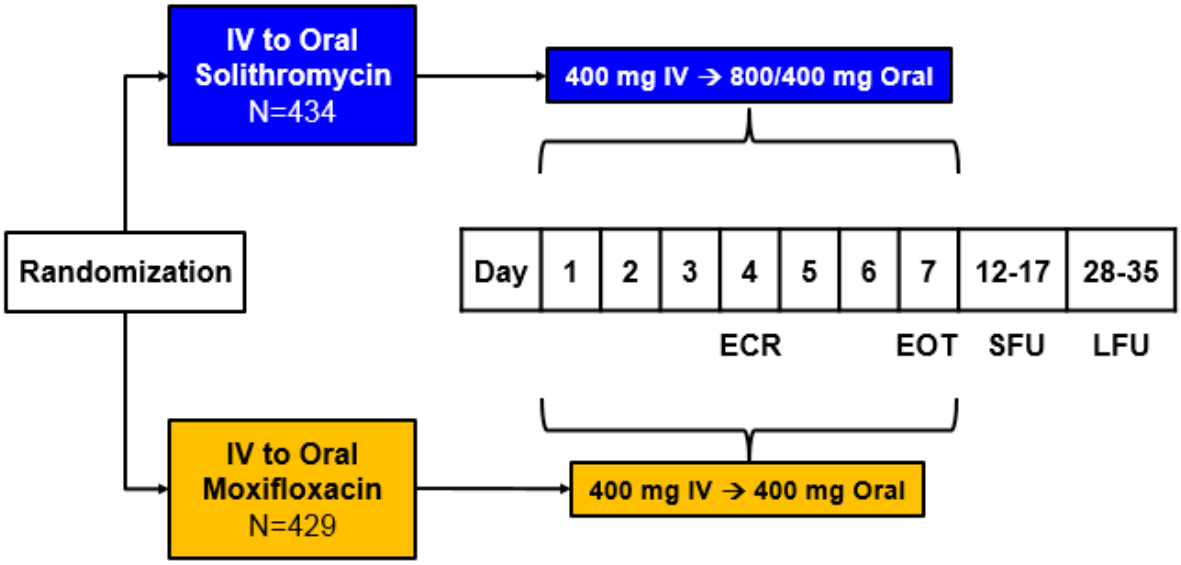


ECR=Early Clinical Response; EOT=end of treatment; SFU=short-term follow-up; LFU=long-term follow up

In Study 301, patients in both treatment groups were administered IV treatment on Day 1 and could be maintained on IV treatment QD for the full 7-day treatment course. Beginning on Day 2, patients could be transitioned to oral therapy at the investigator's discretion if they met clinical improvement criteria. Patients in the solithromycin group received an IV treatment regimen of

400 mg QD. For patients who transitioned to oral solithromycin, the first oral dose was 800 mg administered as a single dose, followed by 400 mg oral QD for the remainder of the 7-day study drug administration period. Moxifloxacin was administered as an IV treatment regimen of 400 mg QD and for patients transitioning to oral therapy as 400 mg QD on each oral dosing day.

Figure 4 Study 301 Design: IV to Oral Dosing



IV=intravenous; ECR=Early Clinical Response; EOT=end of treatment; SFU=short-term follow-up; LFU=long-term follow up

Both studies enrolled adult patients with CABP diagnosed by the presence of major clinical signs and symptoms of CABP and confirmed by pulmonary imaging. Inclusion and exclusion criteria were similar in both studies, with the notable exception being overall greater CABP severity enrollment in Study 301 based upon the Pneumonia Outcomes Research Team (PORT) score criteria. The key enrollment criteria were as follows:

- Presence of at least 3 of the following 4 cardinal symptoms of CABP:
  - Cough, chest pain, dyspnea, production of purulent sputum
- At least 1 of the following: fever, hypothermia, pulmonary rales and/or evidence of pulmonary consolidation
- Radiographically confirmed community-acquired pneumonia
- PORT II, III, or IV pneumonia disease severity
  - Study 300: pneumonia severity index (PSI) score 51 to 105 (PORT II capped at 50%)
  - Study 301: PSI score 51 to 130 (PORT II capped at 25%; and ≥ 25% PORT IV)

As agreed with the Food and Drug Administration (FDA), a single dose of a short-acting antibiotic within 7 days prior to enrollment was allowed in up to 25% of patients in each trial. Otherwise, antibiotic therapy in the prior 7 days was exclusionary. Randomization was stratified by

geographic region, history of asthma and/or chronic obstructive pulmonary disease (COPD), and PORT II vs III/IV in both studies.

Efficacy analyses were conducted at 72 hours (-12/+36 for Study 300 and -13/+36 for Study 301) following the first dose of study drug (Day 4 visit) for assessment of the primary outcome of early clinical response (ECR), at the end of treatment (EOT) visit, and at the short-term follow-up (SFU) visit 5 to 10 days after last dose of study drug. In addition, all-cause mortality was assessed through the late follow-up (LFU) visit 28 to 35 days after the first dose of study drug.

Populations for analysis were defined as follows:

- Intent-to-treat (ITT): all randomized
- Microbiological ITT (mITT): ITT + any amount of study drug + pathogen
- Microbiological ITT-2 (mITT-2): ITT + any amount of study drug + pathogen detected by traditional, primarily culture-based methods (mITT-2 is a subset of mITT requested by FDA to evaluate pathogen-specific outcomes)
- Clinically Evaluable (CE): ITT, met key inclusion criteria, did not meet key exclusion criteria, met minimal dosing criteria, and did not use a confounding antibiotic or have another factor that could confound the assessment of efficacy (full definitions can be found in Appendix 11.1)
    - CE-ECR: clinically evaluable for the ECR assessment
    - CE-EOT: clinically evaluable at the EOT visit
    - CE-SFU: clinically evaluable at the SFU visit
- Microbiologically Evaluable (ME or ME-2): in the mITT and CE populations (ME) or in the mITT-2 and CE populations (ME-2)
    - ME-ECR/ME-ECR-2: microbiologically evaluable for the ECR assessment
    - ME-EOT/ME-EOT-2: microbiologically evaluable at the EOT visit
    - ME-SFU/ME-SFU-2: microbiologically evaluable at the SFU visit

The primary endpoint of ECR was defined as improvement at 72 hours after the first dose of study drug in at least 2 of the 4 cardinal CABP symptoms (cough, shortness of breath, chest pain, difficulty with sputum production), as outlined in the FDA 2009 and 2014 draft CABP guidance documents, with no worsening of any symptom, and no receipt of rescue antibiotics. Additionally, to be an ECR responder, the patient must have survived through the LFU visit (Day 28 to 35). Each symptom was scored from 0 (absent) to 3 (severe). Improvement in each symptom was defined as a decrease of at least one point from the baseline score for the symptom, and worsening of a symptom was defined as an increase of at least one point from the baseline score for the symptom. In Study 300, co-primary endpoints were ECR in the ITT population (10% non-inferiority margin) and ECR in the pooled (across studies 300 and 301) mITT population (15% non-inferiority margin). In Study 301, the primary endpoint was ECR in the ITT population (10% non-inferiority margin).

Investigators assessed clinical response (success, failure, or indeterminate) at the EOT and SFU visits as a secondary endpoint. The investigator assessment of clinical response at SFU represented the traditional TOC endpoint utilized in previous CABP clinical development programs. A patient achieving clinical success at EOT was considered by the investigator to have a complete or near-complete resolution of the baseline signs and symptoms of CABP. Patients who were failures at EOT could not be considered successes at the SFU visit.

Additional efficacy endpoints based on CABP symptoms were also analyzed at EOT and SFU.

Efficacy Findings

Demographics and baseline disease characteristics were comparable between treatment groups in each study. Slightly more than half of patients in each trial were male and approximately 80% of patients in the studies were white. In Study 300, approximately 34% of patients were ≥ 65 years of age and about 15% of patients were ≥ 75 years of age. The population was slightly older for Study 301 with approximately 45% of patients ≥ 65 years of age and about 19% of patients ≥ 75 years of age. The studies enrolled patients from North America, Europe, Latin America, and other regions. Europe was the highest enrolling region.

In accordance with enrollment targets and criteria in each study, patients on average had greater baseline CABP disease severity in Study 301. In Study 300, approximately half of patients were PORT Risk Class II (49.3%, solithromycin; 51.4% moxifloxacin). In Study 301, < 25% of patients were PORT Risk Class II (24.4%, solithromycin; 22.4% moxifloxacin) and > 30% were PORT Risk Class IV/V (30.4%, solithromycin; 30.1% moxifloxacin; there were 6 PORT V patients in total).

Baseline pathogens were balanced by treatment group in each study. The most common pathogens in the mITT population were *S. pneumoniae, H. influenzae, L. pneumophila*, and *M. pneumoniae*. The most common pathogens in the mITT-2 population were similar, with the exception of fewer numbers of *L. pneumophila* due to the exclusion of serological diagnoses in this population. Among pneumococcal isolates in the pooled mITT-2 population with susceptibility data available, 25.4% were macrolide resistant; all of these isolates had solithromycin MICs ≤ 1 µg/mL, the proposed susceptible breakpoint for *S. pneumoniae*. Approximately 55% of patients with serotype data available had *S. pneumoniae* not covered by the 13-valent pneumococcal conjugate vaccine and 37% were not covered by the 23-valent pneumococcal polysaccharide vaccine.

In each of the Phase 3 studies, approximately 95% of patients in each treatment group completed the trial. In Study 300, 7.0% and 6.0% of patients in the solithromycin and moxifloxacin groups prematurely discontinued study drug during the trial. In Study 301, 10.6% and 8.9% in the solithromycin and moxifloxacin groups prematurely discontinued study drug. The higher rate of early drug discontinuation in Study 301 was mostly attributable to the higher rate of discontinuations due to infusion-related adverse events (AEs) in the solithromycin group (2.3% with solithromycin, 0.2% with moxifloxacin).

In each of the Phase 3 studies, solithromycin was found to be non-inferior to moxifloxacin for the primary endpoint of ECR. For Study 300, the co-primary outcomes of ECR in the ITT and ECR in the pooled mITT population from Studies 300 and 301 are presented in Table 4. In the ITT

population, 78.2% and 77.9% of solithromycin and moxifloxacin patients were responders with a lower bound of the 95% confidence interval (CI) for the treatment difference -5.5%, meeting the 10% non-inferiority margin. In the pooled mITT population, 77.2% and 78.9% of solithromycin and moxifloxacin patients were responders, with a lower bound of the 95% CI for the treatment difference -7.4%, meeting the 15% non-inferiority margin for that population. Thus, solithromycin was shown to be non-inferior to moxifloxacin for ECR in the ITT and pooled mITT populations. Sensitivity analyses supported the primary analysis findings.

Table 4 Study 300: Co-Primary Efficacy Endpoints - Early Clinical Response in the ITT Population and Pooled Phase 3 mITT Population

	Study 300 ITT Population		Pooled Studies 300 and 301 mITT Population[a]	
Early Clinical Response	**Solithromycin Oral N=426 n (%)**	**Moxifloxacin Oral N=434 n (%)**	**Solithromycin Pooled N=408 n (%)**	**Moxifloxacin Pooled N=379 n (%)**
Responder	333 (78.2)	338 (77.9)	315 (77.2)	299 (78.9)
Difference (95% CI)[b]	0.29 (-5.5, 6.1)		-1.69 (-7.4, 4.2)	
Non-responder (including indeterminate)	93 (21.8)	96 (22.1)	93 (22.8)	80 (21.1)
Non-responder	81 (19.0)	84 (19.4)	81 (19.9)	72 (19.0)
Indeterminate	12 (2.8)	12 (2.8)	12 (2.9)	8 (2.1)

ITT=intent-to-treat; mITT=microbiological intent-to-treat

N=number of patients in the ITT or pooled mITT population; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).

The window for assessment of early clinical response in Study 300 was 72 [-12/+36] hours, and in Study 301 was 72 [-13/+36] hours.

a. Pooled mITT population from Studies 300 and 301, including patients from Site 710 in Study 300.

b. Observed difference in clinical responder rates (solithromycin minus moxifloxacin). For ITT population, CI was calculated using an unadjusted continuity corrected Z-test. For pooled mITT population, adjusted confidence intervals were calculated using the Miettinen and Nurminen method with adjustment for the stratification factor of study. Stratum weights were the inverse variance of each effect size

Findings for secondary and additional endpoints (Table 5) were consistent with the primary analysis in Study 300. Solithromycin demonstrated comparable efficacy to moxifloxacin in an analysis of ECR with the additional criterion of improvement in baseline vital signs in the ITT population and in the assessment of ECR in the mITT population (Study 300 only). For the investigator assessment of clinical success at the SFU visit, high and comparable success rates were observed in both the ITT and CE-SFU populations. Additional efficacy assessments based on CABP symptoms at the SFU visit also demonstrated comparable efficacy between groups at this time point.

Table 5 Study 300: Secondary and Additional Endpoints

Efficacy Outcome	Solithromycin Oral n/N (%)	Moxifloxacin Oral n/N (%)	Treatment Difference (95% CI)
ECR, with Inclusion of Improvement of Vital Signs, ITT Population			
Responder	207/426 (48.6)	210/434 (48.4)	0.20 (-6.7, 7.1)
ECR, mITT Population			
Responder	176/235 (74.9)	178/226 (78.8)	-3.87 (-12.0, 4.3)
Clinical Response at SFU Based on Investigator Assessment			
Success, ITT Population	360/426 (84.5)	376/434 (86.6)	-2.13 (-7.1, 2.8)
Success, CE-SFU Population	342/388 (88.1)	356/390 (91.3)	-3.14 (-7.7, 1.4)
Symptom response at SFU by Major CABP Symptoms[a], ITT population			
Responder	315/426 (73.9)	329/434 (75.8)	-1.86 (-7.9, 4.2)
Sustained ECR at SFU Visit[b], ITT population			
Responder	273/426 (64.1)	277/434 (63.8)	0.26 (-6.4, 6.9)
Resolution of All CABP Symptoms at SFU[c], ITT population			
Responder	219/394 (55.6)	232/404 (57.4)	-1.84 (-9.0, 5.3)

CI=confidence interval; ITT=intent-to-treat; mITT= microbiological ITT.

n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).

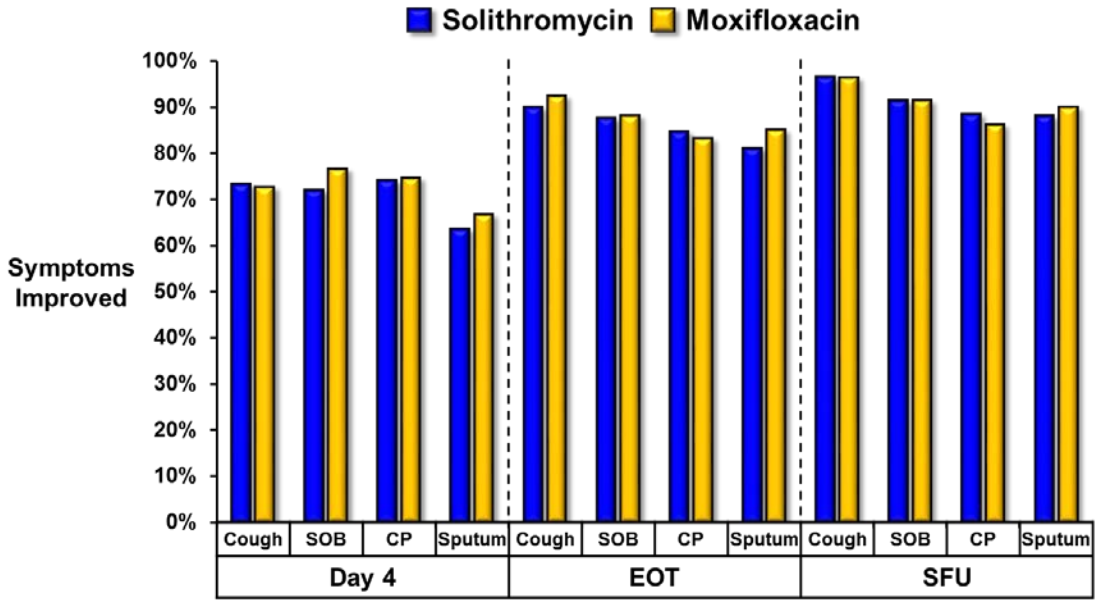
a. Symptom Response at SFU by Major CABP Symptoms was defined as the absence of chest pain and sputum production, and the absence of, or improvement from baseline in, cough and dyspnea.

b. Sustained ECR was defined as response for the primary efficacy outcome, which was maintained through SFU, requiring chest pain and sputum production to be absent, and cough and dyspnea to be absent or improved since baseline.

c. Resolution of all CABP signs/symptoms was defined as the absence of cough, dyspnea, chest pain due to pneumonia, and difficulty with sputum production. N=number of patients in the ITT population with non-missing assessments of all baseline signs and symptoms at the specified visit.

As shown in Figure 5, rates of symptom improvement at the Day 4 (ECR), EOT, and SFU visits were high and similar between treatment groups.

Figure 5 Study 300: Percentage of Patients with CABP Symptom Improvement Compared with Baseline at Day 4, EOT, and SFU in the ITT Population



SOB=shortness of breath; CP=Chest pain; EOT=end of treatment; SFU=short-term follow-up

For Study 301, the primary outcome of ECR in the ITT population is presented in Table 6. Solithromycin was shown to be non-inferior to moxifloxacin for ECR. In the solithromycin and moxifloxacin treatment groups, 79.3% and 79.7% were responders, respectively, with a lower bound of the 95% CI for the treatment difference -6.1%, meeting the 10% non-inferiority margin. All sensitivity analyses supported the primary analysis.

Table 6 Study 301: Primary Endpoint: Early Clinical Response in the ITT Population

Early Clinical Response	Solithromycin IV to Oral N=434 n (%)	Moxifloxacin IV to Oral N=429 n (%)
Responder	344 (79.3)	342 (79.7)
Difference (95% CI)[a]	-0.46 (-6.1, 5.2)	
Non-responder (including indeterminate)	90 (20.7)	87 (20.3)
Non-responder	76 (17.5)	78 (18.2)
Indeterminate	14 (3.2)	9 (2.1)

ITT=intent-to-treat; CI=confidence interval

N=Number of patients in the ITT population; n=number of patients within a specific category. Percentages were calculated as 100 × (n/N).

a. Difference in clinical responder rates (solithromycin minus moxifloxacin); CI was calculated using an unadjusted continuity corrected Z-test.

Findings for secondary and additional endpoints (Table 7) were generally consistent with the primary analysis. Solithromycin demonstrated similar efficacy to moxifloxacin in an analysis of ECR with the added criteria of improvement in baseline vital signs in the ITT population and in the assessment of ECR in the mITT population (Study 301 only). As in Study 300, rates of investigator assessment of clinical success at SFU were high in each treatment group, but higher in both the ITT and CE-SFU populations in the moxifloxacin group. The treatment difference does not seem to reflect a clinically meaningful difference in antimicrobial efficacy of the two drugs; rather, disassociated events contributed to this difference (e.g. a study drug supply issue affecting 5 solithromycin patients and a higher incidence of discontinuations due to infusion site pain in the solithromycin group; Section 7.4). As shown in Table 7, for symptom-based efficacy endpoints at SFU, solithromycin and moxifloxacin outcomes were comparable at this time point.

Table 7 Study 301: Secondary and Additional Endpoints

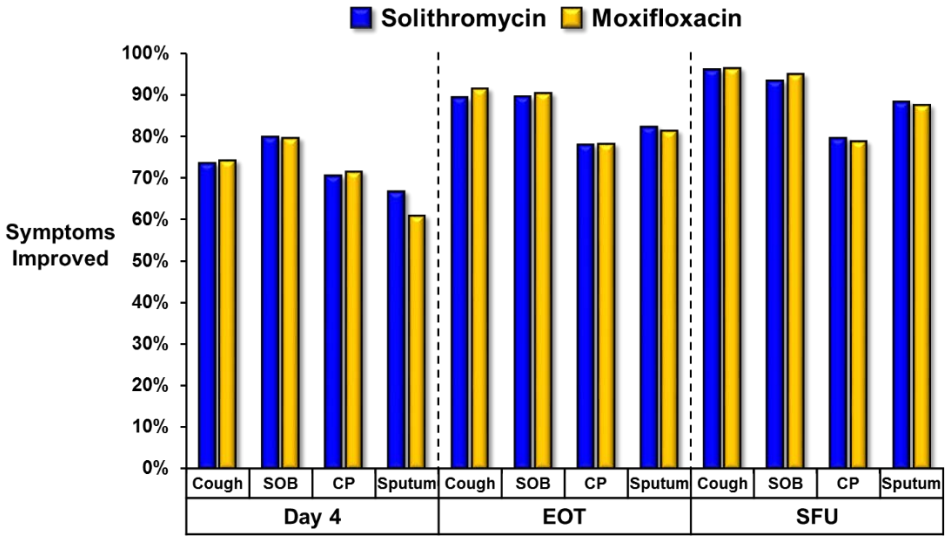
Efficacy Outcome	Solithromycin IV to Oral n/N (%)	Moxifloxacin IV to Oral n/N (%)	Treatment Difference (95% CI)
ECR, with Inclusion of Improvement in Vital Signs, ITT population			
Responder	185/434 (42.6)	167/429 (38.9)	3.70 (-3.1, 10.5)
ECR, mITT Population			
Responder	139/173 (80.3)	121/153 (79.1)	1.26 (-8.1, 10.6)
Clinical Response at SFU Based on Investigator Assessment			
Success, ITT Population	367/434 (84.6)	380/429 (88.6)	-4.02 (-8.8, 0.8)
Success, CE-SFU Population	338/391 (86.4)	359/388 (92.5)	-6.08 (-10.6, -1.5)
Symptom response at SFU by Major CABP Symptoms [a], ITT Population			
Responder	346/434 (79.7)	330/429 (76.9)	2.80 (-2.9, 8.5)
Sustained ECR at SFU Visit [b], ITT Population			
Responder	297/434 (68.4)	290/429 (67.6)	0.83 (-5.6, 7.3)
Resolution of All CABP Signs/Symptoms at SFU[c], ITT Population			
Responder	253/405 (62.5)	240/402 (59.7)	2.77 (-4.2, 9.7)

CI=confidence interval; ITT=intent-to-treat; mITT= microbiological ITT.
N=number of patients in the ITT population with non-missing assessments of all baseline signs and symptoms at the specified visit; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).

a. Symptom Response at SFU by Major CABP Symptoms was defined as the absence of chest pain and sputum production, and the absence of, or improvement from baseline in, cough and dyspnea.
b. Sustained ECR was defined as response for the primary efficacy outcome, which was maintained through SFU, requiring chest pain and sputum production to be absent, and cough and dyspnea to be absent or improved since baseline.
c. Resolution of all CABP signs/symptoms was defined as the absence of cough, dyspnea, chest pain due to pneumonia, and difficulty with sputum production.

As shown in Figure 6, rates of symptom improvement at the Day 4 (ECR), EOT, and SFU visits were high and similar between treatment groups.

Figure 6 Study 301: Percentage of Patients with CABP Symptom Improvement Compared with Baseline at Day 4, EOT, and SFU in the ITT Population



SOB=shortness of breath; CP=Chest pain; EOT=end of treatment; SFU=short-term follow-up

Pooled (studies 300 and 301) efficacy analyses of ECR were conducted utilizing demographic subpopulations (age, gender, body mass index [BMI], race and geographic region), baseline disease severity subpopulations (PORT Risk Class, SIRS criteria, history of asthma and/or COPD), and prior antibiotic use subgroups. Results of these analyses are presented in Section 6.6.3 (Figure 19 and Figure 20) and demonstrate consistent solithromycin efficacy across subpopulations. In patients from North America (comprised mostly of patients from the US), 72.8% and 66.0% of solithromycin and moxifloxacin patients, respectively, were responders for ECR. Solithromycin responder rates were similar to moxifloxacin in patients with more severe disease and risk factors (PORT Risk Class III/IV and concurrent asthma and/or COPD). Responder rates were comparable between treatment groups for patients receiving and not receiving a prior antibiotic, and were slightly higher in patients who received a prior antibiotic.

Integrated analyses also examined ECR and investigator assessment of clinical response at SFU by baseline pathogen (Section 6.6.1). ECR responder and clinical success rates were high and comparable between the solithromycin and moxifloxacin groups for Gram-positive, Gram-negative, and atypical bacterial pathogens, including the subgroup of patients with macrolide-resistant *S. pneumoniae.*

1.6 Safety Experience in Development

More than 2000 individuals have been exposed to solithromycin as of July 31, 2016. The major sources of safety data are the two Phase 3 pivotal studies in adult patients with CABP, where 856 patients were treated with solithromycin. A total of 920 adult CABP patients who received solithromycin are integrated from the Phase 2 and 3 studies.

1.6.1 Overview of Adverse Events

In the pooled Phase 3 studies, because of the higher incidence for infusion site reactions with solithromycin than moxifloxacin in Study 301 (Table 8), the overall incidence of treatment-emergent adverse events (TEAEs) was higher in patients receiving solithromycin than in those receiving moxifloxacin (44% vs 35%). When IV site events are excluded, the overall incidence of systemic TEAEs was similar (35.5% vs. 34.3%).

Table 8 Summary of TEAEs in Individual and Pooled Phase 3 Studies

	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral (N=424) n (%)	Moxi Oral (N=432) n (%)	Soli IV to Oral (N=432) n (%)	Moxi IV to Oral (N=426) n (%)	Soli Pooled (N=856) n (%)	Moxi Pooled (N=858) n (%)
TEAEs	155 (36.6)	154 (35.6)	223 (51.6)	148 (34.7)	378 (44.2)	302 (35.2)
Excluding IV infusion site events	155 (36.6)	154 (35.6)	149 (34.5)	140 (32.9)	304 (35.5)	294 (34.3)
TEAEs leading to premature discontinuation of drug	16 (3.8)	13 (3.0)	25 (5.8)	16 (3.8)	41 (4.8)	29 (3.4)
Excluding IV infusion site events	16 (3.8)	13 (3.0)	16 (3.7)	16 (3.8)	32 (3.7)	29 (3.4)
Severe TEAEs	21 (5.0)	21 (4.9)	28 (6.5)	18 (4.2)	49 (5.7)	39 (4.5)
Excluding IV infusion site events	21 (5.0)	21 (4.9)	21 (4.9)	18 (4.2)	42 (4.9)	39 (4.5)
Serious TEAEs (SAEs)	28 (6.6) [a]	27 (6.3)	30 (6.9)	23 (5.4)	58 (6.8) [a]	50 (5.8)
SAEs leading to death	6 (1.4)	6 (1.4)	5 (1.2)	7 (1.6)	11 (1.3)	13 (1.5)

TEAE=treatment-emergent adverse event; SAE= serious adverse event

a. An additional SAE occurred in the solithromycin group in Study 300 that is not included in the dataset.

Overall, 31.3% of solithromycin patients in Study 301 had infusion site reactions compared to 5.4% of moxifloxacin patients (Table 9). Of the 135 solithromycin patients with infusion site events, 8 patients experienced an event considered severe, but none of the events were considered to be a serious adverse event (SAE). The incidence of discontinuation from study drug due to these events was 2.3% of solithromycin patients and 0.2% of moxifloxacin patients. This finding was not unexpected, as infusion site reactions are a class effect observed with IV macrolides but are not commonly observed with IV fluoroquinolones.

TEAEs occurring at an incidence of ≥ 2% in Studies 300, 301, and the pooled database are shown in Table 9. Infusion site TEAEs were the most frequently reported TEAEs for solithromycin. Other common TEAEs observed with solithromycin in the pooled data were diarrhea (4.3%), headache (4.0%), nausea (3.4%), and dizziness (2.3%).

Table 9 Summary of Most Frequently Reported (≥ 2%) TEAEs in Individual and Pooled Phase 3 Studies

	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral N=424 n (%)	Moxi Oral N=432 n (%)	Soli IV to Oral N=432 n (%)	Moxi IV to Oral N=426 n (%)	Soli Pooled N=856 n (%)	Moxi Pooled N=858 n (%)
Patients with ≥ 1 TEAE	155 (36.6)	154 (35.6)	223 (51.6)	148 (34.7)	378 (44.2)	302 (35.2)
Patients with ≥ 1 TEAE (excluding infusion site events)	155 (36.6)	154 (35.6)	149 (34.5)	140 (32.9)	304 (35.5)	294 (34.3)
Preferred Term (Excluding Infusion Site Events), n (%)						
Diarrhea	18 (4.2)	28 (6.5)	19 (4.4)	25 (5.9)	37 (4.3)	53 (6.2)
Headache	19 (4.5)	11 (2.5)	15 (3.5)	18 (4.2)	34 (4.0)	29 (3.4)
Nausea	15 (3.5)	17 (3.9)	14 (3.2)	7 (1.6)	29 (3.4)	24 (2.8)
Dizziness	9 (2.1)	7 (1.6)	11 (2.5)	5 (1.2)	20 (2.3)	12 (1.4)
Pneumonia	7 (1.7)	5 (1.2)	11 (2.5)	5 (1.2)	18 (2.1)	10 (1.2)
Vomiting	10 (2.4)	10 (2.3)	4 (0.9)	3 (0.7)	14 (1.6)	13 (1.5)
Hypokalemia	2 (0.5)	3 (0.7)	11 (2.5)	9 (2.1)	13 (1.5)	12 (1.4)
Hypertension	6 (1.4)	5 (1.2)	6 (1.4)	10 (2.3)	12 (1.4)	15 (1.7)
Insomnia	2 (0.5)	4 (0.9)	9 (2.1)	5 (1.2)	11 (1.3)	9 (1.0)
Infusion Site Preferred Terms, n (%)			135 (31.3)	23 (5.4)		
Infusion site pain	-	-	45 (10.4)	6 (1.4)	-	-
Infusion site phlebitis	-	-	43 (10.0)	4 (0.9)	-	-
Infusion related reaction	-	-	28 (6.5)	1 (0.2)	-	-
Infusion site erythema	-	-	19 (4.4)	2 (0.5)	-	-
Infusion site thrombosis	-	-	9 (2.1)	7 (1.6)	-	-
Infusion site paresthesia	-	-	9 (2.1)	0	-	-

TEAE=treatment-emergent adverse event

TEAEs leading to discontinuation of study drug were reported for 41 (4.8%) solithromycin patients and 29 (3.4%) moxifloxacin patients. The most frequently reported TEAEs resulting in premature discontinuation of study drug for solithromycin patients were infusion site pain and (worsening) pneumonia; most other preferred terms associated with premature discontinuation of solithromycin were reported in only a single solithromycin or moxifloxacin patient. The incidence of non-infusion site TEAEs leading to premature discontinuation of study drug was similar between solithromycin (32 patients; 3.7%) and moxifloxacin (29 patients; 3.4%).

The incidence of SAEs was comparable in the pooled solithromycin (6.8%) and moxifloxacin (5.8%) treatment groups. There were no differences in incidence of specific events among these SAEs that indicated increased risk with solithromycin. Clinical events reported as SAEs were generally consistent with CABP or underlying disease in the population enrolled for study.

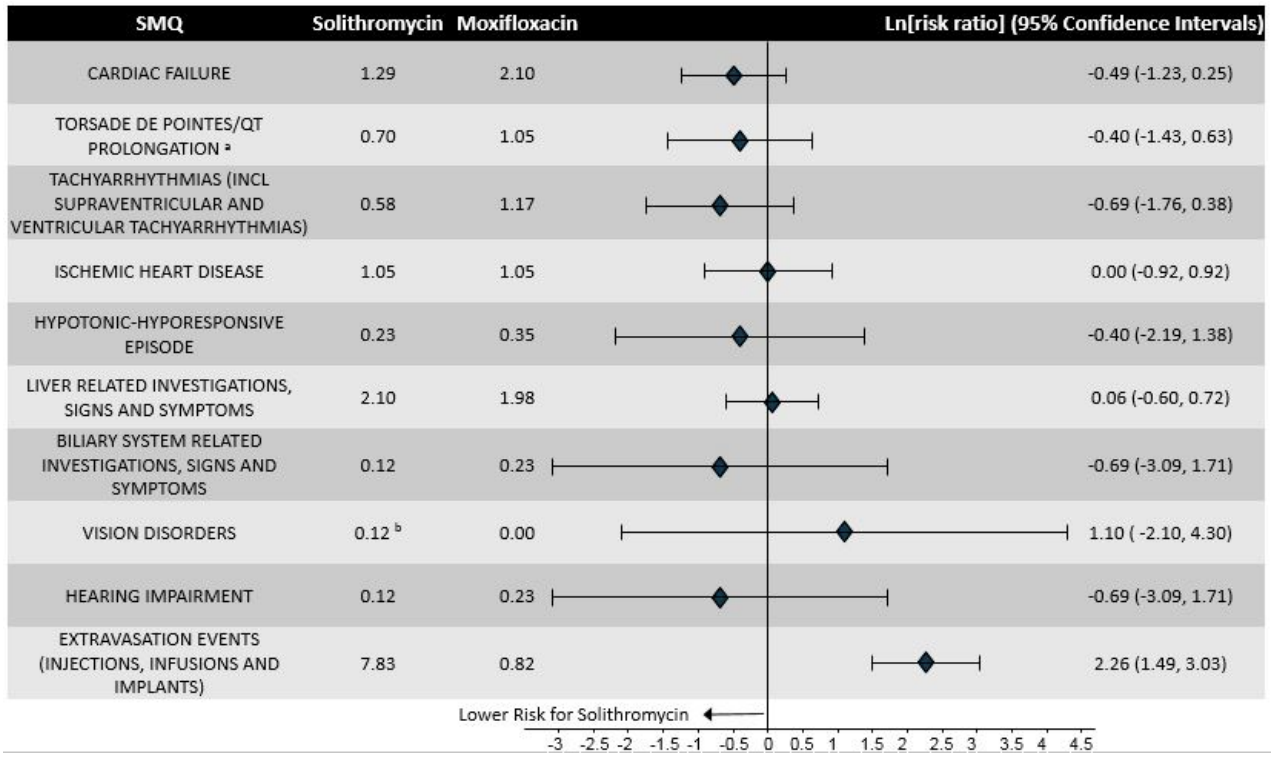
Eleven (11) deaths occurred in solithromycin patients and 13 deaths occurred in moxifloxacin patients in the Phase 3 studies. The majority of deaths in each treatment group were attributable to underlying respiratory or cardiac diseases in patients presenting with multiple comorbidities and risk factors. None were considered to be related to the study drug.

1.6.2 Adverse Events of Special Interest

Hepatic safety, cardiovascular safety, vision and hearing effects were all analyzed as adverse events of special interest (AESIs) based on prior observations with macrolides and the safety events of concern observed with telithromycin. Figure 7 summarizes the findings of standardized MedDRA query (SMQ) adverse event analyses for these topics of interest.

AESIs were rare in the Phase 3 studies and generally observed less frequently with solithromycin administration compared with moxifloxacin.

Figure 7 Summary of AESI Incidence Rates for Solithromycin and Moxifloxacin in the Pooled Phase 3 Studies



SMQ = standardized MedDRA query

a. No episodes of torsade de pointes occurred in either treatment group

b. A single patient reported 'black spots' consistent with floaters; no disorders of visual accommodation were reported

1.6.3 Hepatic Safety

The most commonly observed hepatic effect of macrolides in clinical practice and in clinical studies is asymptomatic elevation of serum aminotransferase levels. All four macrolide antibiotics currently on the market elevate serum aminotransferases.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations above the upper limit of normal (ULN) were noted at baseline (prior to first dose) in 15.1% and 17.9%, respectively, of solithromycin patients in the pooled Phase 3 CABP studies. ALT and AST elevations >3×ULN and >5×ULN occurred more frequently with solithromycin than moxifloxacin in the Phase 3 studies (Table 10). Elevations to >10×ULN were infrequent and comparable (4 solithromycin patients, 3 moxifloxacin patients). Peak elevations in ALT and AST in solithromycin patients were generally observed on Day 4. These elevations were typically asymptomatic, not associated with bilirubin elevation, and resolved rapidly (in many cases during continued study drug dosing).

Table 10 Frequency of Liver-Related Laboratory Assessments >3×ULN, >5×ULN, and >10×ULN at Any Post-Baseline Study Visit

Parameter (unit)	Study 300		Study 301		Pooled Phase 3 Studies	
	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
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)
AST (U/L), n/N1 (%)						
>3×ULN	10/406 (2.5)	8/416 (1.9)	20/416 (4.8)	10/409 (2.4)	30/822 (3.6)	18/825 (2.2)
>5×ULN	4/406 (1.0)	4/416 (1.0)	9/416 (2.2)	2/409 (0.5)	13/822 (1.6)	6/825 (0.7)
>10×ULN	2/406 (0.5)	2/416 (0.5)	2/416 (0.5)	0/409	4/822 (0.5)	2/825 (0.2)
ALP (U/L), n/N1 (%)						
>3×ULN	7/411 (1.7)	2/423 (0.5)	1/417 (0.2)	1/415 (0.2)	8/828 (1.0)	3/838 (0.4)
>5×ULN	3/411 (0.7)	1/423 (0.2)	1/417 (0.2)	0/415	4/828 (0.5)	1/838 (0.1)
>10×ULN	0/411	0/423	1/417 (0.2)	0/415	1/828 (0.1)	0/838
Direct Bilirubin (mg/dL), n/N1 (%)						
>3×ULN	2/402 (0.5)	1/412 (0.2)	1/413 (0.2)	2/407 (0.5)	3/815 (0.4)	3/819 (0.4)
>5×ULN	0/402	0/412	1/413 (0.2)	1/407 (0.2)	1/815 (0.1)	1/819 (0.1)
>10×ULN	0/402	0/412	0/413	1/407 (0.2)	0/815	1/819 (0.1)

Parameter (unit)	Study 300		Study 301		Pooled Phase 3 Studies	
	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
Total Bilirubin (mg/dL), n/N1 (%)						
>3×ULN	1/412 (0.2)	0/422	0/416	1/413 (0.2)	1/828 (0.1)	1/835 (0.1)
>5×ULN	0/412	0/422	0/416	0/413	0/828	0/835
>10×ULN	0/412	0/422	0/416	0/413	0/828	0/835

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; ULN=upper limit of normal

N = Number of patients in the Safety Population. N1 = Number of patients with a post-baseline lab value for the specified parameter. n=Number of patients with a post-baseline value >3×ULN, >5×ULN, or >10×ULN at any post-baseline visit.

Note: Baseline is defined as the last assessment prior to the first dose of study drug. Worst, or most severe, laboratory results during the study are included in the table. Patients can appear in the table only once per parameter.

Treatment-emergent transaminase elevations occurred more frequently among patients in whom these parameters were elevated at baseline. Among solithromycin patients who had baseline ALT or AST values within the normal range, ALT elevation to > 3×ULN occurred in 4.7% of patients and AST elevation to > 3×ULN in 1.6%.

Transaminase elevations in the Phase 3 studies were not associated with concurrent increases in serum bilirubin or impaired hepatic function. Three patients (2 solithromycin and 1 moxifloxacin) met laboratory but not clinical criteria consistent with Hy's Law (a treatment emergent ALT or AST > 3× ULN with a bilirubin > 2×ULN at any post treatment time point). The clinical profiles for each of these patients were reviewed by the investigator, the sponsor, and an expert hepatic safety review panel, and none were considered 'Hy's Law Cases,' as there was an alternative explanation for the identified liver injury.

Solithromycin safety has also been evaluated with DILIsym® modeling software, which provides a computational model of drug induced liver injury (DILI). These modeling experiments predicted that no Hy's Law cases would occur with the oral or IV to oral solithromycin CABP dosing regimens.

1.6.4 Cardiac Safety

A thorough QT study demonstrated that solithromycin does not prolong QT in healthy adult subjects when administered at supratherapeutic exposures. Solithromycin is the first macrolide antibiotic with a negative thorough QT study; these findings were confirmed by exposure-response modeling which showed the absence of solithromycin-induced QTc prolongation. These observations are supported by data from the Phase 3 studies, which enrolled patients with preexisting chronic heart diseases. Mean changes from baseline for QTcF at all time points were higher for moxifloxacin than solithromycin. Categorical changes from baseline were low overall, and observed changes were greater in moxifloxacin patients.

The thorough QT and other Phase 1 studies demonstrated that solithromycin has the potential to increase heart rate in healthy adults. In the Phase 3 studies, the central tendency for patients with pneumonia, who frequently presented with tachycardia due to stress, fever, and hypoxia, was for heart rate to decline with solithromycin therapy.

1.7 Conclusion

The spread of antibiotic resistance has created a need for effective new antimicrobial treatment options for CABP. CABP continues to be associated with high morbidity and mortality, and remains the most common infectious disease cause for hospitalization in the US. Because resistance to first and second generation macrolides is highly prevalent in the US and because telithromycin has been associated with deleterious side effects, macrolide monotherapy for CABP is no longer a recommended and viable treatment option. Consequently, physicians and patients are left with a suboptimal treatment paradigm, necessitating overuse of broad-spectrum fluoroquinolones or use of combination therapies pairing a broad-spectrum IV cephalosporin (e.g. ceftaroline, ceftriaxone) with a macrolide. While these treatment strategies are effective, they may worsen the problem of resistance development and cause collateral damage to the gut microbiome, increasing patient risk of *C. difficile* infection. Additionally, there are significant concerns with fluoroquinolone toxicities including neuropathy, tendinopathy, and QT prolongation. There is also a need for treatments that provide the flexibility of both IV and oral formulations, allowing for transition to oral dosing and the potential for reduced hospitalization.

Solithromycin, a fourth generation macrolide and the first fluoroketolide, has enhanced bacterial ribosomal binding that extends its antibacterial activity beyond that of older macrolides.

An extensive nonclinical and clinical development program has been conducted to investigate solithromycin as monotherapy for CABP. Over 2000 study subjects and patients have been exposed to solithromycin, and 920 adult patients have received oral and/or IV solithromycin for treatment of CABP in the integrated Phase 2 and 3 clinical studies that support the NDA. Solithromycin was shown to be highly effective against the range of CABP pathogens in the treatment of adults with CABP. In each Phase 3 study, solithromycin was non-inferior to moxifloxacin for the primary outcome of ECR at Day 4. High success rates were also observed at SFU based on investigator assessment of clinical response. Efficacy at SFU was further confirmed utilizing symptom-based efficacy assessments. ECR efficacy findings were consistently observed across subpopulations for demographics, disease severity, and geographic region. Response rates for ECR and clinical success rates at SFU for target CABP pathogens were high and comparable to those observed for moxifloxacin. Solithromycin was effective for Gram-positive, Gram-negative, and atypical pathogens, and demonstrated high success rates for macrolide-resistant *S. pneumoniae*, penicillin-resistant *S. pneumoniae*, and multi-drug-resistant *S. pneumoniae*. These findings suggest that solithromycin monotherapy is an effective treatment option for patients at risk for drug-resistant pneumococcal pneumonia.

Solithromycin has demonstrated a safety profile comparable to that of first and second generation macrolides. Solithromycin was associated with hepatic aminotransferase elevations that occurred early in treatment, were generally asymptomatic, were not associated with bilirubin elevation, and improved during continued dosing or rapidly following completion of a treatment course. Asymptomatic aminotransferase elevation has been observed with all macrolide antibiotics.

A mechanistic model of DILI predicts a solithromycin hepatic safety profile comparable to older macrolides.

Importantly, solithromycin is differentiated from telithromycin, the first approved ketolide for CABP. Telithromycin has been associated with unexpected adverse effects that have limited its use. Telithromycin has been shown to antagonize nACh receptors through its pyridine-imidazole side chain moiety, offering an explanation for its macrolide-atypical profile of side effects. There were no findings that would suggest that solithromycin may be causally associated with the types of safety events of concern previously observed with telithromycin (blurred vision, loss of consciousness, severe exacerbation of myasthenia gravis, and rarely, idiosyncratic hepatic failure). The observation of exposure-related hepatic transaminase elevation in solithromycin patients is distinct from the acute and severe idiosyncratic episodes of liver failure that were reported with telithromycin.

In the IV to oral study, solithromycin had a higher rate of infusion site events than moxifloxacin. All other AEs across both studies occurred at comparable rates to moxifloxacin. Infusion site events are a known issue for IV macrolide therapy. These AEs were generally mild or moderate in severity and resulted in few discontinuations.

Currently available macrolides have been associated with QT prolongation and risk for torsades de pointes. In contrast, solithromycin was negative in a thorough QT study at a supratherapeutic exposure. In the Phase 3 studies, categorical changes from baseline in the QTcF interval occurred less frequently with solithromycin than with moxifloxacin.

While *C. difficile*-associated diarrhea has been reported with all classes of systemic antibacterial agents, macrolides have a lower risk than most other classes. No episodes of *C. difficile*-associated diarrhea were observed with solithromycin administration in any clinical trial while three cases were observed with moxifloxacin.

Solithromycin is both a CYP3A4 and P-gp substrate, and is also a strong inhibitor of CYP3A4 and a moderate inhibitor of P-gp. The profile for potential drug-drug interactions is consistent with that of other macrolides and can be managed in clinical practice.

Dose adjustments are not needed in patients with hepatic impairment or in patients with mild or moderate renal impairment. Dose adjustments are recommended for patients with severe renal impairment due to increased exposure in individuals with $CL_{CR} < 30$ mL/min.

Collectively, data from the solithromycin development program demonstrate a favorable benefit:risk profile for solithromycin for the treatment of CABP. Approval of solithromycin would provide an additional treatment option for CABP with the potential to improve antibiotic stewardship by reducing overuse of fluoroquinolones and the need for combination therapies. Solithromycin can address the current need for an additional first line antibiotic for CABP with both oral and IV dosing options.

2 PROPOSED ROLE FOR SOLITHROMYCIN IN THE TREATMENT OF CABP

2.1 Summary

- CABP is a significant cause of morbidity and hospitalization, and is the leading cause of mortality due to infectious disease in the US.
- Macrolide antibiotics have been favored for treatment of CABP in the past for their spectrum of activity including the atypical bacteria, their activity against intracellular pathogens, their ability to achieve high pulmonary concentrations, their anti-inflammatory activity and their limited potential for disrupting bowel flora. However, currently available macrolides can no longer be relied upon for monotherapy coverage of pneumococcus due to increasing resistance rates.
- Because of their broad spectrum of activity, respiratory fluoroquinolones can select for resistant gram-negative bacteria among intestinal microflora, and pose a higher risk of *C. difficile* infection than many other classes of antibiotics. Recently, the FDA has highlighted concerns with serious fluoroquinolone toxicities.
- Ceftriaxone, the most commonly used IV cephalosporin antibiotic for treatment of CABP, does not have an oral formulation, posing challenges for transition from hospital to outpatient care. β-lactam antibiotics do not cover atypical pathogens, requiring use of a second agent (such as a macrolide) for empiric CABP treatment. Ceftriaxone is itself associated with *C. difficile* infection risk, as is the simultaneous or sequential use of two or more antibiotic classes. From an antibiotic stewardship perspective, this approach to CABP treatment does not seem to be optimal.
- Availability of an effective new macrolide antibiotic with both IV and oral formulations could facilitate optimal IV to oral therapy transition, supporting both inpatient and outpatient care of patients with CABP.

2.2 Community Acquired Bacterial Pneumonia

CABP is a serious bacterial infection of the pulmonary parenchyma and is associated with symptoms that include fever or hypothermia, chills, rigors, cough, sputum production, chest pain, and dyspnea. CABP can be life-threatening and is a significant cause of morbidity and mortality. In the US, approximately 5.6 million patients are diagnosed with community acquired pneumonia annually, with more than 1 million episodes in adults ≥ 65 years of age each year (Broulette 2013; Jackson 2004). CABP is the most common cause of death due to infectious diseases, the most common cause of hospitalization due to infection, and the sixth leading cause of death among people ≥ 65 years of age (Freeman 2013; Donowitz 2010; Donowitz 2007; Pfuntner 2013).

The microbial etiology of CABP includes Gram-positive, Gram-negative, and atypical pathogens; while the recognized CABP pathogen profile has varied across studies and time, *S. pneumoniae* remains the most commonly identified agent worldwide. Other CABP pathogens include *S. aureus*, the atypical pathogens *Mycoplasma pneumoniae* and *Legionella pneumophila*, and the Gram-negative pathogens *H. influenzae* and *M. catarrhalis*. It is a practical reality that the microbial etiology of CABP is rarely known at the time of presentation, and more often than not,

is never identified. Therefore, most patients with CABP must receive empiric antimicrobial therapy which, optimally, will have activity against both typical and atypical pathogens.

2.2.1 Current CABP Treatment Landscape

Antibiotics used to treat CABP include penicillins, tetracyclines, cephalosporins, fluoroquinolones, and macrolides. Ceftaroline (a cephalosporin) was the last drug approved for CABP, in 2010, and is available only for IV use. Telithromycin (a macrolide), approved in 2004, was the last oral drug approved for CABP.

Guidelines (Mandell 2007) from the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS), which are currently undergoing revision, recommend a macrolide or doxycycline as first-line therapy for outpatients with CABP if the risk of high-level pneumococcal macrolide resistance (MIC ≥ 16 μg/mL) is < 25%. For outpatients at risk for macrolide-resistant *S. pneumoniae*, a respiratory fluoroquinolone or the combination of a beta-lactam antibiotic plus a macrolide is recommended. Because high-level pneumococcal macrolide resistance now exceeds 25% throughout the US, empiric macrolide monotherapy can no longer be recommended. Similarly, macrolide monotherapy cannot be routinely recommended for hospitalized patients; in this circumstance, for patients not admitted to an intensive care unit, guidelines recommend treatment with a respiratory fluoroquinolone or the combination of a macrolide plus a beta-lactam antibiotic.

2.2.2 Resistance of CABP Pathogens to Macrolides and Other Classes of Antibiotics

The emergence and spread of pathogens resistant to antibiotics is a global public health concern (O'Neill 2015; Marston 2016). The efficacy of macrolide antibiotics including erythromycin, clarithromycin and azithromycin, which have played a central role in the treatment of serious respiratory tract infections for over 50 years, has been compromised by these resistance trends.

Pneumococcal resistance to currently available antibiotics is a major concern. Surveillance studies have documented a dramatic increase in rates of pneumococcal macrolide resistance, mediated principally by acquisition of efflux (*mefA*) or ribosomal methylation (*ermB*) mechanisms (Appelbaum 2002; Farrell 2008). Pneumococcal resistance to older macrolides, such as azithromycin, is approaching 50% in the US and is ≥ 70% across 11 Asian countries (Jones 2013; Kim 2012; Farrell 2016). In the US from 2008 to 2011, an estimated 1.2 million infections/year, the majority with CABP, were attributed to *S. pneumoniae* resistant to clinically relevant drugs, with 7000 attributable deaths per annum (Marston 2016).

Treatment failures due to macrolide resistance in *S. pneumoniae* have been well documented. Lonks described previously healthy patients who deteriorated clinically and died while receiving IV azithromycin with macrolide-resistant *S. pneumoniae* isolated from blood and pleural fluid (Lonks 2004). Additional reports demonstrate that breakthrough bacteremia and treatment failure can occur in patients infected with macrolide-resistant pneumococcus (Kelley 2000; Lonks 2002), or with emergence of resistance during therapy (Musher 2002). A prospective, population-based surveillance study of pneumococcal bacteremia clearly demonstrated that macrolide-resistance was a cause of failure of outpatient pneumonia therapy. In that study, 60 patients with bacteremia

had recently been treated with a macrolide antibiotic; macrolide resistance was identified in 64% of isolates, while in contrast, among recently antibiotic-naïve patients, macrolide resistance was identified in only 12% (Daneman 2006). Next, this team modeled the impact of applying '25% prevalence of high level (≥ 16 μg/mL) pneumococcal macrolide-resistance' as a threshold to abandon macrolide monotherapy, concluding that the relative risks of death, bacteremia, and prolonged hospitalization were all increased by ignoring the significance of lower level macrolide resistance (MICs of 1-8 μg/mL) (Daneman 2008). Zhanel and colleagues reviewed the clinical cure rates across multiple community-acquired respiratory tract infection trials evaluating azithromycin, and determined that success rates were reduced by 10% with azithromycin resistant vs. sensitive isolates, regardless of whether resistance was low-level (MIC 2-8 μg/mL) or high-level (MIC ≥ 16 μg/mL) (Zhanel 2014).

Pneumococcal antimicrobial resistance and treatment failure concerns are not limited to macrolide antibiotics. After introduction of the 7-valent conjugate vaccine (PCV7) in the US, there was a surge of invasive pneumococcal disease with serotype 19A pneumococcus; this non-vaccine serotype is associated with penicillin non-susceptibility (Moore 2008). In the CDC's Active Bacterial Core surveillance system, 10% of isolates from adults with invasive pneumococcal disease in 2004-2005 were penicillin resistant (MIC >2 μg/mL), and half of these isolates were serotype 19A (Moore 2008). In a study of antibiotic treatment failure for lower respiratory tract infections in United Kingdom primary care from 1991 to 2012, increasing treatment failure rates were observed for macrolides and tetracyclines over time (Currie 2014).

Emerging antibiotic resistance among atypical pathogens is also problematic. *Mycoplasma pneumoniae* is intrinsically resistant to β-lactam antibiotics and is most often treated with a macrolide or fluoroquinolone antibiotic. However, macrolide resistance rates among *M. pneumoniae* patient isolates from the US and Canada currently range from 10 to 13.2% (Diaz 2015; Eshaghi 2013; Zheng 2015), with reported macrolide-resistance rates from Asian countries of up to 80-90% (Cao 2010; Okada 2012). *M. pneumoniae* is increasingly recognized as a significant CABP pathogen in Americans of all ages, perhaps most strikingly in a recent report from the CDC of a fatal outbreak occurring in a nursing home in Nebraska in which 55 cases were identified among patients and visitors with 12 hospitalizations and 7 attributable deaths as a result (Hastings 2015).

Antimicrobial resistance is an issue even with intracellular pathogens such as *Legionella pneumophila* that have long been considered treatable if recognized (Cunha 2016). Reports of isolation of ciprofloxacin-resistant *L. pneumophila* and emergence during therapy of fluoroquinolone resistance mutations extend concern to this pathogen as well (Bruin 2014; Shadoud 2015).

2.2.3 Additional Limitations of Current Treatments

With the loss of macrolide monotherapy as a viable treatment option for CABP, clinicians have turned to three general treatment strategies: monotherapy with a respiratory fluoroquinolone or β-lactam antibiotic, or use of the combination of a β-lactam + a macrolide. Each strategy has its own liabilities.

While fluoroquinolones are highly effective agents for treatment of CABP, their overuse engenders significant antibiotic stewardship concerns due to their selection for pan-resistant gram-negative enteric pathogen strains. Use of respiratory fluoroquinolones has been identified as a significant risk factor for development of *C. difficile* infection (Wilcox 2012; Chalmers 2016), as has the use of broad spectrum cephalosporins and the simultaneous or sequential use of multiple classes of antibiotics to treat CABP. Fluoroquinolones have other long-recognized safety risks, including neuropathy, tendinopathy, and QT prolongation.

The alternative to fluoroquinolone therapy for CABP under current ATS/IDSA treatment guidelines is combination antibiotic therapy, usually pairing a β-lactam antibiotic and a macrolide. β-lactam antibiotics lack of activity against important atypical CABP pathogens, creates the need for a second agent to assure empiric coverage for legionella, mycoplasma, and chlamydophila infection. Treatment with multiple antibiotics, however, increases selection pressure for the development of multi-drug resistance and increases the risk of collateral damage in the gut flora of treated patients, increasing *C. difficile* risk. Combination regimens are also clinically burdensome, as patients must deal with the side effects and drug interaction profiles of multiple drugs. β-lactams, like macrolides, face ongoing resistance issues. The activity of oral β-lactam antibiotics commonly used in CABP (e.g. amoxicillin, ampicillin, amoxicillin/clavulanate) has been eroded by increasing β-lactam resistance. Newer β-lactams, such as ceftaroline, help address the resistance issue but are only available in IV formulations.

Use of β-lactam antibiotic monotherapy relies upon physician discernment to identify infection with atypical pathogens, which can be challenging. Two examples include the nursing home mycoplasma outbreak reviewed above and, more recently, a cooling tower associated legionella outbreak in Brooklyn, NY, which resulted in 128 recognized cases of disease and 12 deaths prior to remediation of the point source (CDC 2015). Atypical pathogens may account for up to 10% or more of cases of CABP in reported series; accordingly, the ATS/IDSA guidelines recommend their coverage in selection of empiric antibiotic regimens.

A macrolide such as solithromycin with improved activity, an acceptable safety profile and availability in both IV and oral dosing formulations may offer clinicians an important new therapeutic option for treatment of CABP.

2.3 Solithromycin as a Treatment for CABP

2.3.1 Solithromycin Profile

Solithromycin is a fourth generation macrolide antibiotic, and the first fluoroketolide in the class. Solithromycin has potent in vitro and in vivo activity against community-acquired respiratory pathogens and retains potent activity against macrolide-resistant strains of *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and other species.

Solithromycin was developed for CABP using the new FDA primary endpoint of symptom-based response 72 hours after the first dose of study drug (early clinical response [ECR]), with the traditional endpoint of investigator assessment of clinical success following completion of dosing as an important secondary endpoint. In two global Phase 3 trials in adults with CABP, solithromycin as a 5-day oral regimen or a 7-day IV to oral regimen was demonstrated to be non-

inferior to moxifloxacin. The safety profile of solithromycin was acceptable in the CABP population, including in the approximately 40% percent of the study population that was ≥ 65 years of age.

2.3.2 US Regulatory Status for CABP

Three Investigational New Drug Applications (INDs) are in effect in the Division of Anti-infective Products for solithromycin capsules, solithromycin for injection, and solithromycin for oral suspension. The adult CABP trials were conducted under the capsule and injection INDs. The Phase 2/3 safety and efficacy study in pediatric patients with CABP includes the suspension product as well, and is ongoing under all three INDs.

NDAs for solithromycin capsules and for solithromycin for injection for the treatment of CABP in adults were submitted on April 27 and April 28, 2016, respectively. The suspension product is planned for submission in a supplemental NDA when the pediatric studies in CABP are completed. FDA has designated all three formulations of solithromycin as Qualified Infectious Disease Products (QIDP) for the indication of CABP, in accordance with the 2012 Generating Antibiotics Incentives Now (GAIN) Act. The GAIN Act was enacted to provide incentives for the development of new antibacterial and antifungal agents in response to the increasing incidence of resistant and emerging organisms. The QIDP designations give the NDAs priority review status.

In addition to the ongoing global study in pediatric patients with CABP, solithromycin is being studied for the treatment of uncomplicated gonococcal infection in patients ≥ 15 years of age, and has also been designated as a QIDP for this indication.

3 MICROBIOLOGY

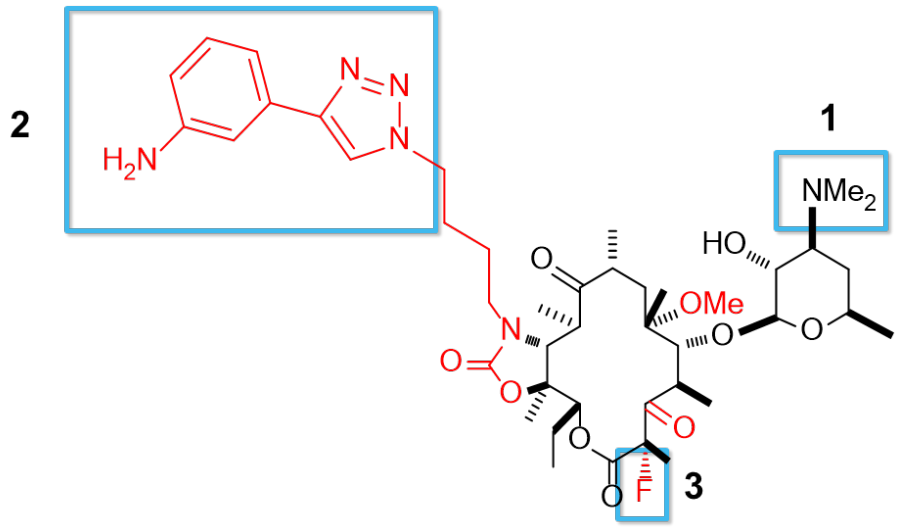
3.1 Summary

- Solithromycin is a fourth generation macrolide antibiotic, and the first member of the fluoroketolide subclass.
- Solithromycin binds to the bacterial ribosome and inhibits protein synthesis. Unlike older macrolides, which only have one binding site, solithromycin has additional interaction sites with the ribosome that contribute to its mostly bactericidal activity, low resistance rates, and potent activity against macrolide-resistant strains.
- Solithromycin has been shown to bind to ribosomes prepared from cells carrying the *erm* methyltransferase gene, consistent with its activity against many *erm* resistant bacteria, and is also active against pneumococci with *mef* and ribosomal protein mutations that confer resistance to the older macrolides.
- Solithromycin has a spectrum of activity that covers the most common CABP pathogens, including both typical and atypical bacteria.
- Solithromycin has potent intracellular activity with concentrations in the macrophage that are more than two-fold higher than azithromycin.

3.2 Mechanism of Action

Solithromycin (Figure 8) is a semi-synthetic derivative of clarithromycin with a novel structure that confers activity against macrolide-resistant *S. pneumoniae* and *M. pneumoniae*, and many macrolide-resistant *S. aureus* isolates. Replacement of the cladinose sugar on clarithromycin by a keto group at Carbon-3 of the macrolide core identifies solithromycin as a ketolide, akin to telithromycin, the first ketolide in the macrolide class. The aryl alkyl side chain of solithromycin differs significantly from that of telithromycin and provides greater metabolic stability. The addition of a fluorine at Carbon-2 changes the chemical behavior of the keto group (preventing enolization and thus stabilizing the ring conformation), and supports characterization of solithromycin as a unique fluoroketolide antibiotic.

Figure 8 Solithromycin Chemical Structure



Like other macrolides, solithromycin selectively disrupts prokaryotic protein synthesis by binding to bacterial 23S ribosomal ribonucleic acid (rRNA). Solithromycin binds to domain V with the N-dimethyl and lies in the peptide tunnel like other macrolides (Figure 8, Box 1) and interacts with domain II via the side chain like other ketolides (Figure 8, Box 2). X-ray crystallographic analysis of solithromycin bound to the 70S *E. coli* ribosome demonstrated a third site of interaction between the fluorine at position C-2 of solithromycin and the peptide tunnel (Figure 8, Box 3). These additional interactions likely account for the low resistance rates and improved activity against macrolide-resistant strains, including against telithromycin-resistant strains.

3.3 Overview of Solithromycin Antibacterial Activity

3.3.1 Activity in vitro

Solithromycin has potent antibiotic activity against Gram-positive and fastidious Gram-negative CABP pathogens. It is active against a broad range of respiratory pathogens, including strains resistant to β-lactams, fluoroquinolones, and other macrolides. The microbiological activity of solithromycin is generally superior to that of other macrolides (azithromycin, clarithromycin, erythromycin, and the ketolide, telithromycin). Solithromycin is 8- to 16-fold more potent than azithromycin against macrolide-susceptible *S. pneumoniae*. In the 2014 global surveillance program, pneumococcal macrolide resistance rates were 37.6% globally and 48.4% in the US. Consistent with previous surveillance studies, solithromycin MICs were ≤ 1 µg/mL against all *S. pneumoniae* (Table 11).

Table 11 Activity of Solithromycin and Azithromycin against Bacterial Pathogens from the Global Surveillance Program for 2014

Organism Group (no. tested)	Solithromycin MIC (µg/mL)			Azithromycin MIC (µg/mL)		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
S. pneumoniae (1713)	0.008	0.12	0.002 - 1	0.12	>32	0.015 - >32
Macrolide-Resistant (644)	0.06	0.25	0.008 - 1	>32	>32	2 - >32
Penicillin-Resistant (246)	0.12	0.25	0.004 - 1	>32	>32	0.03 - >32
Multidrug-Resistant (515)	0.03	0.25	0.004 - 1	>32	>32	0.03 - >32
S. pyogenes (689)	0.008	0.015	0.008 - 0.25	0.12	2	0.03 - >32
S. agalactiae (579)	0.015	0.06	0.004 - 0.5	0.12	>32	0.03 - >32
S. dysgalactiae (225)	0.015	0.015	0.008 - 0.25	0.12	>32	0.06 - >32
S. aureus, MSSA (667)	0.06	0.06	0.03 - >32	1	>32	0.008 - >32
S. aureus, MRSA[a] (357)	0.06	>32	0.008 - >32	>32	>32	0.25 - >32
H. influenzae (1308)	1	2	≤ 0.06 - >8	0.5	1	≤ 0.03 - >4
β-lactamase positive (287)	1	2	0.12 - >8	0.5	1	≤ 0.03 - >4
M. catarrhalis (577)	0.06	0.12	0.002 - 2	0.03	0.06	0.002 - 0.5

MIC=minimum inhibitory concentration; MIC_{50}=MIC required to inhibit growth of 50% of isolates tested; MIC_{90}= MIC required to inhibit growth of 90% of isolates tested; MSSA=methicillin-susceptible *S. aureus*; MRSA=methicillin-resistant *S. aureus*

a. Solithromycin is active against community-associated CA-MRSA, but has reduced activity against hospital-associated MRSA.

Older macrolide antibiotics cannot be relied upon for treatment of staphylococcal pneumonia, given high intrinsic rates of resistance both in MSSA and methicillin-resistant *S. aureus* (MRSA). In global surveillance data from 2014, the MIC_{50} and MIC_{90} for MSSA isolates (n=667) for azithromycin were 1 µg/mL and > 32 µg/mL, respectively, and for solithromycin, 0.06 and 0.06 µg/mL, respectively. MRSA isolates are intrinsically resistant to most β-lactam antibiotics (ceftaroline is an exception), to respiratory fluoroquinolones, and to the older macrolides. In the same global surveillance study, the MIC_{50} and MIC_{90} for MRSA isolates (n=357) for azithromycin were both > 32 µg/mL and for solithromycin, 0.06 µg/mL and > 32 µg/mL, respectively.

Solithromycin also has potent activity against the atypical CABP pathogens *M. pneumoniae*, including macrolide-resistant strains, *L. pneumophila*, and *C. pneumoniae* (Table 12).

Table 12 Activity of Solithromycin against Atypical Bacterial Pathogens

Organism Group (no. tested)	Solithromycin MIC (µg/mL)			Azithromycin MIC (µg/mL)		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
M. pneumoniae (36)	0.000032	0.000125	≤ 0.000000063 - 0.5	0.00025	0.0005	≤ 0.000016 - >32
L. pneumophila (300)	0.008	0.016	≤ 0.004 - 0.06	0.06	0.25	0.008 - 1
C. pneumoniae (10)	0.25	0.25	0.25 - 1	0.125	0.125	0.015 - 0.125

MIC=minimum inhibitory concentration; MIC_{50}=MIC required to inhibit growth of 50% of isolates tested; MIC_{90}= MIC required to inhibit growth of 90% of isolates tested

Solithromycin is bactericidal against most isolates of *H. influenzae, F. tularensis, S. pyogenes,* and *S. pneumoniae*, including macrolide-resistant isolates. As with other macrolides, solithromycin is mostly bacteriostatic against *S. aureus.*

The cellular uptake of solithromycin in macrophages is superior to that of other macrolides and proceeds almost linearly over time, reaching an accumulation level approximately 350-fold the extracellular concentration within 24 hours, and 2-fold that observed with azithromycin. Unlike azithromycin, solithromycin undergoes rapid efflux from the cell.

Solithromycin retains activity intracellularly and is more potent than azithromycin against phagocytosed *S. aureus* and the intracellular pathogens *L. pneumophila,* and *L. monocytogenes.*

3.3.2 Low Potential for Resistance

Macrolide resistance among pneumococci is most often attributable to ribosomal methylation (encoded by the *erm* gene), macrolide efflux mechanisms (encoded by the *mef* gene), and mutations in ribosomal proteins (L4 or L22). Unlike earlier generations of macrolides, solithromycin retains ribosomal binding and antibacterial activity against *erm*-containing pneumococci and is active against bacteria that express *mef* and/or *erm* resistance determinants.

A collection of *S. pneumoniae* (N=221) enriched with strains with defined mechanisms of macrolide resistance was tested for susceptibility to solithromycin and other antibiotics. Solithromycin exhibited potent activity against all pneumococci tested, including all macrolide-resistant, penicillin-resistant, and quinolone-resistant types, with all solithromycin MICs ≤ 1 µg/mL (McGhee 2010, Table 13).

Table 13 Activity of Solithromycin and Azithromycin against Resistant Pneumococcus Strains

Pneumococcal Isolates	N	Solithromycin MIC (µg/mL)		Azithromycin MIC (µg/mL)	
		Range	MIC_{90}	Range	MIC_{90}
Total	221	0.002 - 1	0.25	0.06 - >64	>64
Penicillin S	53	0.002 - 0.25	0.125	0.06 - >64	>64
Penicillin I	63	0.002 - 0.25	0.25	0.06 - >64	>64
Penicillin R	105	0.004 - 1	0.25	0.06 - >64	>64
Macrolide S	50	0.002 - 0.015	0.015	0.06 - 0.25	0.125
Macrolide R (*ermB*)	54	0.004 - 1	0.5	>64 - >64	>64
Macrolide R (*mefA*)	51	0.008 - 0.25	0.125	1 - >64	8
Macrolide R (*ermA*)	4	0.008 - 0.015	-	2 - 8	-
Macrolide R (*ermB* and *mefA*)	31	0.015 - 1	0.25	2 - >64	>64
Macrolide R (L4 mutations)	27	0.03 - 0.125	0.125	2 - >64	>64
Macrolide R (23S rRNA mutations)	4	0.002 - 0.03	-	32 - >64	-
Quinolone S	195	0.002 - 1	0.25	0.06 - >64	>64
Quinolone R	27	0.004 - 0.25	0.06	0.06 - >64	>64

MIC=minimum inhibitory concentration; MIC_{90}= MIC required to inhibit growth of 90% of isolates tested (not calculated if <10 isolates); rRNA=ribosomal ribonucleic acid

Solithromycin had a low rate of spontaneous mutations (mostly $<10^{-9}$ to $<10^{-10}$) in single-step mutational analyses and a low occurrence of decreased susceptibility in multi-step resistance analyses of *S. pneumoniae*, *S. pyogenes*, and *S. aureus*. In a 50-day serial passage study of *S. pneumoniae* strains that carried known macrolide resistance genes, only 1 of 8 had an increase in MIC that exceeded 1 µg/mL, and that occurred only after 18 passages, reaching an MIC of 32 µg/mL. This parental strain was *ermB* and *mefA* positive with a baseline MIC of 1 µg/mL.

3.3.3 Efficacy in Animal Models

Solithromycin was effective in protecting mice from lethal systemic infections caused by *S. pneumoniae*, *S. pyogenes*, and *S. aureus*; and in effectively reducing viable bacterial counts in abscesses caused by *S. pneumoniae* and *S. pyogenes*, in neutropenic thigh infections caused by *S. pneumoniae* and *S. aureus*, and in pulmonary infections caused by *S. pneumoniae*. Solithromycin was also effective in treating *H. influenzae* pneumonia in neutropenic rats.

Solithromycin demonstrated efficacy against the potential bioterror pathogens, *B. anthracis* and *F. tularensis*, in nonhuman primate lethal aerosol challenge studies.

4 PHARMACOLOGY

4.1 Summary

- The overall metabolic profiles in nonclinical species were qualitatively similar to humans with adequate coverage for the main circulating human metabolites.
- Consistent with nonclinical toxicity studies with other macrolides, the liver was a target organ in repeat dose oral toxicology studies.
- Solithromycin did not impair fertility nor have an effect on embryo-fetal development in reproductive toxicity studies.
- Solithromycin was not genotoxic in a standard battery of genotoxicity tests.
- Solithromycin is well absorbed (67% oral bioavailability at a 400 mg dose), and bioavailability is not influenced by food.
- Solithromycin is eliminated primarily through hepatic metabolism with excretion in the feces.
- No dose adjustment is needed for mild to severe hepatic impairment or in mild to moderate renal impairment. A dose adjustment is warranted for severe renal impairment due to increased exposure in these patients.
- Clinically relevant drug-drug interactions that would affect solithromycin concentrations primarily include concomitant drugs that are inducers of CYP3A4/P-gp.
- Clinically relevant drug-drug interactions where solithromycin would affect concomitant drug concentrations primarily include substrates of CYP3A4.
- With 5 days of oral dosing, solithromycin achieves alveolar macrophage levels and ELF levels that are 200 times and 10 times the concurrent plasma levels, respectively.
- Total-drug ELF and free-drug plasma AUC_{0-24}:MIC ratios were determined to be the nonclinical PK/PD indices best associated with efficacy.

4.2 Nonclinical Toxicology

The primary target organ identified in oral repeat-dose studies up to 13 weeks in rats and monkeys is the liver, the target organ for all macrolides. Hepatic effects were most apparent in the 28-day oral repeat-dose rat study, with almost all findings of note at doses ≥ 100 mg/kg/day (changes in liver-associated clinical chemistry parameters, increased liver weights, and microscopic changes of biliary inflammation [≥ 250 mg/kg/day] and centrilobular hepatocellular degeneration/necrosis [500 mg/kg/day only]). These changes were generally reversible after a 28-day recovery period.

Clarithromycin and telithromycin were also evaluated in the 28-day study. Results for all three drugs were similar at doses ≤ 250 mg/kg/day, except that liver microscopic findings were noted in the high dose telithromycin females at recovery. In comparison, published summaries of other 28-day studies in rats noted liver necrosis and non-reversal of liver weights with telithromycin at 300 mg/kg/day and non-reversal of AST/ALT with clarithromycin at 200 mg/kg/day.

In the 13-week repeat-dose study in rats, no liver related adverse effects were seen at doses up to 125 mg/kg/day. Kupffer cell hyperplasia, a finding consistent with hepatic phospholipidosis, was observed and considered toxicologically insignificant. Published summaries of other 13-week studies in rats noted increased AST/ALT levels and hepatocellular necrosis with telithromycin at ≥ 150 mg/kg/day, and focal necrosis and increased AST/ALT that did not reverse with clarithromycin at ≥ 40 mg/kg/day.

Monkeys were less sensitive to the hepatic effects of solithromycin than rats. In monkeys given oral solithromycin for 14 days, dose-related increases in AST and ALT were noted at doses ≥ 100 mg/kg/day, with values approaching baseline levels following the 14-day recovery period. In the 13-week oral repeat-dose monkey study, elevated serum liver enzyme activities (ALT, AST and GGT) were noted at 125 mg/kg/day, with hepatocyte vacuolation and Kupffer cell hyperplasia attributed to phospholipidosis observed microscopically. These changes were reversible during the recovery period.

Relative to oral administration, fewer hepatic findings were observed after IV administration in dogs and monkeys in studies up to 28 days in duration. In the 28-day IV study in dogs, dosing up to 15 mg/kg/day resulted in minor changes in clinical chemistry parameters. In the 28-day IV study in monkeys, no liver related findings were reported at doses up to 25 mg/kg/day. Similar to the oral studies, ALT elevations with no evidence of hepatocellular necrosis were observed.

Phospholipidosis is also an established effect of the macrolide class. Following repeat oral dosing of solithromycin, findings consistent with phospholipidosis were found in the livers of rats and monkeys, as well as in the lungs, lymphoid tissues, and gastrointestinal tract. Phospholipidosis was found to a lesser extent in IV repeat-dose studies in rats and dogs up to 28 days in duration. Like azithromycin, solithromycin induces phospholipidosis through inhibition of lysosomal phospholipase A1, with drug accumulation in lysosomes. Unlike gentamicin, solithromycin does not induce phospholipidosis associated apoptosis. Unlike azithromycin, the drug exits the cell rapidly and phospholipidosis is short-lived once drug exposure is removed.

Developmental toxicities were not observed with oral solithromycin in reproductive toxicity studies. Solithromycin had no effect on male or female fertility in the rat at doses up to 220 mg/kg/day, the highest dose tested. Embryo-fetal toxicity studies in rats and rabbits showed no evidence of any teratogenic effect at doses up to 220 mg/kg/day in the rat and 200 mg/kg/day in the rabbit. In a prenatal and postnatal toxicity study in rats, decreased pup weight was noted during the preweaning period at a maternal dose of 200 mg/kg/day; however, this was likely secondary to reduced maternal food consumption at this dose. Solithromycin was secreted in high concentrations in milk.

Solithromycin did not show evidence of mutagenic or clastogenic effects in any of 4 genetic toxicity studies: bacterial reverse mutation assay, TK +/- mouse lymphoma forward mutation assay, and chromosomal aberration assay in vitro; and rat bone marrow micronucleus study in vivo.

4.3 Nonclinical Pharmacokinetic/Pharmacodynamic Assessments

Nonclinical PK/PD targets were determined based on data from a murine neutropenic lung infection model with *S. pneumoniae* in which the relationship between free-drug plasma PK/PD indices and change in $\log_{10}$ CFU was assessed. While attempts were made to evaluate *H. influenzae* in neutropenic murine lung infection models, persistent infection was not achieved to use for PK/PD evaluation.

Neutropenic mice were infected with *S. pneumoniae* isolates by intranasal instillation. Treatment was initiated 2 hours post-infection, and mice were administered various dosage regimens of solithromycin by oral gavage over a 24-hour period. Untreated mice were used as controls. The infected mice were sacrificed immediately prior to and at 24 hours following administration of the first dose of solithromycin, and the bacterial burden in the lung tissue was determined.

Using a PK model based on plasma and ELF solithromycin concentrations in uninfected mice, free-drug plasma concentration vs. time profiles for solithromycin dosing regimens administered to the infected mice were simulated, and the ratio of the free-drug plasma area under the concentration-time profile over 24 hours to the MIC (AUC_{0-24}:MIC ratio), the ratio of the peak concentration over 24 hours to the MIC (C_{max}:MIC ratio) and percent of the dosing interval that free-drug plasma concentrations remained above the MIC (% T > MIC) were estimated. Evaluation of the relationships between change in $\log_{10}$ CFU and these PK/PD indices demonstrated free-drug plasma AUC_{0-24}:MIC ratio ($r^2 = 0.848$) to be the PK/PD index best associated with efficacy. The ratio of the total-drug ELF to free-drug plasma AUC_{0-24} was 2.7, which is a lower penetration into ELF than observed in humans. Similar to free-drug plasma, total-drug ELF AUC_{0-24}:MIC ratio was highly predictive of efficacy ($r^2 = 0.847$).

Free-drug plasma and total-drug ELF AUC_{0-24}:MIC ratio targets associated with net bacterial stasis and a 1- and 2-$\log_{10}$ CFU reduction from baseline were determined. For the pooled data, free-drug plasma AUC_{0-24}:MIC ratios associated with net bacterial stasis and a 1- and 2-$\log_{10}$ CFU reduction from baseline were 1.65, 6.31, and 12.8, respectively. Corresponding total-drug ELF AUC_{0-24}:MIC ratios associated with net bacterial stasis and a 1- and 2-$\log_{10}$ CFU reduction from baseline were 1.26, 15.1, and 59.8.

4.4 Key Clinical Pharmacology Characteristics of Solithromycin

4.4.1 Pharmacokinetics

4.4.1.1 Absorption

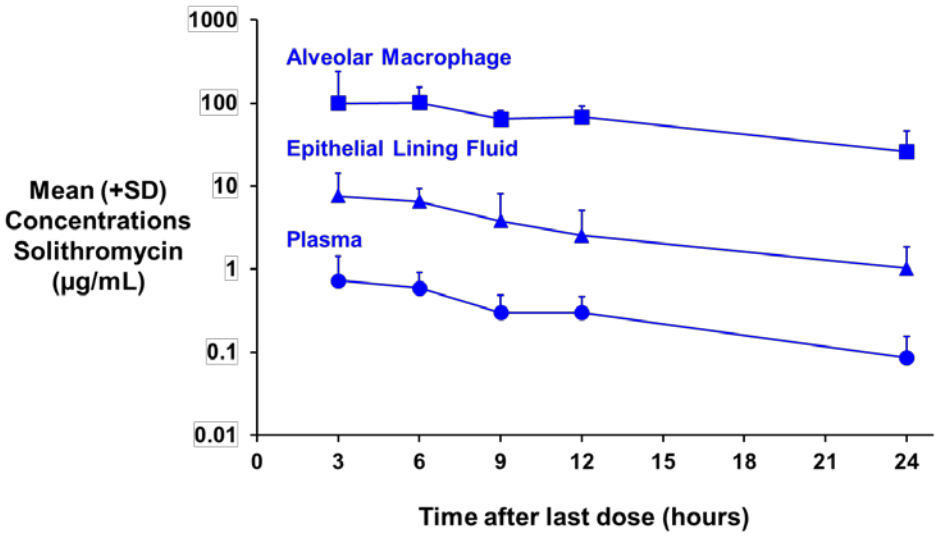
The bioavailability of solithromycin capsules is approximately 67% at the 400 mg dose and is not influenced by food. Solithromycin is absorbed relatively slowly following administration of multiple oral doses of 400 mg to healthy adult subjects, with a C_{max} of approximately 1 µg/mL and time to maximum plasma concentration (T_{max}) of approximately 3.5 hours. The PK of solithromycin is greater than dose proportional at doses less than 400 mg and approximately dose proportional at higher doses. This is likely due to auto-inhibition of CYP3A4 by solithromycin that affects first pass (liver and gastrointestinal tract) metabolism. IV solithromycin also exhibits

nonlinear PK after infusion with greater than dose-proportional increases in AUC; C_{max} values depend primarily on the duration of infusion.

4.4.1.2 Distribution

Protein binding of solithromycin in plasma is approximately 81%, similar to other macrolides. The steady-state volume of distribution in patients with CABP was approximately 400 L, suggesting that solithromycin distributes widely throughout the body. Once-daily oral dosing of solithromycin at 400 mg for 5 days in healthy human subjects produced steady-state concentrations that were significantly higher in ELF and alveolar macrophages than in simultaneous plasma concentrations throughout the 24-hour period after the last dose (Figure 9).

Figure 9 Epithelial Lining Fluid, Alveolar Macrophage and Plasma Concentrations of Solithromycin after 5 Days of 400 mg Oral Dosing



In non-human species, solithromycin is widely distributed to most tissues after a single dose, with similar patterns of tissue distribution in animals dosed orally or IV. Concentrations are highest in the liver, spleen, and gastrointestinal tract, with significant concentrations also present in the lung. Solithromycin does not penetrate the blood-brain barrier.

4.4.1.3 Metabolism

Solithromycin is the major component in plasma (60 to 94% of radioactivity over 24 hours after a single dose in a mass balance study). Two minor metabolites, a primary alcohol oxidation product and *N*-acetylated solithromycin, each circulate in the plasma at levels <5% of the parent.

Approximately 19% of the dose is metabolized via first pass (liver and gastrointestinal tract). Overall, metabolic clearance represents as much as 76% of the dose.

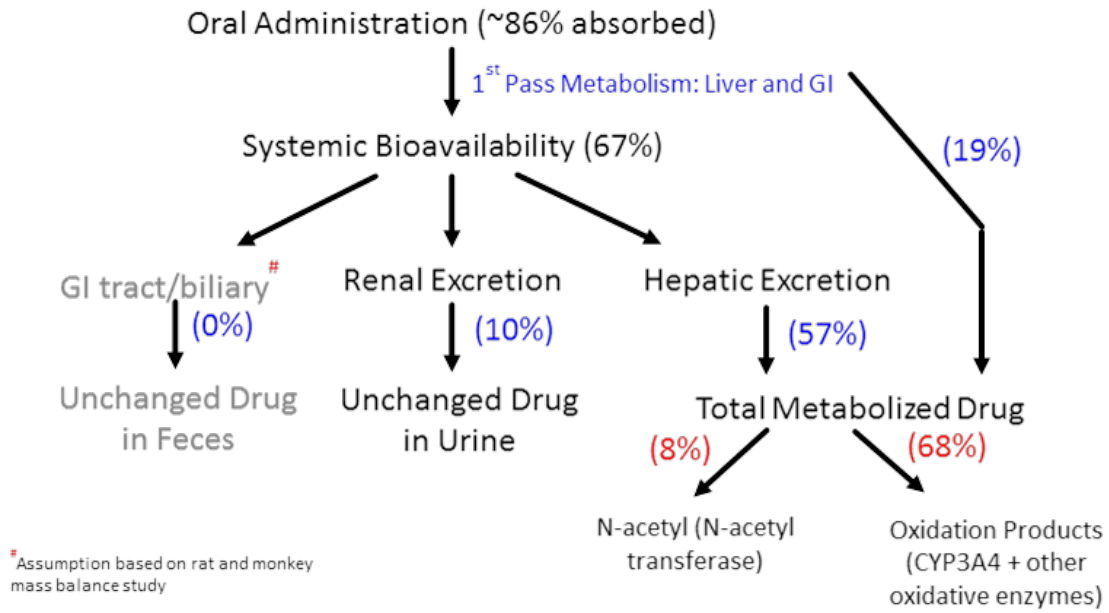
Metabolic pathways occur primarily at the side chain and include alkyl side chain oxidation, *N*-oxidation, *N*-acetylation, *N*-formylation, and *N*-demethylation. The most prominent pathway represented by the largest amount of recovered radioactivity was through oxidative loss of the

triazolyl-phenylamino moiety, with subsequent oxidation of the resulting primary alcohol to a carboxylic acid. Formation of the alcohol appeared minor in all matrices and quantifiable amounts of the carboxylic acid were found only in the feces. In vitro experiments indicate that solithromycin is primarily metabolized by CYP3A4 with minimal contribution from other CYPs, and the side chain is metabolized by *N*-acetyl transferase.

4.4.1.4 Excretion

Solithromycin is predominantly metabolized and subsequently excreted via the feces (approximately 74% of administered dose; Figure 10). Based on studies in rat and monkey that suggest solithromycin is not eliminated unchanged in the feces, the 14% of solithromycin measured in human feces would be unabsorbed drug, giving an estimate of 86% for dose absorption. Urinary excretion is a minor contributor to elimination, with approximately 10% excreted as unchanged solithromycin.

Figure 10 Summary of Solithromycin Elimination Pathways



In IV-dosed rats and monkeys no solithromycin was recovered in feces over 24 hours.
In orally dosed rats unchanged solithromycin accounted for <2% of the radioactive dose excreted in bile.
In orally dosed monkeys unchanged solithromycin accounted for <1% of the radioactive dose excreted in bile.

4.4.1.5 Effect of Hepatic and Renal Impairment on PK

Plasma PK of oral solithromycin in subjects with mild and moderate hepatic impairment was similar to PK in control subjects with normal liver function. Solithromycin plasma exposure was reduced by 41% in subjects with severe hepatic impairment (Child-Pugh class C), which may be related to greater body mass and increased peripheral distribution secondary to hypoalbuminemia and fluid overload. No dose adjustment is needed for hepatic impairment.

No dose adjustment is needed for mild or moderate renal impairment. Based on an approximate 2-fold increase in solithromycin exposure in subjects with CL_{CR} < 30 mL/minute in a PK study, dose adjustment is recommended in patients with severe renal impairment (Section 7.7.4).

4.4.1.6 Population PK in Patients with CABP

Using pooled PK data collected from selected Phase 1 studies and both Phase 3 studies, a population PK analysis was carried out. Solithromycin PK parameter estimates in patients from Study 300 and 301 derived from these analyses are summarized in Table 14 and Table 15, respectively.

Table 14 Study 300: Summary Statistics for Model-derived Solithromycin Plasma Exposure and PK Parameters on Days 1 and 4

Parameter	Geometric Mean (CV%)	
	Solithromycin Day 1 800 mg dose (n = 386)	Solithromycin Day 4 400 mg QD (n = 368)[a]
AUC_{0-24} (µg•h/mL)	18.9 (71.8)	12.6 (80.5)
C_{max} (µg/mL)	1.54 (70.2)	1.05 (73.6)
T_{max} (h) [b]	3.5 (1 - 14.5)	3.5 (1.17 - 7.5)
CLav (L/h) [c]	41.8 (76.6)	31.7 (80)
V_{ss} (L) [c]	388 (63.7)	387 (64.2)
$T_{1/2}$ (h) [c]	9.58 (28.4)	10.5 (32.9)

AUC_{0-24} =area under the concentration time curve from hours 0 to 24; C_{max}=maximum plasma concentration; T_{max}=time to C_{max}; $T_{1/2}$ =half-life; CLav/F=apparent oral clearance; Vss/F=apparent oral steady-state volume of distribution; CV=coefficient of variation.

a. 18 patients did not receive a solithromycin dose on Day 4, & these 18 patients were excluded for solithromycin Day 4 exposure and secondary PK parameters calculation.
b. T_{max} is summarized using median (min. – max.).
c. CLav and $T_{1/2}$ derived using non-compartmental methods applied to the fitted solithromycin concentration-time profile for each patient. V_{ss} is derived as the sum of the 3 volumes of distribution (V_c + V_{p1} + V_{p2}). CLav and V_{ss} are conditioned on F for the values reported while on oral solithromycin.

Table 15 Study 301: Summary Statistics for Model-derived Solithromycin Plasma Exposure and PK Parameters on Day 1 and Day of First Oral Dose

Parameter	Geometric Mean (CV%)	
	Solithromycin 400 mg First IV dose (n=405)	Solithromycin 800 mg First oral dose (n=280)[a]
Absolute bioavailability[b]	-	0.663 (32.7)
AUC_{0-24} (µg•h/mL)	21.5 (43.8)	26.9 (62.4)
C_{max} (µg/mL)	3.08 (35.1)	2.20 (54.0)
T_{max} (h)[c]	1 (1 - 2)	3.58 (1.17 - 8.25)
CLav (L/h)[d]	22.8 (47.8)	30.1 (61.7)
V_{ss} (L)[d]	215 (24.1)	349 (48.2)
$T_{1/2}$ (h)[d]	10.1 (27.0)	10.2 (32.2)

AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours after a dose; C_{max}=maximum plasma concentration; PK=pharmacokinetic; $T_{1/2}$=terminal elimination half-life; V_{ss}=steady state volume of distribution; CLav=apparent clearance.

a. Parameters derived from the first day of oral dosing (Days 2 - 7) in subjects who received at least 1 oral dose.
b. Absolute bioavailability derived from the population PK model and summarized as arithmetic mean (CV%) as the individual estimates do not conform to a log-normal distribution.
c. T_{max} is summarized using median (min. - max.).
d. CLav and $T_{1/2}$ derived using non-compartmental methods applied to the fitted solithromycin concentration-time profile for each patient. V_{ss} is derived from the population PK model as the sum of the 3 volumes of distribution ($V_c + V_{p1} + V_{p2}$). CLav and V_{ss} are conditioned on F for the values reported while on oral solithromycin.

Given that solithromycin inhibits its own metabolism, differences in solithromycin plasma PK are seen when multiple doses are given. In Study 300, the average solithromycin clearance dropped with repeated dosing (from geometric mean of 41.8 to 31.7 L/h), and the AUC_{0-24} was higher than would be predicted given that the dose on Day 4 is one-half of the dose on Day 1.

The effect of multiple dosing was less apparent when CABP patients were administered solithromycin IV at the start of therapy and then switched to oral drug due to the complexity of comparing patients who switched to oral at different times after IV dosing or never switched. There is an increase in the AUC_{0-24} after administration of the 800 mg oral dose on the day of the IV to oral switch.

4.4.2 Drug-Drug Interactions

As solithromycin can potentially be concomitantly administered with drugs from a wide variety of therapeutic indications, in vitro studies were performed to understand the mechanisms associated with potential drug-drug interactions.

Solithromycin inhibited the OATP1B3-mediated substrate transport with a concentration required for 50% inhibition (IC_{50}) value of 23 µM, which is not anticipated to be relevant at therapeutic concentrations. Solithromycin did not significantly inhibit other efflux or uptake transporters including BSEP, BCRP, OATP1B1, OCT1, OCT2, OAT1, OAT3, NTCP and MRP4.

Table 16 Summary of Results of Human Biomaterial Studies Relevant to Drug Interactions

Enzyme/Transporter	Induction	Inhibition IC_{50} (μM)	Substrate
CYP1A2	No induction	>39	No
CYP2A6	ND	ND	No
CYP2B6	No induction	ND	No
CYP2C8	ND	>39	No
CYP2C9	No induction	>39	No
CYP2C19	ND	>39	No
CYP2D6	ND	>39	No
CYP2E1	ND	ND	No
CYP3A4	No induction	MDI K_i = 0.045 μM K_{inact} = 0.022 min-1	Yes
P-gp	ND	1.6	Yes
OATP1B1	ND	>23	No
OATP1B3	ND	19	No
BCRP	ND	>30	ND
BSEP	ND	>30	ND
OCT1	ND	>30	No
OCT2	ND	>30	No
OAT1	ND	>30	ND
OAT3	ND	>30	ND

BCRP=breast cancer resistance protein; BSEP=human bile salt export pump; CYP=cytochrome P450; IC_{50}=concentration giving 50% of the maximum inhibition; K_i=concentration required for half-maximal inactivation; K_{inact}=rate constant of maximal inactivation at saturation; MDI=metabolism-dependent inhibition; ND=not determined; OAT=organic anion transporter; OATP=organic anion transporter polypeptide; OCT=organic cation transporter; P-gp=P-glycoprotein

The in vitro studies identified effects on CYP3A4 and P-gp as clinically relevant mechanisms that could result in clinical drug-drug interactions with solithromycin, both as an object and a precipitant. Accordingly, four clinical drug interaction studies were conducted.

Solithromycin is a substrate of CYP3A4 and P-gp. Concomitant administration with rifampin, a potent CYP3A/P-gp inducer, decreased both the C_{max} and AUC of solithromycin by > 97%.

Concomitant administration with ketoconazole, a potent CYP3A inhibitor, increased the single-dose C_{max} and AUC of solithromycin by 1.6- and 2.6-fold, respectively. However, because solithromycin auto-inhibits CYP3A4, the effect of concomitantly administered CYP3A inhibitors on solithromycin PK is expected to be minimal upon repeat dosing.

Solithromycin is a metabolism-dependent inhibitor of CYP3A4, like most other macrolides. Concomitant administration with midazolam, a CYP3A substrate, resulted in a 2.5- and 9-fold increase in geometric mean midazolam C_{max} and AUC, respectively, over midazolam alone. Consequently, administration of solithromycin and another drug that is metabolized primarily by

CYP3A may result in increased plasma concentrations of that drug, which could increase or prolong both its therapeutic and adverse effects.

Solithromycin is both a substrate and an inhibitor of P-gp. The effect of P-gp on the absorption of solithromycin may have an impact at subtherapeutic doses; however, at therapeutic doses, inhibition of P-gp by solithromycin would negate any P-gp substrate effects.

Concomitant administration of solithromycin with digoxin, a sensitive P-gp substrate, increased plasma digoxin $AUC_{0\text{-}tau}$ and C_{max} by 38% and 46%, respectively, based on geometric mean ratios, relative to digoxin alone. While this effect was modest, concomitant administration of solithromycin and a drug that is transported by P-gp may result in increased plasma concentrations of that drug, which could increase or prolong both therapeutic and adverse effects of the concomitant drug.

Based on these data, solithromycin should not be administered to patients who are receiving strong or moderate CYP3A/P-gp inducers because of the risk of subtherapeutic exposure and loss of efficacy. Concomitant administration of solithromycin with sensitive CYP3A and/or P-gp substrates that have potential adverse effects due to increased plasma concentrations (e.g. digoxin) may require monitoring and/or dose adjustment of the concomitantly administered drug. Concomitant administration of solithromycin and CYP3A substrates that are considered QT prolonging should be avoided.

Because solithromycin inhibits CYP3A4 and P-gp, drugs that are CYP3A4 and P-gp inhibitors are not expected to significantly increase solithromycin concentration on repeat dose. Drug-drug interactions through other CYP mechanisms or OATP inhibition (e.g. non-CYP3A4 metabolized statins such as rosuvastatin or pravastatin) are not anticipated.

4.4.3 Pharmacodynamics

In a thorough QT study, solithromycin administered as a supratherapeutic IV dose of 800 mg infused over 40 minutes had no significant impact on the QT interval but modestly increased heart rate. Cardiovascular safety is discussed in Section 7.7.2.

In an intestinal microflora study, solithromycin was detectable by bioassay in feces out to the last measurement 2 weeks after the last of 7 daily oral doses. Gram positive aerobes and anaerobes, as well as some Gram-negative enteric bacteria, were decreased. *Bacteroides* spp., the major protective species in the intestine, were minimally affected. All species recovered after completion of dosing, and no *C. difficile* strains or toxins were identified.

4.4.4 Pharmacokinetic/Pharmacodynamic Analyses

Using the population PK model based on the analysis described in Section 4.4.1, enriched using the population mean parameters driving ELF penetration, and Monte Carlo simulation, PK/PD target attainment analyses were carried out to evaluate the proposed solithromycin dosing regimens. Percent probabilities of PK/PD target attainment were assessed based on the average 24-hour total-drug ELF and free-drug plasma AUC from 0 to 48 hours for oral, IV and IV to oral regimens. In addition, the total-drug ELF and free-drug plasma AUC over the 24-hour period after the first oral dose were assessed for each potential switch day in the IV to oral regimen. PK/PD

targets for efficacy that were evaluated included total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with net bacterial stasis and 1- and 2-$\log_{10}$ CFU reductions from baseline for *S. pneumoniae* derived from a murine neutropenic lung infection model (Section 4.3). Emphasis was placed on PK/PD target attainment results for the total-drug ELF AUC:MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline given the importance of assessing effect site exposure.

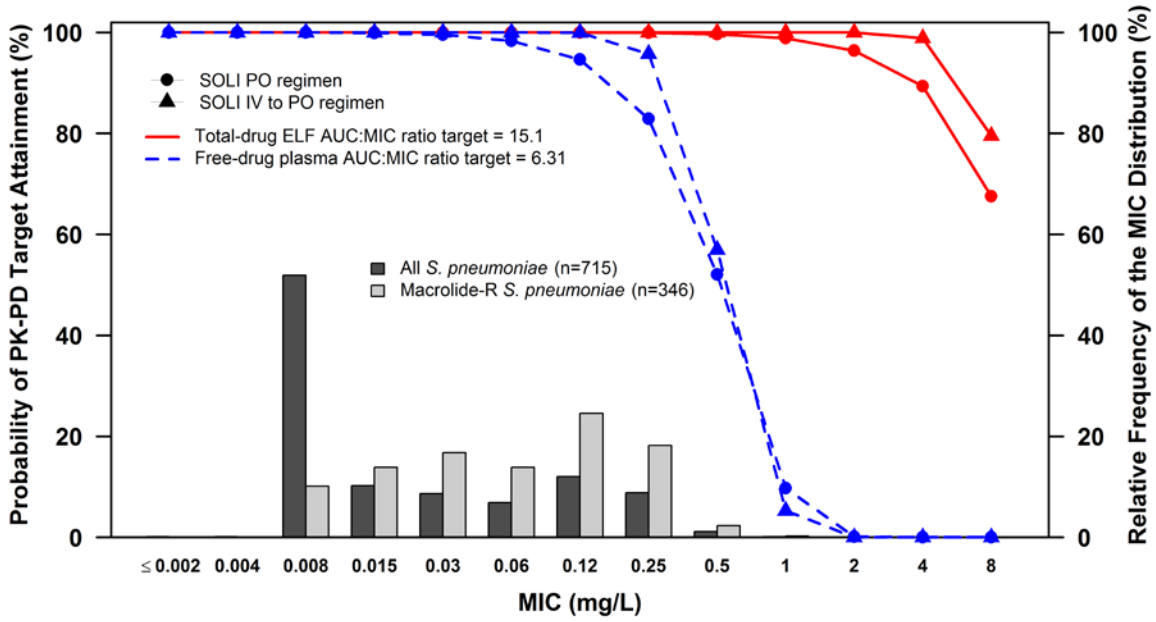
Percent probabilities of PK/PD target attainment over the first 48 hours by MIC value for solithromycin dosing regimens based on the total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* overlaid upon the MIC distributions for *S. pneumoniae* isolates from the US are shown in Figure 11. Percent probabilities of PK/PD target attainment for the total-drug ELF AUC:MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline ranged from 98.9 to 100% at an MIC value of 1 µg/mL. At an MIC value of 4 µg/mL, percent probabilities of PK/PD target attainment ranged from 89.3 to 98.9%. While emphasis was placed on the evaluation of PK/PD target attainment early in treatment, percent probabilities of PK/PD target attainment were also assessed on the day of the switch for the IV to oral dosing regimens, for which the first oral dose was an 800 mg oral loading dose. Percent probabilities of PK/PD target attainment on the day of the switch for the total-drug ELF AUC:MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline ranged from 99.8 to 99.9% for dosing regimens for which the switch occurred on Days 2, 3, 4, 5, 6 or 7. At an MIC value of 4 µg/mL, percent probabilities of PK/PD target attainment on the day of the switch ranged from 95.9 to 97.5%.

However, the utility of the 800 mg oral loading dose was best observed using results of the PK/PD target attainment analyses based on the assessment of the free-drug plasma AUC:MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline at the upper margins of the solithromycin MIC distribution for *S. pneumoniae* (MIC values of 0.25 and 0.5 µg/mL). Percent probabilities of PK/PD target attainment on the day of the switch ranged from 92.7 to 95.4% and 73.4 to 82.8% at MIC values of 0.25 and 0.5 µg/mL, respectively. In contrast, for dosing regimens for which patients were switched to 400 mg oral, percent probabilities of PK/PD target attainment ranged from 78.1 to 86.2% and 37.6 to 56.7%, respectively, at these two MIC values.

The selected dosing regimens account for PK variability in patients and variability in the susceptibility in *S. pneumoniae*. Results of the PK/PD target attainment analyses suggest that solithromycin would be effective for treatment of pneumococcal pneumonia due to isolates with MIC values up to 4 µg/mL. While isolates with an MIC value of 4 µg/mL have not been observed in surveillance studies, at the MIC_{90} for *S. pneumoniae* in the 2014 surveillance (0.12 µg/mL), target attainment was $\geq$ 95% for free-drug plasma and 100% for ELF AUC:MIC ratio targets across the oral and IV to oral dosing regimens (Figure 11).

The robust exposure margins are expected to limit the development of resistant organisms related to ineffective treatment. These results support the selected dosing regimens for the treatment of pneumococcal CABP with or without bacteremia.

Figure 11 Percent Probabilities of PK/PD Target Attainment for Solithromycin Dosing Regimens Based on Targets Associated with a 1-log$_{10}$ CFU Reduction from Baseline for *S. pneumoniae*



PK=pharmacokinetic; PD=pharmacodynamic; IV=intravenous; PO=oral; ELF=epithelial lining fluid; AUC:MIC=area under the plasma concentration time curve; MIC=minimum inhibitory concentration; R=resistant
MIC distribution is of *S. pneumoniae* isolates collected from the US during a 2014 surveillance study.

5 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

5.1 Summary

- The solithromycin clinical development program for CABP included a Phase 2 Study 200 (oral) and two pivotal Phase 3 trials, Study 300 (oral) and Study 301 (IV to oral).
- Study 200 demonstrated comparable efficacy outcomes for oral solithromycin and oral levofloxacin in the treatment of CABP in 132 patients, enabling progression to Phase 3 studies.
- Study 300 was a randomized, double-blind, non-inferiority study of oral solithromycin in a 5-day regimen compared with oral moxifloxacin in a 7-day regimen in the treatment of CABP. The study had co-primary efficacy endpoints of ECR in the ITT population and ECR in the pooled mITT population from Studies 300 and 301.
- Study 301 was a randomized, double-blind, non-inferiority study of IV to oral solithromycin in a 7-day regimen compared with IV to oral moxifloxacin in a 7-day regimen in the treatment of CABP, with a primary efficacy endpoint of ECR in the ITT population.
- The Phase 3 CABP studies were the first to be conducted using ECR as the prespecified primary outcome.
- The Phase 3 study designs were consistent with FDA guidance on CABP studies, including primary endpoint selection and non-inferiority margins.

5.2 Clinical Studies that Support the Solithromycin CABP Indication in Adults

An overview of the Phase 2 oral CABP study and the Phase 3 oral and IV to oral CABP studies that support this indication in adults is shown in Table 17. Supporting Phase 1 biopharmaceutical and clinical pharmacology studies are shown in Appendix 11.2. Results from the Phase 3 studies are presented in Section 6, and the Phase 2 study results are presented below in Section 5.2.1.

Table 17 Overview of Solithromycin Clinical Studies in Adult Patients with CABP

Study	Design	Solithromycin Regimen/ Number of Patients	Active Control Regimen/ Number of Patients
Phase 3 – Oral			
300	Randomized, double-blind, multicenter, non-inferiority, efficacy and safety study in adult patients with CABP	Solithromycin: Day 1: 800 mg PO QD Days 2–5: 400 mg PO QD Days 6–7: Placebo N=426	Moxifloxacin: Days 1–7: 400 mg PO QD N=434
Phase 3 – Intravenous to Oral			
301	Randomized, double-blind, multicenter, non-inferiority, efficacy and safety study in adult patients with CABP	Solithromycin: Days 1–7: 400 mg IV QD with an optional transition to oral (800 mg first oral day followed by 400 mg PO QD for remainder of treatment) N=434	Moxifloxacin: Days 1–7: 400 mg IV QD with optional transition to oral (400 mg PO QD for remainder of treatment) N=429
Phase 2 – Oral			
200	Randomized, double-blind, multicenter, efficacy and safety study in adult patients with CABP	Solithromycin: Day 1: 800 mg PO Days 2–5: 400 mg PO QD N=65	Levofloxacin: Days 1–5: 750 mg PO QD N=67

Note: Patient numbers represent the ITT population in each study

5.2.1 Efficacy Findings in Study 200

Study 200 was a Phase 2, randomized, double-blind, multicenter study that compared the safety and efficacy of oral solithromycin (800 mg on Day 1 followed by 400 mg QD on Days 2 through 5) with oral levofloxacin (750 mg QD on Days 1 through 5) in 132 patients with CABP. The primary objective was to evaluate the investigator assessment of clinical success rates of oral solithromycin compared with oral levofloxacin in adult patients with CABP. Co-primary efficacy outcomes were investigator assessment of clinical success at TOC (4 to 11 days after the last dose of study drug) in the ITT and CE populations. Clinical success at TOC was defined as continued improvement or complete resolution of baseline signs and symptoms and, if available, an improved/stable chest radiograph after EOT. This endpoint was similar to the Phase 3 secondary efficacy outcome of investigator assessment of clinical response.

Patients were randomized in a 1:1 ratio to solithromycin (n=65) or levofloxacin (n=67). Demographic and baseline characteristics were similar between groups.

Oral solithromycin demonstrated comparable efficacy to oral levofloxacin for the primary and key secondary analyses in the study (Table 18). Success rates for the co-primary outcomes in the ITT and CE populations were high and generally comparable between treatment groups. A symptom-based response at Day 3, using criteria similar to those subsequently adopted in the 2009 FDA draft CABP Guidance, was observed for 47/65 (72.3%) of solithromycin patients and 48/67 (71.6%) of levofloxacin patients.

Table 18 Study 200: Clinical Success Rates at TOC and Day 3

Clinical Success Rates		Solithromycin		Levofloxacin	
Visit	**Population**	**n/N (%)**	**[95% CI]**	**n/N (%)**	**[95% CI]**
TOC	ITT (co-primary efficacy outcome)	55/65 (84.6)	[73.5-92.4]	58/67 (86.6)	[76.0-93.7]
	CE (co-primary efficacy outcome)	46/55 (83.6)	[71.2-92.2]	54/58 (93.1)	[83.3-98.1]
	mITT	14/18 (77.8)	[52.4-93.6]	10/14 (71.4)	[41.9-91.6]
	ME	12/15 (80.0)	[51.9-95.7]	10/13 (76.9)	[46.2-95.0]
Day 3	ITT (Biomarkers Consortium criteria)[a]	47/65 (72.3)	[59.8-82.7]	48/67 (71.6)	[59.3-82.0]

ITT=intent-to-treat; CE=clinically evaluable; mITT=microbiological intent-to-treat; ME=microbiologically evaluable.
a. Criteria similar to those subsequently adopted in FDA CABP guidance

5.3 FDA Guidance on the CABP Development Program

Regulatory considerations for the most appropriate designs for CABP trials were evolving during the design and conduct of the Phase 3 studies. The study designs, which are described in Section 5.4, are in concordance with the principles in the 2009 and 2014 draft FDA guidances for CABP studies (*Community-acquired Bacterial Pneumonia: Developing Drugs for Treatment - Draft Guidances March 2009 and January 2014*) and the November 2011 meeting of the Anti-infective Drugs Advisory Committee (AIDAC) on design considerations for studies in CABP. The Phase 3 CABP studies were the first to be conducted using ECR as the prespecified primary outcome.

A number of meetings, teleconferences, and other communications with FDA occurred throughout the course of development of solithromycin. Key agreements with the FDA on the design of the Phase 3 trials are outlined below:

- Study 300 had co-primary efficacy endpoints of ECR in the ITT population and ECR in the pooled (across Studies 300 and 301) mITT population based on the 2009 FDA draft CABP guidance and discussions at the November 2011 AIDAC meeting. The non-inferiority margins were 10% for the ITT population and 15% for the pooled mITT population.

- Study 301 had a primary efficacy endpoint of ECR in the ITT population, in alignment with the 2014 FDA draft guidance. The non-inferiority margin was 10% for the ITT population.

- The Study 300 protocol was amended to allow for inclusion of patients who had taken a single dose of a short-acting antibiotic within the 7 days prior to randomization (allowed for up to 25% of enrolled patients). For Study 301, this provision was included in the original protocol.

- Microbiological populations (mITT-2 and ME-2) that were a subset of the mITT and ME populations based on more traditional diagnostic techniques for pathogen identification (limited to culture-based methods from blood or high quality sputum specimens and *Legionella* detection via urinary antigen test [UAT]) were added to both Studies 300 and 301. These were the FDA-preferred populations for summarizing pathogen-specific

outcomes due to the more definitive nature of the diagnoses and the fact that the majority of pathogens would have susceptibility data available for analyses supporting breakpoints.

5.4 Phase 3 CABP Study Design Considerations

5.4.1 Non-inferiority Design and Margins Established for Phase 3 Studies

A randomized, double-blind, non-inferiority design was selected for the Phase 3 studies in accordance with the 2009 draft CABP guidance. Both the 2009 and 2014 guidance documents provide a justification of the non-inferiority margin based on the historical literature. The guidances describe a large treatment effect of antibiotics at an early endpoint (3 to 5 days following treatment initiation) based on improvement of signs and symptoms. A conservative estimate of the treatment effect, based on improvement in symptoms accounting for the uncertainties in the historical literature, is 20% and the guidance documents indicate that these data support a non-inferiority margin of 12.5% in the ITT population. However, the more conservative non-inferiority margin of 10% in the ITT population agreed to with the FDA at the initiation of the solithromycin Phase 3 trials was maintained. The 2009 draft guidance, which proposed ECR in the pooled mITT population across studies as a primary endpoint, noted that a 15% non-inferiority margin is acceptable for the mITT population, as the treatment effect may be larger in those patients with an identified bacterial diagnosis.

5.4.2 Selection of Comparator

Moxifloxacin, the comparator in the Phase 3 trials, has established efficacy in the treatment of CABP, with potent activity against the key CABP pathogens. Moxifloxacin is recommended for empiric therapy for moderately severe CABP in the IDSA/ATS Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (Mandell 2007). The approved dose of IV and oral moxifloxacin for the treatment of CABP is 400 mg QD across the countries in which the studies were conducted, with a recommended duration of treatment of 7 to 14 days. Levofloxacin, the fluoroquinolone comparator in the Phase 2 trial, is not approved at the same dose worldwide.

A macrolide was not selected as the active comparator given that prevailing antibiotic resistance patterns preclude empiric use of an existing macrolide as monotherapy for CABP in many regions where the studies were conducted. A β-lactam was not a suitable comparator, as β-lactams are ineffective for atypical CABP pathogens and lack IV to oral treatment options.

5.4.3 Selection of Solithromycin Dosing Regimens Used in CABP Studies

The solithromycin dosing regimens in the Phase 3 CABP studies were selected based on susceptibility profiles, the results of PK/PD target attainment analyses that used population PK models (Section 4.4.1), nonclinical PK/PD targets for efficacy (Section 4.3), experience in Phase 1 studies in healthy subjects, and the Phase 2 study results in patients with CABP.

Monte Carlo simulations were conducted, and these data were used to evaluate the probabilities of PK/PD target attainment for various solithromycin dosing regimens. These simulations were conducted using a population PK model that was developed based on plasma and ELF solithromycin concentrations from Phase 1 studies and PK/PD targets for *S. pneumoniae* obtained

from the murine lung infection model summarized in Section 4.3. The PK/PD target attainment analyses demonstrated that a loading dose on Day 1 would allow for earlier and more effective coverage of *S. pneumoniae* with higher MICs. The lower maintenance dose of 400 mg was possible because of the auto-inhibition of solithromycin metabolism and consequent accumulation of solithromycin with repeat dosing.

Study 200 evaluated solithromycin in the treatment of CABP with an oral dosing regimen of 800 mg administered as a single dose on Day 1 followed by 400 mg QD on Days 2 through 5. The duration of 5 days was based on clinical data that support treatment of CABP for a minimum of 5 days (Mandell 2007).

The dosing strategies for Studies 300 and 301 were based on the efficacy outcomes in Study 200 and the results of updated PK/PD target attainment analyses. The oral dosing regimen for Study 300 was the same as that used in Study 200. The IV to oral solithromycin dosing regimen evaluated in Study 301 was 400 mg IV QD on Day 1, continued through Day 7 or until predefined oral switch criteria were met and the investigator felt it was appropriate to transition the patient to oral treatment. The increased duration of dosing to 7 days was based on the increased severity of disease in these patients relative to patients in the oral study. This duration is consistent with the minimum of 7 days of treatment indicated for most IV and IV to oral antibiotic regimens for the treatment of CABP.

If a patient was switched to oral therapy in Study 301, the first oral dose of solithromycin was 800 mg, followed by 400 mg oral QD for the remainder of study drug administration, for a total of 7 days of treatment. Given the 67% oral bioavailability, the use of the oral loading dose after IV dosing was designed to maintain high total-drug ELF and free-drug plasma exposures during the transition to oral therapy.

6 EFFICACY IN PHASE 3 SOLITHROMYCIN CABP STUDIES

6.1 Summary

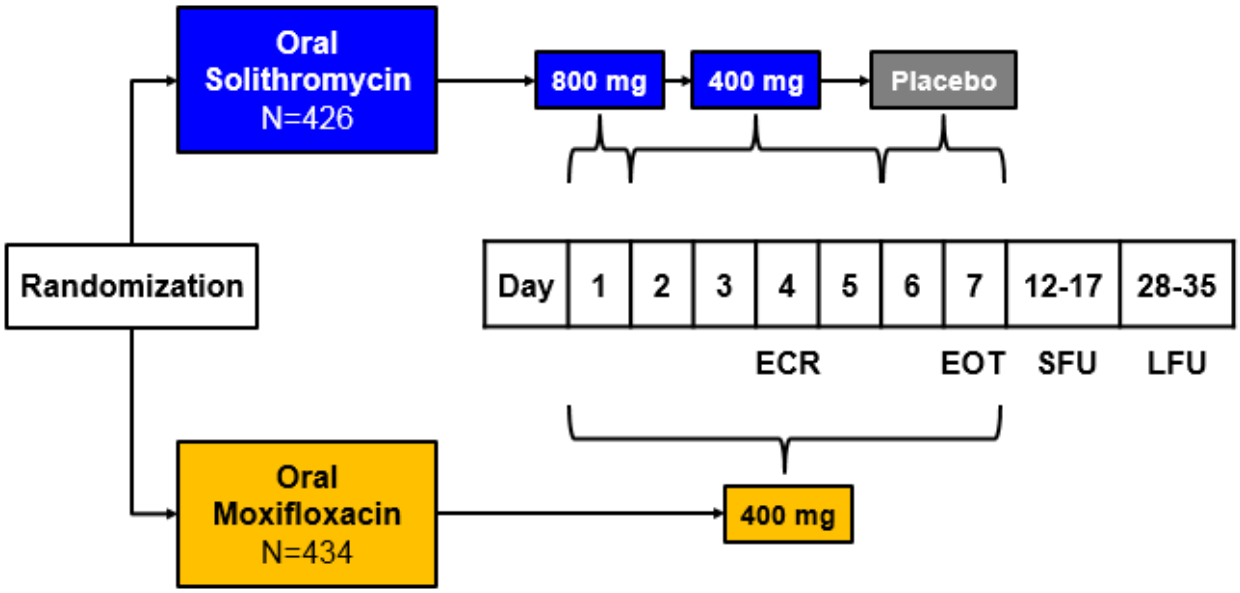
- In Study 300, oral solithromycin was non-inferior to oral moxifloxacin for the primary endpoint of ECR in the ITT population. A total of 78.2% of patients in the solithromycin group and 77.9% of patients in the moxifloxacin group were responders, with a treatment difference of 0.29% (95% CI: -5.5, 6.1).
- In the pooled analyses in the mITT population of Studies 300 and 301 (a co-primary endpoint for Study 300), 77.2% of patients in the solithromycin group and 78.9% of patients in the moxifloxacin group were responders, with a treatment difference of -1.69% (95% CI: -7.4, 4.2).
- In Study 301, IV to oral solithromycin was found to be non-inferior to IV to oral moxifloxacin for the primary endpoint of ECR in the ITT population. A total of 79.3% of patients in the solithromycin group and 79.7% of patients in the moxifloxacin group were responders, with a treatment difference of -0.46% (95% CI: -6.1, 5.2).
- Efficacy results for the primary outcomes were consistent across relevant subpopulations for demographics, disease severity, geographic region, and prior antibiotic use.
- Clinical success rates at the SFU visit, as assessed by investigators, were high (≥ 85%) in each treatment group in both studies. Additional symptom based secondary efficacy endpoints demonstrated similar efficacy at SFU between solithromycin and moxifloxacin patients.
- By-pathogen success rates for target CABP pathogens were high and comparable to those observed for moxifloxacin in outcomes of ECR and clinical success at the SFU visit.

6.2 Study Design

Studies 300 and 301 were Phase 3, randomized, double-blind, multicenter, non-inferiority studies to evaluate oral (Study 300) and IV to oral (Study 301) solithromycin compared with moxifloxacin in the treatment of adult patients with CABP. The study designs are illustrated in Figure 12 (Study 300) and Figure 13 (Study 301).

In Study 300, the dosing regimen of solithromycin evaluated a single 800 mg dose on Day 1 followed by 400 mg QD on Days 2 through 5, with blinded placebo taken on Days 6 and 7. The oral moxifloxacin dosing regimen was 400 mg QD on Days 1 through 7.

Figure 12 Study 300: Oral Clinical Trial Design



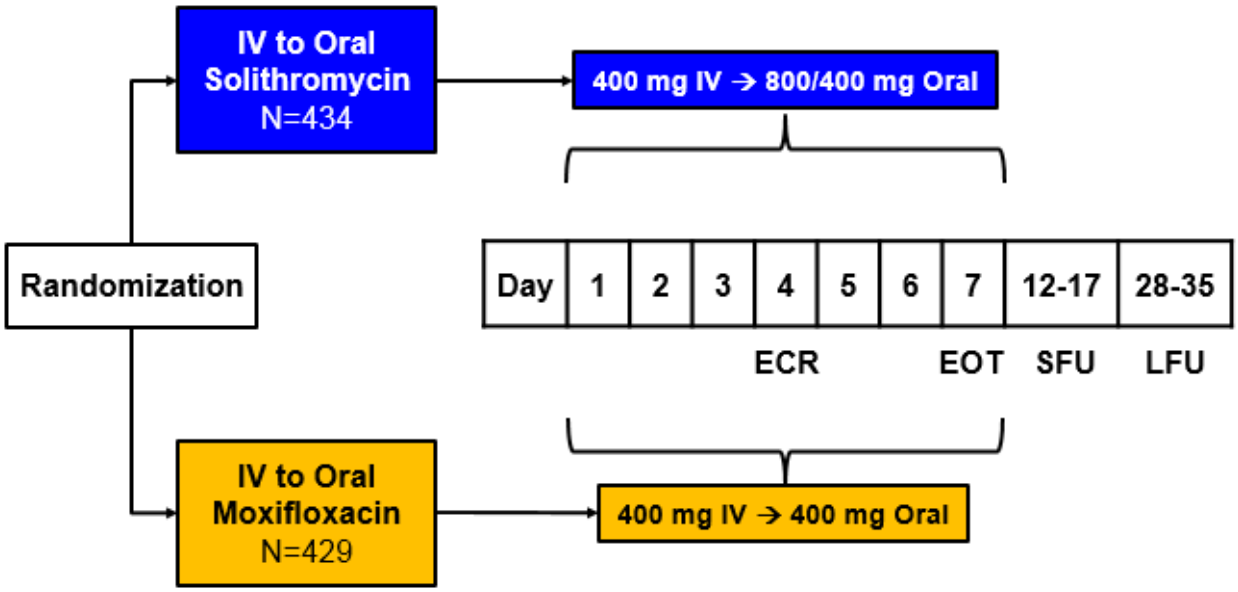
ECR=early clinical response assessment; EOT=end of treatment; SFU=short-term follow-up; LFU=long-term follow up

In Study 301, patients in each treatment group received 7 days of active study drug. All patients were started with IV study drug and could transition to oral study drug at the investigator's discretion if the following predefined criteria were met and if the investigator felt it was appropriate to transition the patient to oral therapy:

- Baseline clinical signs and symptoms were improving
- Temperature < 38ºC measured orally, < 38.5ºC measured tympanically or by temporal artery thermometry, < 37.5 ºC by axillary measurement, or < 39 ºC measured rectally
- Respiratory rate ≤ 24 breaths per minute
- Systolic blood pressure ≥ 90 mmHg
- Oxygen saturation as determined by pulse oximetry ≥ 90% on room air or ≥ pre-CABP baseline oxygen saturation on room air

Patients remained on IV study drug for the full 7 days if they did not meet oral switch criteria or if the investigator felt it was in the patient's best interest to remain on IV drug. Patients in the solithromycin group received an IV treatment regimen of 400 mg QD. For patients who transitioned to oral solithromycin, the first oral dose was 800 mg administered as a single dose, followed by 400 mg oral QD for the remainder of the 7-day study drug administration period. Moxifloxacin was administered as an IV treatment regimen of 400 mg QD and for patients transitioning to oral therapy as 400 mg QD on each oral dosing day.

Figure 13 Study 301: IV to Oral Clinical Trial Design



ECR=early clinical response assessment; EOT=end of treatment; SFU=short-term follow-up; LFU=long-term follow up

Both studies included the following visits:

- Screening/Baseline/Day 1: Screening occurred within 12 hours of the first dose of study drug. Day 1 was the first dose of study drug
- Day 4 (72 hours after the first dose of study drug): assessment of ECR
- EOT: Last dose of study drug (+2 days), investigator assessment of clinical response
- SFU: 5 to 10 days after the last dose of study drug (per protocol, on Day 7), investigator assessment of clinical response
- LFU: 28 to 35 days after the first dose of study drug, assessment of all-cause mortality only

Safety was monitored from informed consent through the LFU Visit.

6.2.1 Patient Population

The studies enrolled adult patients with CABP diagnosed by the presence of major clinical signs and symptoms of CABP and confirmed by pulmonary imaging. Enrollment criteria were nearly identical between the two studies (Table 19).

The pneumonia severity index (PSI) or PORT score is a clinical scoring system used to calculate the probability of morbidity and mortality in CABP patients, and to assist in the determination of whether patients should be treated as outpatients or hospitalized. Patients are categorized as PORT Risk Class I (less risk), II, III, IV and V (highest risk). Additional detail about the PORT scores and risk classes is given in Appendix 11.3. The Phase 3 studies enrolled patients who were PORT Risk Class II, III and IV.

Enrolled patients with PORT Risk Class II severity pneumonia were limited to no more than 50% in Study 300 and no more than 25% in Study 301. In Study 301, at least 25% of enrolled patients were to have PORT Risk Class IV. Enrolled patients who received a single dose of a short-acting antibiotic were limited to 25% in each trial. Enrolled patients < 65 years of age were limited to 80%. Enrolled patients outside North America (US, Canada, and Puerto Rico) had a target limit of 75%.

Randomization was stratified by geographic region, history of asthma and/or COPD, and PORT Risk Class: II vs III/IV.

Appendix 11.4 includes a complete list of inclusion criteria for Studies 300 and 301. Table 19 provides a comparison of the key inclusion criteria in the two studies.

Table 19 Comparison of Phase 3 Study Key Inclusion Criteria

	Study 300	Study 301
Sex	**Male and females**	**Male and females**
Age	**≥ 18 years of age**	**≥ 18 years of age**
Signs and symptoms	Acute onset ≥ 3 of the following (new or worsening): • Cough • Production of purulent sputum • Shortness of breath (dyspnea) • Chest pain due to pneumonia ≥ 1 of the following: • Fever • Hypothermia Presence of pulmonary rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)	
Prior systemic antibiotics	None other than single dose of short-acting antibiotic (penicillins, cephalosporins [not ceftriaxone], tetracyclines, or trimethoprim-sulfamethoxazole) in 7 days prior to enrollment (capped at 25%)	
PORT Risk Class	II, III, or IV (pneumonia severity scores of 51 to 105, inclusive); PORT Risk Class II was capped at 50%.	II, III, or IV (pneumonia severity scores of 51 to 130, inclusive); PORT Risk Class II was capped at 25%; at least 25% were to be PORT Risk Class IV.
Pulmonary imaging study	Presence of lobar, multilobar, or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia (e.g. CXR posteroanterior and lateral preferred; single view acceptable if conclusive or CT of thorax) within 48 hours before first dose of study drug	

CT=computed tomography; CXR=chest radiograph; PORT=Pneumonia Outcomes Research Team.

6.2.2 Key Exclusion Criteria

Full lists of exclusion criteria for Studies 300 and 301 are in Appendix 11.4.

Key exclusion criteria are summarized below:

1. Ventilator- or healthcare-associated pneumonia
2. Severe COPD or bronchiectasis
3. Certain non-CABP conditions:
    - Viral or fungal pneumonia, *Pneumocystis jiroveci* pneumonia, aspiration pneumonia, other non-infectious causes of pulmonary infiltrates, primary or metastatic lung cancer, cystic fibrosis, tuberculosis, empyema
4. Mean QTcF > 450 msec on screening electrocardiogram (ECG) (amended to > 460 msec for Study 301 only, following analysis of the thorough QT study).
5. Concomitant use of drugs known to prolong the QT interval.
6. Concomitant use of drugs, foods, or herbal products known to be moderate to potent inhibitors of CYP3A4 isozymes.
7. Any use within the prior 7 days of drugs or herbal products known to be moderate to potent inducers of CYP3A4 isozymes.
8. Required current use of drugs with narrow therapeutic indices that are principally metabolized by CYP3A4 or transported by P-gp, for which a drug interaction with solithromycin could result in higher and possibly unsafe exposures to these drugs.
9. Known history of significant and ongoing renal, hepatic, or hematologic impairment; current treatment for HCV infection; known HIV infection.
10. Any of the following laboratory parameters:
    - CR_{CL} <30 mL/min calculated by the Cockcroft-Gault formula
    - AST or ALT > 3× ULN
    - Total bilirubin > 2×ULN
    - Neutrophil count ≤ 500 neutrophils/mm^3 as measured by differential on complete blood count (CBC) or inferred by total white blood cells (WBCs) > 1000/µL (Study 300)
    - Platelet count < 50,000 cells/mm^3
11. Known history of myasthenia gravis.
12. Women who were pregnant or nursing.
13. History of intolerance or hypersensitivity to fluoroquinolone or macrolide antibiotics.
14. Clinical presentation with pneumonia of severity sufficient to result in direct admission to a hospital intensive care unit (regardless of PORT score) (Study 300) or that would require mechanical ventilation (Study 301).

6.2.3 Microbial Diagnostics

The Phase 3 studies utilized multiple approaches to obtain an etiological diagnosis for enrolled patients. These approaches included traditional techniques such as culture of blood or respiratory specimens, as well as newer diagnostic methods utilized to enrich the assessment of microbial

etiology, including quantitative polymerase chain reaction (PCR) assays and serological techniques. These methods were as follows:

- culture of blood or respiratory specimens
- detection of *L. pneumophila* or pneumococcal antigen in urine
- diagnostic rises in pathogen-specific antibody responses (*L. pneumophila* and *M. pneumoniae*)
- culture of *M. pneumoniae* from an oropharyngeal swab
- identification meeting diagnostic criteria using a quantitative repMp1 PCR assay for the detection of *M. pneumoniae* from oropharyngeal swabs (Dumke 2007).
- identification meeting diagnostic criteria using a *lytA* quantitative PCR assay for the detection and quantification of *S. pneumoniae* from nasopharyngeal swab specimens (Carvalho 2007; Albrich 2012).
- semi-quantitative multiplex PCR of sputum for a panel of pathogens that includes *S. pneumoniae*, *S. aureus*, *H. influenzae*, *M. catarrhalis*, and *K. pneumoniae* using the CE-marked Unyvero™ P50/LRT Pneumonia Cartridge (Curetis AG, Holzgerlingen, Germany) (Study CE01-300 only).

As discussed in Section 6.2.5, two different approaches were utilized to define microbiological analysis populations. The mITT population utilized each of the methods listed above, whereas the mITT-2 population utilized only culture-based methods of diagnosis and detection of *L. pneumophila* via urinary antigen.

6.2.4 Oral and IV Formulations

Oral study drug was supplied in gelatin capsules. A double-dummy design was utilized, with solithromycin placebo capsules identical in appearance to solithromycin 200 mg capsules and moxifloxacin placebo over-encapsulated tablets identical in appearance to moxifloxacin 400 mg over-encapsulated tablets. The capsules were provided in blister packs to facilitate dispensing and patient use.

Solithromycin for Injection is supplied in vials that contain sterile lyophilized powder equivalent to a 400 mg single dose of solithromycin. Each vial was reconstituted with 20 mL sterile water for injection and diluted into a 250 mL bag of 0.9% Sodium Chloride Injection, USP. After reconstitution and dilution, solithromycin was administered via IV infusion over 60 minutes. Commercial moxifloxacin 400 mg ready-to-use flexibags were used for infusion of moxifloxacin over 60 minutes. Solithromycin and moxifloxacin infusions were blinded by covering the infusion bags, infusion lines and IV catheter site.

6.2.5 Analysis Populations

The ITT population included all randomized patients.

The CE population consisted of ITT patients who met key inclusion/exclusion criteria, minimal dosing criteria, had no confounding use of prohibited antibiotics and no other factor that could

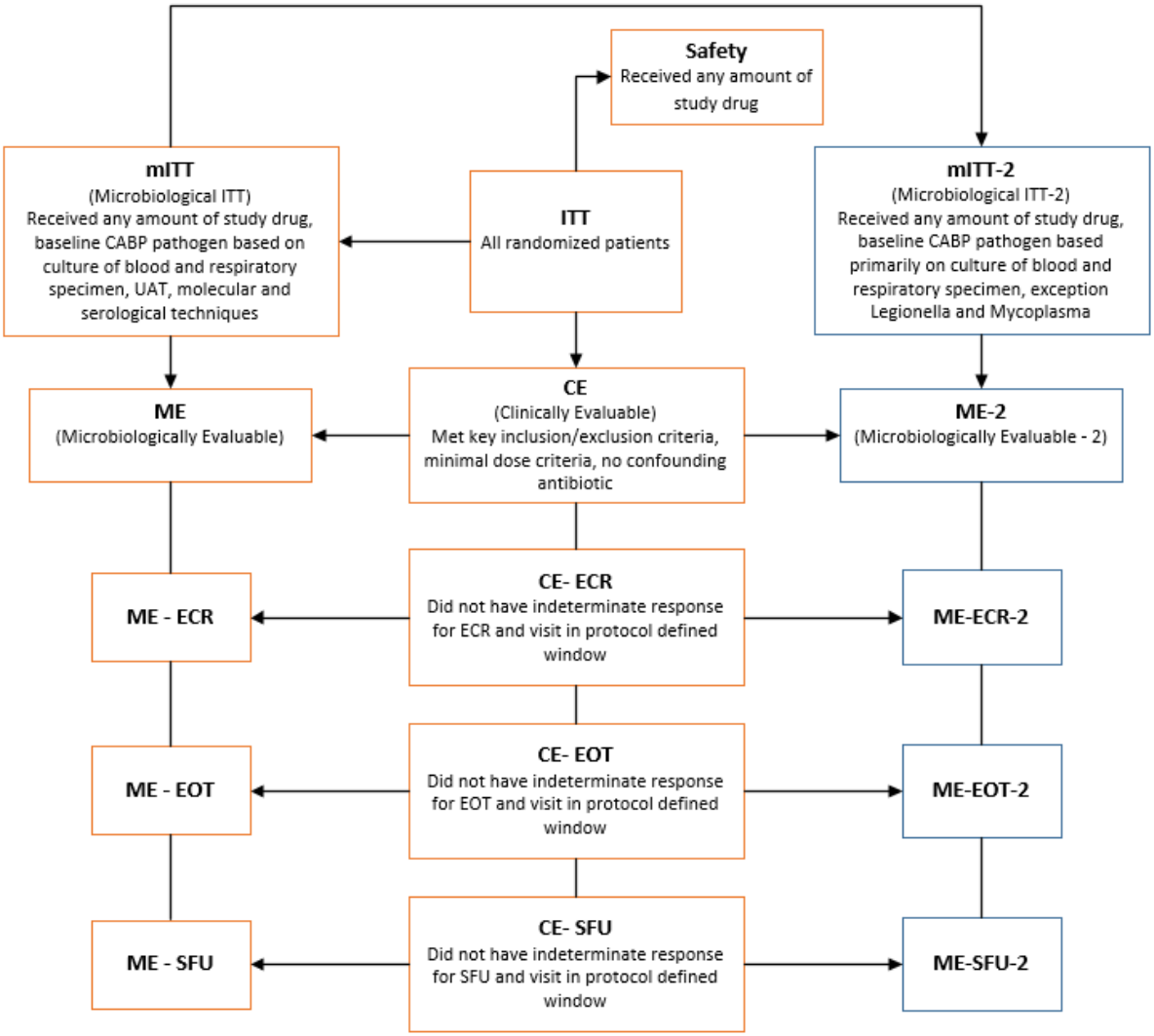
confound the assessment of efficacy (details in Appendix 11.1). Three populations were defined: CE-ECR, CE-EOT, and CE-SFU populations. The CE-ECR population was not prespecified in the SAP and was defined based on FDA recommendations to provide a per-protocol type analysis for ECR.

The microbiological ITT (mITT) population included randomized patients who received any amount of study drug and had a baseline CABP pathogen identified based on culture of blood or respiratory specimen (sputum, bronchoalveolar lavage, pleural fluid, or oropharyngeal swab [for *M. pneumoniae*]), UAT, molecular quantitative PCR (qPCR), or serological techniques. Appendix 11.5 provides a complete description of how pathogens were identified in the mITT population.

The mITT-2 and ME-2 populations were defined based on recommendations by the FDA to perform pathogen-specific analyses in a population where diagnoses are based on more traditional methods with accompanying susceptibility data. The mITT-2 population included patients who received any amount of study drug with a baseline pathogen identified by isolation from a blood or respiratory specimen, including culture of *M. pneumoniae* from an oropharyngeal swab. Due to the small number of patients in either trial with *L. pneumophila* diagnosed by culture, with agreement by FDA, diagnosis of *L. pneumophila* by UAT was also allowed in the mITT-2. Appendix 11.5 provides a complete description of how pathogens were identified in the mITT-2 population.

The ME populations were based on the intersection of the mITT populations and the CE populations. Patients in the ME populations met criteria for inclusion in the mITT and CE populations at the specified assessment or visit (ME-ECR, ME-EOT, and ME-SFU). Patients in the ME-2 populations met criteria for inclusion in the mITT-2 and CE populations at the specified assessment or visit (ME-ECR-2, ME-EOT-2, and ME-SFU-2).

Figure 14 Overview of Efficacy Analysis Populations in Studies 300 and 301



ITT=intent-to-treat; mITT=microbiological intent-to-treat; ME=microbiologically evaluable; CE=clinically evaluable; ECR=early clinical response; EOT=end of treatment; SFU=short-term follow-up.

6.2.6 Study Endpoints

6.2.6.1 Primary Endpoint

Study 300 had co-primary endpoints. The co-primary endpoints were ECR, which was assessed at 72 hours (-12/+36 hours for Study 300, Day 4 Visit) following the first dose of study drug, in the ITT population and ECR in the mITT population in the pooled Phase 3 Studies 300 and 301. The primary endpoint in Study 301 was ECR (assessed at 72 hours -13/+36 hours, Day 4 Visit, following the first dose of study drug) in the ITT population.

The definitions for symptom severity used in the assessment of ECR are shown in Table 20. A patient was programmatically defined as a responder if the following criteria were met in the protocol-specified window:

- Improvement in ≥ 2 of the symptoms of CABP that the patient presented with at baseline. Improvement was defined as a decrease by ≥ 1 point in the score.
- No worsening of any symptom; worsening was defined as an increase in the score for any symptom by ≥ 1 point.
- Did not receive an antibiotic for the treatment of CABP from the first dose of study drug through 108 hours after the first dose (i.e. the maximum time point used for the assessment of ECR).

A patient was programmatically defined as a non-responder if any of the following criteria were met:

- Did not show an improvement in at least 2 of the symptoms of CABP with which the patient presented at baseline (improvement was defined as a decrease by at least 1 point in the score)
- Worsening of any symptom (defined as an increase in the score for any symptom by at least 1 point)
- Received an antibiotic for the treatment of CABP from the first dose of study drug through 108 hours after the first dose (i.e. the maximum time point used for the assessment of ECR)
- Died from any cause through the LFU visit

Patients were defined as indeterminate if they had missing data where response could not be determined, were lost to follow up, or if their ECR evaluation fell outside of the protocol-specified windows. Patients with an indeterminate response for the primary endpoint were included in the denominator for the calculation of the response rate and thus were considered non-responders for the primary analysis.

Table 20 Symptom Assessment for Early Clinical Response

Symptom	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Cough	Resolution (to pre-CABP baseline) or absence of cough	Transient, does not interfere with normal activity	Frequent, interferes with normal activity or sleep	Constant, interferes with most or all activities or sleep
Dyspnea/ Shortness of Breath	Resolution (to pre-CABP baseline) or absence of dyspnea	Dyspnea on exertion (e.g. climbing stairs)	Dyspnea with normal/routine activities (e.g. walking)	Dyspnea at rest or requiring oxygen therapy
Chest Pain due to Pneumonia	Resolution or absence of chest pain related to CABP	Transient, does not interfere with normal activity	Frequent, interferes with normal activity or sleep	Constant, interferes with most or all activities or sleep
Difficulty with Sputum Production	Resolution (to pre-CABP baseline) or absence of sputum production	Sputum production rarely causes difficulty or distress	Sputum production often causes difficulty or distress	Constant difficulty with sputum production

6.2.6.2 Secondary and Additional Endpoints

Secondary and additional efficacy endpoints in the Phase 3 studies included the following:

- ECR with improvement in vital signs (i.e. body temperature, blood pressure, heart rate, and respiratory rate) in the ITT population. If vital signs were normal at baseline, none could have worsened. Abnormal vital signs were defined as:
  - fever [body temperature > 38ºC (100.4ºF) orally, > 38.5ºC (101.3ºF) tympanically, > 39ºC (102.2ºF) rectally, or > 37.5ºC (99.5 ºF) via axillary measurement]
  - hypotension (systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg);
  - tachycardia (heart rate ≥ 100 beats per minute [bpm])
  - tachypnea (respiratory rate ≥ 20 breaths/min)
- ECR in the mITT population in the individual studies
- Investigator assessment of clinical response was evaluated at EOT and SFU in the ITT and CE populations. The investigator assessment of treatment success at SFU (5 to 10 days after the last dose of study drug) represented the traditional test of cure endpoint utilized in previous CABP trials. Investigators made a clinical assessment as to whether the patient was a clinical success, failure, or indeterminate at EOT and SFU based on the definitions in Table 21.

Table 21 Investigator Assessment of Clinical Response at EOT and SFU

Outcome	EOT	SFU
Clinical Success	Complete or near-complete resolution of the baseline signs and symptoms of CABP	Continued complete or near-complete resolution of the baseline signs and symptoms of CABP
Clinical Failure	A patient is a clinical failure if any of the following are met: • Lack of resolution, or worsening of baseline CABP-specific signs and symptoms and requires additional antibacterial medication • Development of new signs and symptoms, complications, or radiologic findings of CABP and requires additional antibacterial medications • Study drug discontinued due to an AE and requires additional antibacterial medication • Death from any cause.	A patient is a clinical failure if any of the following are met: • Classified as a failure at the EOT assessment • Development of new signs and symptoms, complications, or radiologic findings of CABP and requires additional antibacterial medications • Death from any cause
Indeterminate	A patient has an indeterminate clinical outcome if any of the following are met: • Lost to follow-up prior to the EOT assessment, or missed visit • Other reason	A patient has an indeterminate clinical outcome if any of the following are met: • Indeterminate at the EOT assessment • Lost to follow-up • Other reason

EOT=End of Treatment, SFU=Short-term Follow-Up.

- Investigator assessment of clinical response at EOT and SFU in the mITT populations.
- ECR by pathogen, and investigator assessment of clinical response at EOT and SFU by pathogen.
- Symptom response endpoints at SFU in the ITT population:
  - Symptom response by major CABP symptoms was evaluated, requiring that chest pain and sputum production were absent, and the absence of or improvement in cough and dyspnea.
  - Sustained ECR was defined as being a responder at ECR and maintaining that response through SFU, with the added requirement that chest pain and sputum production be absent, and cough and dyspnea be absent or improved over baseline.
  - Resolution of all CABP symptoms, defined as absence of all baseline symptoms of CABP (i.e. cough, dyspnea, chest pain, and difficulty with sputum production).
- Improvement in each CABP symptom at Day 4, EOT and SFU.

6.2.7 Statistical Analyses

Studies 300 and 301 were designed to test for non-inferiority (with a 10% non-inferiority margin in the ITT population and 15% in the pooled mITT population) in the primary outcome measure of ECR of solithromycin compared with moxifloxacin.

The sample size was determined based on ensuring sufficient power for the primary efficacy analysis of ECR in the ITT population, as well as ECR in the mITT population (Study 300) for the pooled studies. Assuming a 1-sided alpha of 0.025 and using the continuity corrected Z-test for determination of sample size, the power for each primary outcome measure is shown in Table 22.

Table 22 Power for the Primary and Co-Primary Outcome Measures

	Primary Outcome (Early Clinical Response)	Co-Primary Outcome (Study 300) (Early Clinical Response)
Population	ITT	Pooled mITT
NI Margin	10%	15%
Evaluability Rate	N/A	25%[a]
Outcome Rate	73%	73%
N	860	430
Power	90%	94%

ITT=intent-to-treat; mITT=microbiological intent-to-treat; N/A=not applicable; NI=non-inferiority
a. 25% for the pooled Phase 3 studies

The non-inferiority hypothesis test was a 1-sided hypothesis test performed at the 2.5% level of significance. This was based on the lower limit of the 2-sided 95% CI for the observed difference in ECR rate (solithromycin group minus the moxifloxacin group) for both the ITT and pooled mITT populations. For the ITT population, an unadjusted CI was calculated using a continuity corrected Z-test. For the pooled mITT population, an adjusted (for study) CI was calculated using the method of Miettinen and Nurminen. If the lower limit of the 95% CI for the difference in response rates in the ITT population was greater than -10% and in the pooled mITT population was greater than -15% (for Study 300 only), then the null hypothesis was rejected and the non-inferiority of solithromycin to moxifloxacin was concluded.

Sensitivity analyses of ECR included an analysis adjusted for the stratification factors of geographic region, asthma/COPD, and PORT Risk Class stratum based on the randomization stratum to which the patient correctly belongs. A second analysis was conducted where patients with missing data (i.e. indeterminates) were considered as responders. A third sensitivity analysis utilized multiple imputation conducted using a Markov chain Monte Carlo full data imputation to define missing data (i.e. indeterminate response). Ten data sets were created using this technique in which geographic region, PORT Risk Class, asthma/COPD, and receipt of prior antibiotics for CABP were included as predictive variables.

Subpopulation analyses of ECR were performed in the pooled Studies 300 and 301 based on key demographic and baseline characteristics (age, gender, race, BMI, and geographic region), and baseline disease severity characteristics (PORT Risk Class, SIRS criteria, history of asthma and/or

COPD, prior antibiotic use, and bacteremia). For the subpopulation analyses, weighted treatment differences were calculated, as were stratified (for study) 95% CIs, using the inverse variance for the stratum weights.

With the exception of ECR in the pooled mITT population (co-primary endpoint for Study 300), 4 patients from a single site (Site 710) from Study 300 were not included (3 patients randomized to moxifloxacin and 1 patient randomized to solithromycin) in the integrated efficacy analysis, due to data integrity issues at this site discovered after study completion. These patients are retained in the Study 300 individual data presentations and in the integrated safety analyses.

6.3 Demographic and Baseline Characteristics

6.3.1 Demographics and Baseline Disease Characteristics

Table 23 presents a summary of demographic characteristics in each Phase 3 study. Demographic characteristics were similar between studies and treatment groups. In Study 300, approximately 34% of patients were ≥ 65 years of age and about 15% of patients were ≥ 75 years of age. The population was slightly older for Study 301 with approximately 45% of patients ≥ 65 years of age and about 19% of patients ≥ 75 years of age. Slightly more than half of patients in the Phase 3 studies were male. Approximately 80% of the patients were white.

Table 23 Demographics and Baseline Characteristics in the ITT Population

	Study 300		Study 301	
	Solithromycin Oral (N=426)	Moxifloxacin Oral (N=434)	Solithromycin IV to Oral (N=434)	Moxifloxacin IV to Oral (N=429)
Age (years)				
Mean (SD)	58.5 (14.69)	56.7 (15.52)	60.5 (15.48)	61.1 (15.05)
Median (Min, Max)	60.0 (18, 93)	58.0 (18, 90)	62.0 (19, 94)	63.0 (18, 92)
Age (years), n (%)				
<65	271 (63.6)	297 (68.4)	246 (56.7)	232 (54.1)
≥65	155 (36.4)	137 (31.6)	188 (43.3)	197 (45.9)
≥75	62 (14.6)	63 (14.5)	83 (19.1)	77 (17.9)
Gender, n (%)				
Female	199 (46.7)	205 (47.2)	222 (51.2)	193 (45.0)
Male	227 (53.3)	229 (52.8)	212 (48.8)	236 (55.0)
Race, n (%)				
White	347 (81.5)	367 (84.6)	344 (79.3)	334 (77.9)
Black / African American	46 (10.8)	40 (9.2)	22 (5.1)	22 (5.1)
Asian	4 (0.9)	4 (0.9)	61 (14.1)	63 (14.7)
American Indian or Alaskan Native	0	0	0	2 (0.5)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0	0	0
Other Race	28 (6.6)	23 (5.3)	7 (1.6)	8 (1.9)
Ethnicity, n (%)				
Hispanic or Latino	101 (23.8)	101 (23.4)	18 (4.1)	27 (6.3)
Not Hispanic or Latino	325 (76.3)	333 (76.7)	416 (95.9)	402 (93.7)
BMI (kg/m^2)				
Mean (SD)	27.6 (6.22)	28.1 (6.6)	26.8 (6.16)	27.4 (6.45)
Median (min, max)	26.8 (15.2, 56.2)	27.1 (15.5, 58.6)	26.1 (14.1, 68.4)	26.5 (13.7, 53.2)

BMI=body mass index; ITT=intent-to-treat; IV=intravenous; Max=maximum; Min=minimum.
N=Number of patients in the ITT population. n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).

Consistent with enrollment targets and criteria in each respective study, patients on average had greater baseline CABP disease severity in the IV to oral Study 301 as compared to Study 300 where only oral study drug was administered (Table 24). In Study 300, approximately half of patients were PORT Risk Class II (49.3%, solithromycin; 51.4% moxifloxacin. In Study 301, <25% of patients were PORT Risk Class II (24.4%, solithromycin; 22.4% moxifloxacin) and >30% of patients were PORT Risk Class IV/V (30.4%, solithromycin; 30.1% moxifloxacin; there were 6 PORT V patients in total).

Table 24 Disease Severity Factors in the ITT Population

	Study 300		Study 301	
	Solithromycin Oral (N=426)	**Moxifloxacin Oral (N=434)**	**Solithromycin IV to Oral (N=434)**	**Moxifloxacin IV to Oral (N=429)**
History of asthma and/or COPD, n (%)	62 (14.6)	64 (14.7)	95 (21.9)	92 (21.4)
PORT Score				
Mean (SD)	71.7 (13.4)	71.2 (13.3)	81.8 (18.30)	82.6 (17.43)
Median (Min, Max)	71.0 (48,108)	69.0 (51,112)	80.0 (51,133)	81.0 (51,139)
PORT Risk Class, n (%)				
II (51-70)	210 (49.3)[a]	223 (51.4)	106 (24.4)	96 (22.4)
III (71-90)	168 (39.4)	173 (39.9)	196 (45.2)	204 (47.6)
IV (91-130)	48 (11.3)	38 (8.8)	130 (30.0)	125 (29.1)
V (≥ 131)[b]	0	0	2 (0.5)	4 (0.9)
Met SIRS Criteria[c], n (%)	231 (54.2)	262 (60.4)	313 (72.1)	294 (68.5)
Met Modified ATS Severity Criteria[d]	24 (5.6)	40 (9.2)	55 (12.7)	46 (10.7)
Prior use of an antibiotic within 7 days of randomization, n (%)	53 (12.4)	44 (10.1)	102 (23.5)	110 (25.6)
C Reactive Protein (mg/L) Mean (SD)	89.2 (99.11)	90.8 (102.97)	93.8 (100.81)	95.1 (103.87)
Procalcitonin (ng/mL) Mean (SD)	1.5 (7.68)	2.1 (14.80)	1.9 (8.25)	1.2 (4.52)

ITT=intent-to-treat; Max=maximum; Min=minimum; PORT=Pneumonia Outcomes Research Team; SIRS=Systemic Inflammatory Response Syndrome. ATS=American Thoracic Society

N=number of patients in the ITT population; n=number of patients in the specific category; Percentages were calculated as 100 x (n/N).

a. One patient (Solithromycin patient, Study 300) was randomized with a PORT Risk Class of I and was counted in the PORT Risk Class II section.
b. Enrollment of patients with PORT risk class V (≥ 131) was a protocol deviation.
c. Met SIRS criteria is derived from the eCRF and is defined as ≥ 2 of the following 4 symptoms at baseline: temperature <36°C or >38°C, heart rate >90 bpm, respiratory rate >20 breaths/minute, WBC <4000 cells/mm^3 or WBC >12,000 cells/mm^3, or immature PMNs >10%.
d. Modified ATS severity criteria for severe community-acquired pneumonia are derived from the eCRF data and is defined as presence of ≥ 3 of the following 9 criteria at baseline: respiratory rate ≥ 30 breaths/min, O_2 saturation < 90% or PaO_2 < 60 mmHg, BUN ≥ 20 mg/dL, WBC <4000 cells/mm^3, confusion, multilobar infiltrates, platelets < 100,000 cells/mm^3, temperature < 36°C, and systolic blood pressure < 90 mmHg.

In Study 300, 860 patients were enrolled from 114 centers in North America (n=204), Latin America (n=106), Europe (n=448), and Rest of World (i.e. South Africa, n=102). In Study 301, 863 patients were enrolled from 147 centers in North America (n=103), Latin America (n=16), Europe (n=581) and Rest of World (i.e. South Africa and Asia Pacific, n=163). Europe was the highest enrolling region in both studies (Table 25).

Table 25 Regions of Enrollment in the ITT Population

Region of Enrollment	Study 300		Study 301	
	Solithromycin Oral (N=426) n (%)	Moxifloxacin Oral (N=434) n (%)	Solithromycin IV to Oral (N=434) n (%)	Moxifloxacin IV to Oral (N=429) n (%)
Europe	223 (52.3)	225 (51.8)	301 (69.4)	280 (65.3)
Latin America	52 (12.2)	54 (12.5)	5 (1.2)	11 (2.6)
North America	99 (23.3)	105 (24.4)	52 (12.0)	51 (11.9)
Rest of World[a]	52 (12.2)	50 (11.6)	76 (17.5)	87 (20.3)

ITT=intent-to-treat
N=number of patients in the ITT population; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).
a. Rest of World is South Africa for Study 300 and South Africa and Asia Pacific for Study 301.

6.3.2 Baseline Clinical Signs and Symptoms

Table 26 provides a summary of the numbers and percentages of patients in the Phase 3 CABP studies with the cardinal symptoms of CABP by severity. These cardinal symptoms were the component symptoms assessed for ECR. The proportions of patients experiencing each symptom and the distribution by severity of each symptom were similar in the solithromycin and moxifloxacin treatment groups.

Table 26 Severity of Cardinal Symptoms of CABP at Baseline in the Pooled ITT Population

	Study 300		Study 301	
	Solithromycin Oral (N=426) n (%)	Moxifloxacin Oral (N=434) n (%)	Solithromycin IV to Oral (N=434) n (%)	Moxifloxacin IV to Oral (N=429) n (%)
Cough, N1	426	434	434	428
Absent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mild	39 (9.2)	42 (9.7)	57 (13.1)	51 (11.9)
Moderate	278 (65.3)	280 (64.5)	258 (59.4)	268 (62.6)
Severe	109 (25.6)	112 (25.8)	119 (27.4)	109 (25.5)
Dyspnea/ Shortness of Breath, N1	426	434	434	428
Absent	16 (3.8)	22 (5.1)	19 (4.4)	15 (3.5)
Mild	137 (32.2)	118 (27.2)	118 (27.2)	117 (27.3)
Moderate	227 (53.3)	231 (53.2)	221 (50.9)	224 (52.3)
Severe	46 (10.8)	63 (14.5)	76 (17.5)	72 (16.8)
Chest Pain due to Pneumonia, N1	426	434	434	428
Absent	47 (11.0)	57 (13.1)	86 (19.8)	87 (20.3)
Mild	138 (32.4)	122 (28.1)	134 (30.9)	116 (27.1)
Moderate	181 (42.5)	211 (48.6)	167 (38.5)	175 (40.9)
Severe	60 (14.1)	44 (10.1)	47 (10.8)	50 (11.7)
Difficulty with Sputum Production, N1	426	434	434	428
Absent	35 (8.2)	20 (4.6)	37 (8.5)	41 (9.6)
Mild	140 (32.9)	147 (33.9)	137 (31.6)	130 (30.4)
Moderate	191 (44.8)	195 (44.9)	193 (44.5)	192 (44.9)
Severe	60 (14.1)	72 (16.6)	67 (15.4)	65 (15.2)

ITT=intent-to-treat.

N=Number of patients in the ITT population; n=number of patients within the specific category; N1=number of patients with an assessment of the specified symptom at baseline. Percentages were calculated as 100 x (n/N1).

Note: Baseline was defined as the last assessment prior to the first dose of study drug.

6.3.3 Baseline Pathogens

The pooled mITT population comprised 785 patients (45.7% of ITT) with 408 (47.5%) in the solithromycin group and 377 patients (43.8%) in the moxifloxacin group.

The most common pathogens identified in the pooled mITT population were *S. pneumoniae* (44.8%), *H. influenzae* (22.0%), *L. pneumophila* (20.3%), *M. pneumoniae* (18.7%), *S. aureus* (9.3%) and *M. catarrhalis* (7.8%). Table 27 shows the distribution of all pathogens in the mITT population.

In the pooled mITT-2 population, the most frequently identified pathogens were *S. pneumoniae* (27.8%), *H. influenzae* (24.2%), *M. pneumoniae* (18.9%), *S. aureus* (13.9%), *M. catarrhalis* (5.3%), *K. pneumoniae* (4.8%), *P. aeruginosa* (3.1%), and *L. pneumophila* (2.4%). Table 28 shows the distribution of all pathogens in the mITT-2 population. While the pooled mITT-2 population included fewer patients with an identified pathogen than the mITT population, these two microbiological analysis populations were qualitatively similar in terms of pathogen distribution. The main differences were fewer diagnoses of *S. pneumoniae* in the mITT-2 population due to the censoring of diagnoses established by urine antigen or respiratory sample molecular diagnostic testing and fewer patients with diagnosed *L. pneumophila* due to exclusion of serological diagnoses in this population.

Among patients with pneumococcal pneumonia in the pooled mITT-2 population with serotype data available (n=115), 55% had an *S. pneumoniae* not covered by the 13-valent pneumococcal conjugate vaccine and 37% had an *S. pneumoniae* not covered by the 23-valent pneumococcal polysaccharide vaccine.

Twenty (20) patients in the solithromycin group and 21 patients in the moxifloxacin group had bacteremia at baseline in the pooled studies. The most common pathogen isolated from blood was *S. pneumoniae* in each treatment group (solithromycin: 12 patients; moxifloxacin: 16 patients). No other pathogens were isolated from blood in > 3 patients in either treatment group.

Table 27 CABP Pathogens in the mITT Population in Individual and Pooled Phase 3 Studies

Baseline Pathogen	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral (N=235) n (%)	Moxi Oral (N=226) n (%)	Soli IV to Oral (N=173) n (%)	Moxi IV to Oral (N=153) n (%)	Soli Pooled (N=408) n (%)	Moxi Pooled (N=377) n (%)
Gram-positive Bacteria						
Streptococcus pneumoniae	96 (40.9)	102 (45.1)	79 (45.7)	76 (49.7)	175 (42.9)	177 (46.9)
Beta-haemolytic streptococci	3 (1.3)	4 (1.8)	2 (1.2)	1 (0.7)	5 (1.2)	5 (1.3)
Staphylococcus aureus	22 (9.4)	14 (6.2)	21 (12.1)	16 (10.5)	43 (10.5)	30 (8.0)
Nocardia cyriacigeorgica	0	0	0	1 (0.7)	0	1 (0.3)
Gram-negative Bacteria						
Haemophilus influenzae	80 (34.0)	55 (24.3)	18 (10.4)	20 (13.1)	98 (24.0)	75 (19.9)
Haemophilus parainfluenzae	6 (2.6)	5 (2.2)	2 (1.2)	2 (1.3)	8 (2.0)	7 (1.9)
Moraxella catarrhalis	28 (11.9)	23 (10.2)	4 (2.3)	3 (2.0)	32 (7.8)	26 (6.9)
Enterobacter cloacae	1 (0.4)	0	0	0	1 (0.2)	0
Escherichia coli	0	3 (1.3)	2 (1.2)	1 (0.7)	2 (0.5)	4 (1.1)
Klebsiella oxytoca	0	1 (0.4)	0	0	0	1 (0.3)
Klebsiella pneumoniae	7 (3.0)	5 (2.2)	9 (5.2)	3 (2.0)	16 (3.9)	8 (2.1)
Morganella morganii	0	1 (0.4)	0	0	0	1 (0.3)
Salmonella species	0	1 (0.4)	0	0	0	1 (0.3)
Serratia liquefaciens	1 (0.4)	0	0	0	1 (0.2)	0
Serratia marcescens	1 (0.4)	1 (0.4)	1 (0.6)	1 (0.7)	2 (0.5)	2 (0.5)
Acinetobacter calcoaceticus	0	0	1 (0.6)	1 (0.7)	1 (0.2)	1 (0.3)
Alcaligenes xylosoxidans	0	0	0	1 (0.7)	0	1 (0.3)
Bordetella bronchiseptica	1 (0.4)	0	0	0	1 (0.2)	0
Pasteurella multocida	0	0	1 (0.6)	0	1 (0.2)	0
Pseudomonas aeruginosa	3 (1.3)	1 (0.4)	4 (2.3)	6 (3.9)	7 (1.7)	7 (1.9)
Atypical Bacteria						
Mycoplasma pneumoniae	37 (15.7)	42 (18.6)	39 (22.5)	30 (19.6)	76 (18.6)	71 (18.8)
Legionella dumoffii	0	1 (0.4)	0	0	0	1 (0.3)
Legionella longbeachae	0	0	1 (0.6)	0	1 (0.2)	0
Legionella pneumophila	61 (26.0)	63 (27.9)	18 (10.4)	17 (11.1)	79 (19.4)	80 (21.2)

Note: Patients from Site 710 in Study 300 are excluded from the pooled data displays (2 patients in the mITT population).

Table 28 CABP Pathogens in the mITT-2 Population in Individual and Pooled Phase 3 Studies

Baseline Pathogen	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral (N=119) n (%)	Moxi Oral (N=106) n (%)	Soli IV to Oral (N=103) n (%)	Moxi IV to Oral (N=90) n (%)	Soli Pooled (N=222) n (%)	Moxi Pooled (N=196) n (%)
Gram-positive Bacteria						
Streptococcus pneumoniae	28 (23.5)	37 (34.9)	25 (24.3)	26 (28.9)	53 (23.9)	63 (32.1)
Beta-haemolytic streptococci	3 (2.5)	3 (2.8)	2 (1.9)	1 (1.1)	5 (2.3)	4 (2.0)
Staphylococcus aureus	14 (11.8)	7 (6.6)	21 (20.4)	16 (17.8)	35 (15.8)	23 (11.7)
Nocardia cyriacigeorgica	0	0	0	1 (1.1)	0	1 (0.5)
Gram-negative Bacteria						
Haemophilus influenzae	37 (31.1)	26 (24.5)	18 (17.5)	20 (22.2)	55 (24.8)	46 (23.5)
Haemophilus parainfluenzae	6 (5.0)	5 (4.7)	2 (1.9)	2 (2.2)	8 (3.6)	7 (3.6)
Moraxella catarrhalis	11 (9.2)	4 (3.8)	4 (3.9)	3 (3.3)	15 (6.8)	7 (3.6)
Enterobacter cloacae	1 (0.8)	0	0	0	1 (0.5)	0
Escherichia coli	0	3 (2.8)	2 (1.9)	1 (1.1)	2 (0.9)	4 (2.0)
Klebsiella oxytoca	0	1 (0.9)	0	0	0	1 (0.5)
Klebsiella pneumoniae	5 (4.2)	3 (2.8)	9 (8.7)	3 (3.3)	14 (6.3)	6 (3.1)
Morganella morganii	0	1 (0.9)	0	0	0	1 (0.5)
Salmonella species	0	1 (0.9)	0	0	0	1 (0.5)
Serratia liquefaciens	1 (0.8)	0	0	0	1 (0.5)	0
Serratia marcescens	1 (0.8)	1 (0.9)	1 (1.0)	1 (1.1)	2 (0.9)	2 (1.0)
Acinetobacter calcoaceticus	0	0	1 (1.0)	1 (1.1)	1 (0.5)	1 (0.5)
Alcaligenes xylosoxidans	0	0	0	1 (1.1)	0	1 (0.5)
Pateurella multocida	0	0	1 (1.0)	0	1 (0.5)	0
Pseudomonas aeruginosa	3 (2.5)	1 (0.9)	3 (2.9)	6 (6.7)	6 (2.7)	7 (3.6)
Atypical Bacteria						
Mycoplasma pneumoniae	18 (15.1)	22 (20.8)	21 (20.4)	18 (20.0)	39 (17.6)	40 (20.4)
Legionella dumoffii	0	1 (0.9)	0	0	0	1 (0.5)
Legionella longbeachae	0	0	1 (1.0)	0	1 (0.5)	0
Legionella pneumophila [a]	7 (5.9)	2 (1.9)	1 (1.0)	0	8 (3.6)	2 (1.0)
Positive via Culture	3 (2.5)	2 (1.9)	0	0	3 (1.4)	2 (1.0)
Positive via Urinary Antigen	5 (4.2)	0	1 (1.0)	0	6 (2.7)	0

Note: There were no patients from site 710 in the mITT-2 population

a. For *L. pneumophila* only, diagnosis could be by culture or urinary antigen testing in the mITT-2 population.

Solithromycin and moxifloxacin MICs for the target baseline pathogens in the mITT-2 population are shown in Table 29. When the proposed breakpoints for solithromycin were applied to the MICs of pathogens (≤ 1 µg/mL susceptible for *S. pneumoniae*, MSSA, and *M. catarrhalis*, and ≤ 4 µg/mL susceptible for *H. influenzae*), no target pathogens in the trials were resistant to solithromycin. Using CLSI breakpoints for moxifloxacin, 3.6% of MSSA were resistant to moxifloxacin and 2.1% of *H. influenzae* were non-susceptible to moxifloxacin. Although MRSA was not a target pathogen, there were 3 patients with MRSA in the pooled mITT-2 population, and 2 of these isolates were resistant to both solithromycin and moxifloxacin.

Among *S. pneumoniae* in the pooled mITT-2 population with susceptibility data (114 isolates), 29 isolates, or 25%, were macrolide-resistant. These rates of macrolide resistance are consistent with those observed in Europe (approximately 29% in the 2014 global surveillance) where the majority of *S. pneumoniae* were isolated in the trials. Solithromycin MICs were ≤ 1 µg/mL against all *S. pneumoniae*. As a class comparison, azithromycin MICs for target pathogens are shown in Table 30.

Table 29 Solithromycin and Moxifloxacin MIC Values against Target Baseline Pathogens in the Pooled mITT-2 Population

Target Baseline CABP Pathogens	Phase 3 Pooled Studies						
		Solithromycin MIC (µg/mL)			Moxifloxacin MIC (µg/mL)		
	N	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
S. pneumoniae	114	0.008	0.03	0.002 - 1	0.12	0.25	≤ 0.008 - 0.5
Macrolide-resistant	29	0.015	0.5	0.004 - 1	0.12	0.25	0.03 - 0.5
S. aureus (MSSA)	55	0.12	0.12	0.03 - 0.12	0.06	0.12	0.015 - 2
H. influenzae	94	2	2	0.25 - 4	0.03	0.06	0.008 - 8
M. catarrhalis	21	0.12	0.25	0.03 - 0.25	0.06	0.06	0.03 - 0.12
M. pneumoniae	52	≤ 0.000032	≤ 0.000032	≤ 0.000032 - 0.25	0.125	0.125	0.03 - 0.125
L. pneumophila	5	NA	NA	≤ 0.00024 - 0.016	NA	NA	0.016 - 0.016

MIC=minimum inhibitory concentration; MIC_{50}=minimum inhibitory concentration required to inhibit 50% of isolates; MIC_{90}=minimum inhibitory concentration required to inhibit 90% of isolates; MSSA=methicillin-susceptible *S. aureus*

Table 30 Azithromycin MIC Values against Target Baseline Pathogens in the Pooled mITT-2 Population

Target Baseline CABP Pathogens	Phase 3 Pooled Studies			
		Azithromycin MIC (µg/mL)		
	N	MIC_{50}	MIC_{90}	Range
S. pneumoniae	114	0.12	>32	≤ 0.015 - >32
Macrolide-resistant	29	>32	>32	0.12[a] - >32
S. aureus (MSSA)	55	2	>32	1 - >32
H. influenzae	94	1	2	0.25 - 8
M. catarrhalis	21	0.03	0.12	≤ 0.015 - 0.25
M. pneumoniae	52	0.00025	0.0005	0.000063 - 32
L. pneumophila	5	NA	NA	0.004 – 0.063

MIC=minimum inhibitory concentration; MIC_{50}=minimum inhibitory concentration required to inhibit 50% of isolates; MIC_{90}=minimum inhibitory concentration required to inhibit 90% of isolates; MSSA=methicillin-susceptible *S. aureus*
a. One macrolide-resistant isolate was resistant to erythromycin (MIC >32 µg/mL) but not azithromycin.

6.4 Study 300: Oral Solithromycin

6.4.1 Disposition of Patients

A total of 426 patients were randomized to solithromycin and 434 patients were randomized to moxifloxacin. Two patients in each group did not receive study drug and were included in the ITT population, but excluded from the Safety population. The majority of patients completed the study (> 95% in each treatment group).

Table 31 Study 300: Patient Disposition in the ITT Population

	Solithromycin Oral N=426 n (%)	Moxifloxacin Oral N=434 n (%)
Patients completing the study	**406 (95.3)**	**413 (95.2)**
Patients prematurely withdrawn from study	**20 (4.7)**	**21 (4.8)**
Reason for premature withdrawal		
Lost to follow-up	2 (0.5)	5 (1.2)
Withdrew consent	11 (2.6)	5 (1.2)
Unwilling to comply with required protocol procedures	0	1 (0.2)
Death	6 (1.4)	6 (1.4)
Other	1 (0.2)	4 (0.9)
Patients prematurely discontinuing study drug	**30 (7.0)**	**26 (6.0)**
Reason for premature discontinuation		
Adverse event	16 (3.8)	11 (2.5)
Development of a clinically significant laboratory abnormality	0	1 (0.2)
Clinical failure	6 (1.4)	5 (1.2)
Study drug not taken	2 (0.5)	2 (0.5)
Other	6 (1.4)	7 (1.6)

ITT=intent-to-treat.
N=Number of patients in the ITT population; n=number of patients within a specific category. Percentages were calculated as 100 x (n/N).

6.4.2 Co-Primary Efficacy Outcomes: Early Clinical Response in the ITT and Pooled mITT Populations

In the ITT population of Study 300, 78.2% of patients in the solithromycin group and 77.9% of patients in the moxifloxacin group met ECR criteria and were responders (treatment difference: 0.29; 95% CI: -5.5, 6.1) (Table 32). The lower bound of the 95% CI for the treatment difference was greater than -10%, demonstrating that solithromycin was non-inferior to moxifloxacin. The most common reason for nonresponse in each group was failure to achieve improvement in ≥ 2 baseline symptoms of CABP (61.7% of solithromycin non-responders; 65.5% of moxifloxacin non-responders; Table 33).

ECR in the pooled mITT population for Study 300 and 301 was a co-primary efficacy outcome for Study 300. In the pooled mITT analysis, responder rates for ECR were 77.2% in the solithromycin group and 78.9% in the moxifloxacin group (treatment difference: -1.69; 95% CI: -7.4, 4.2; Table 32). The lower bound of the 95% CI for the treatment difference was greater than -15%, demonstrating that solithromycin was non-inferior to moxifloxacin.

Table 32 Study 300: Early Clinical Response in the ITT Population and Pooled Phase 3 mITT Population

Early Clinical Response	Study 300 ITT Population		Pooled Studies 300 and 301 mITT Population[a]	
	Solithromycin Oral N=426 n (%)	Moxifloxacin Oral N=434 n (%)	Solithromycin Pooled N=408 n (%)	Moxifloxacin Pooled N=379 n (%)
Responder	333 (78.2)	338 (77.9)	315 (77.2)	299 (78.9)
Difference (95% CI)[b]	0.29 (-5.5, 6.1)		-1.69 (-7.4, 4.2)	
Non-responder (including indeterminate)	93 (21.8)	96 (22.1)	93 (22.8)	80 (21.1)
Non-responder	81 (19.0)	84 (19.4)	81 (19.9)	72 (19.0)
Indeterminate	12 (2.8)	12 (2.8)	12 (2.9)	8 (2.1)

ECR=Early Clinical Response; ITT=intent-to-treat; mITT=microbiological intent-to-treat.
N=number of patients in the ITT or pooled mITT population; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).
a. Pooled mITT population from studies 300 and 301, including patients from Site 710 in Study 300.
b. Observed difference in clinical responder rates (solithromycin minus moxifloxacin). For ITT population, CI was calculated using an unadjusted continuity corrected Z-test. For pooled mITT population, adjusted confidence intervals were calculated using the Miettinen and Nurminen method with adjustment for the stratification factor of study. Stratum weights were the inverse variance of each effect size.

Table 33 Study 300: Reasons for Nonresponse in the ITT Population

	Solithromycin Oral n (%)	Moxifloxacin Oral n (%)
Non-responders, N	81	84
Did not improve in ≥ 2 symptoms of CABP	50 (61.7)	55 (65.5)
Worsening of any symptom of CABP	31 (38.3)	28 (33.3)
Received a concomitant antibiotic for treatment of CABP prior to assessment of ECR	10 (12.3)	11 (13.1)
Died from any cause through the LFU visit	6 (7.4)	6 (7.1)

ECR=Early Clinical Response; ITT=intent-to-treat; LFU=Late Follow-up.
N=number of non-responders in the ITT population; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).

6.4.2.1 Sensitivity Analyses

Sensitivity analyses were conducted in the ITT population to determine a CI adjusted for the randomization strata and to assess the effect of missing data on the treatment difference and CI (Table 34). The adjusted CIs (adjusted for either the as-randomized strata or the actual strata per the electronic case report form [eCRF]) were only slightly different from the unadjusted CIs, and the lower bound remained above -10% in all analyses.

In the primary analysis, patients with missing data and indeterminate response at the ECR assessment were treated as failures. For the sensitivity analyses, 2 different approaches were utilized. In one sensitivity analysis, patients with missing data (i.e. indeterminate response) were considered responders rather than non-responders. In the other analysis, multiple imputation methods were utilized. Results of both analyses demonstrated that missing data had no notable impact on the primary efficacy results (Table 34).

Table 34 Study 300: ECR by As-randomized Strata, Strata per the eCRF, and Patients with Missing Data Considered Responders in the ITT Population

Sensitivity Analysis Early Clinical Response	Solithromycin Oral N=426 n (%)	Moxifloxacin Oral N=434 n (%)	Treatment Difference (95% CI)
As-randomized strata			
Responder	333 (78.2)	338 (77.9)	0.29 (-5.3, 5.8)
Strata per the eCRF			
Responder	333 (78.2)	338 (77.9)	0.29 (-5.2, 5.9)
Patients with missing data considered responders, as randomized strata			
Responder	345 (81.0)	350 (80.6)	0.34 (-5.2, 5.8)
Multiple Imputation Analysis[a]			
Responder	(80.2)	(80.0)	0.3 (-5.2,5.8)

CI=confidence interval; eCRF=electronic case report form; ITT=intent-to-treat.
N=number of patients in the ITT population; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).
Note: Difference in clinical responder rates is solithromycin minus moxifloxacin. Adjusted CIs were calculated using the Miettinen and Nurminen method with adjustment for the stratification factors of geographic region and PORT risk class. Due to small numbers in the cells, adjustment for asthma/COPD could not be done and Europe and North America were combined into one region. Cochran-Mantel-Haenszel weights were used for the strata.
a. Markov chain Monte Carlo full data imputation used. 10 datasets created using geographic region, PORT risk class, asthma/chronic obstructive pulmonary disease, and receipt of prior antibiotics for CABP as predictive variables.

6.4.3 Secondary and Additional Efficacy Endpoints

6.4.3.1 ECR with Vital Signs in ITT Population

An additional endpoint evaluated in the ITT population was ECR including criteria for improvement in abnormal baseline vital signs (i.e. fever, hypotension, tachycardia, and tachypnea) to normal at the ECR visit. Similar percentages of solithromycin (48.6%) and moxifloxacin (48.4%) patients achieved ECR with vital signs endpoint improvement (treatment difference: 0.20; 95% CI: -6.7, 7.1; Table 35). Tachypnea was the vital sign most often responsible for non-response in patients who were ECR responders but who failed to meet this endpoint (accounting for nonresponse in 88% and 84% of moxifloxacin and solithromycin patients, respectively, who had met response criteria for ECR).

Table 35 Study 300: ECR with Inclusion of Improvement in Vital Signs in the ITT Population

Early Clinical Response	Solithromycin Oral N=426 n (%)	Moxifloxacin Oral N=434 n (%)
Responder	207 (48.6)	210 (48.4)
Difference (95% CI)	0.20 (-6.7, 7.1)	
Non-responder (including indeterminate)	219 (51.4)	224 (51.6)
Non-responder	207 (48.6)	212 (48.8)
Indeterminate	12 (2.8)	12 (2.8)

CI=confidence interval; ITT=intent-to-treat.
N=number of patients in the ITT population; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).
Note: Difference in clinical responder rates is solithromycin minus moxifloxacin; CIs were calculated using an unadjusted continuity corrected Z-test

6.4.3.2 ECR in mITT Population

The percentage of responders was 74.9% for solithromycin and 78.8% for moxifloxacin (treatment difference: -3.87; 95% CI: -12.0, 4.3; Table 36). Solithromycin was non-inferior to moxifloxacin in this single study in the mITT population given that the lower bound of the 95% CI for the treatment difference was greater than -15%. The most common reason for nonresponse was failure to achieve improvement in ≥ 2 symptoms of CABP.

Table 36 Study 300: Early Clinical Response in the mITT Population

Early Clinical Response	Solithromycin Oral N=235 n (%)	Moxifloxacin Oral N=226 n (%)
Responder	176 (74.9)	178 (78.8)
Difference (95% CI)[a]	-3.87 (-12.0, 4.3)	
Non-responder (including indeterminate)	59 (25.1)	48 (21.2)
Non-responder	53 (22.6)	42 (18.6)
Indeterminate	6 (2.6)	6 (2.7)
Reasons for non-response[b]		
Did not improve in ≥ 2 symptoms of CABP	35 (66.0)	28 (66.7)
Received a concomitant antibiotic for treatment of CABP prior to assessment of ECR	4 (7.5)	6 (14.3)
Died from any cause through the LFU visit	3 (5.7)	4 (9.5)

CI=confidence interval; ECR=early clinical response; LFU=late follow-up; mITT=microbiological intent-to-treat
N=number of patients in the mITT population; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).

a. Difference in clinical responder rates is solithromycin minus moxifloxacin; CI was calculated using an unadjusted continuity corrected Z-test
b. Percentages of non-responders

6.4.3.3 Investigator Assessment of Clinical Response at SFU

Clinical success rates at SFU as determined by the investigator were high in both treatment groups. In the ITT population, 360 (84.5%) patients in the solithromycin group and 376 (86.6%) patients in the moxifloxacin group achieved clinical success at SFU based on investigator assessment (Table 37).

The primary reason for failure at SFU in both treatment groups was that the patient was assessed as a failure at the EOT Visit (10.1% for solithromycin and 7.1% for moxifloxacin) and thus considered a failure at SFU. The number of failures after EOT (i.e. newly determined from EOT to the SFU Visit) was low in both treatment groups (1.4% for solithromycin and 1.6% for moxifloxacin).

In the CE-SFU population, 342 (88.1%) patients in the solithromycin group and 356 (91.3%) patients in the moxifloxacin group achieved clinical success based on investigator assessment.

Table 37 Study 300: Clinical Response at SFU in the ITT and CE-SFU Populations

Population Clinical Response at SFU	Solithromycin Oral n (%)	Moxifloxacin Oral n (%)
ITT Population	N=426	N=434
Success	**360 (84.5)**	**376 (86.6)**
Difference (95% CI)[a]	-2.13 (-7.1, 2.8)	
Failure (includes indeterminate)	**66 (15.5)**	**58 (13.4)**
Failure	49 (11.5)	38 (8.8)
Reasons for clinical failure[b]		
Classified as failure at the EOT assessment and carried forward to SFU	43 (10.1)	31 (7.1)
Lack of resolution or worsening of baseline signs and symptoms and required additional antibacterial medication	25 (5.9)	10 (2.3)
Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication	13 (3.1)	19 (4.4)
Study drug discontinued due to an AE and required additional antibacterial medication	13 (3.1)	7 (1.6)
Death from any cause through EOT	3 (0.7)	2 (0.5)
Classified as failure from EOT through SFU	6 (1.4)	7 (1.6)
Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication	5 (1.2)	6 (1.4)
Death from any cause from EOT to SFU	1 (0.2)	2 (0.5)[c]
Indeterminate	17 (4.0)	20 (4.6)
Reasons for indeterminate clinical response:		
Classified as Indeterminate at the EOT assessment and considered indeterminate at SFU Assessment	10 (2.3)	11 (2.5)
Lost to follow-up prior to EOT assessment, or missed EOT visit	3 (0.7)	3 (0.7)
Other Reason	7 (1.6)	8 (1.8)
Classified as indeterminate at SFU	7 (1.6)	9 (2.1)
Lost to follow-up after EOT assessment, or missed SFU visit	3 (0.7)	6 (1.4)
Other Reason	4 (0.9)	3 (0.7)

Population Clinical Response at SFU	Solithromycin Oral n (%)	Moxifloxacin Oral n (%)
CE-SFU	N=388	N=390
Success	**342 (88.1)**	**356 (91.3)**
Difference (95% CI)[a]	-3.14 (-7.7, 1.4)	
Failure (including indeterminate)	**46 (11.9)**	**34 (8.7)**
Failure	46 (11.9)	33 (8.5)
Indeterminate	0	1 (0.3)[d]

AE=adverse event; CE-SFU=clinically evaluable at short-term follow up visit; CI=confidence interval; EOT=end of treatment; ITT=intent-to-treat; SFU=short-term follow-up.

N=number of patients in the ITT or CE-SFU population; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).

a. Difference in clinical success rates is solithromycin minus moxifloxacin; CIs were calculated using a continuity corrected Z-test.
b. Reasons for failure are not mutually exclusive.
c. One patient was a clinical failure at EOT for lack of resolution of CABP symptoms and died between EOT and SFU.
d. Investigator coded the outcome for this patient as indeterminate. However, study drug was discontinued due to an adverse event (bilateral leg pain after one dose of medication).

6.4.3.4 Outcome at SFU Based on CABP Signs and Symptoms

Several pre-specified efficacy outcomes were programmatically defined at SFU to evaluate symptom-based outcomes at the later time point.

6.4.3.4.1 Response at SFU Based on Major CABP Symptoms

Response at SFU based on major CABP symptoms was defined as the absence of chest pain and sputum production, and the absence of, or improvement from baseline in, cough and dyspnea. Similar proportions of patients in the solithromycin (73.9%) and moxifloxacin (75.8%) groups achieved response at SFU based on analysis of the major CABP symptoms in the ITT population (Table 38). In the CE-SFU population, response rates in each treatment group were slightly higher than in the ITT population and comparable between groups.

Table 38 Study 300: Response at SFU Based on Major Symptoms of CABP in the ITT and CE-SFU Populations

Population	Response at SFU Based on Major Symptoms of CABP	Solithromycin Oral n (%)	Moxifloxacin Oral n (%)
ITT	N	426	434
	Response	315 (73.9)	329 (75.8)
	Difference (95% CI)[a]	-1.86 (-7.9, 4.2)	
	Failure	79 (18.5)	76 (17.5)
	Indeterminate	32 (7.5)	29 (6.7)
CE-SFU	N	388	390
	Response	300 (77.3)	308 (79.0)
	Difference (95% CI)[a]	-1.65 (-7.7, 4.4)	
	Failure	74 (19.1)	71 (18.2)
	Indeterminate	14 (3.6)	11 (2.8)

ITT=intent-to-treat; CI=confidence interval; CE=clinically evaluable; SFU=short-term follow-up
N=number of patients in the ITT or CE-SFU population; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).
a. Difference in clinical success rates is solithromycin minus moxifloxacin; CIs were calculated using a continuity corrected Z-test.

6.4.3.4.2 Sustained ECR

Sustained ECR was defined as response for the primary efficacy outcome that was maintained through SFU, and which required chest pain and sputum production to be absent, and cough and dyspnea to be absent or improved since baseline.

In the ITT population, sustained ECR was achieved by 64.1% of patients in the solithromycin group and 63.8% of patients in the moxifloxacin group (Table 39).

Table 39 Study 300: Sustained ECR at the SFU Visit in the ITT Population

Sustained Early Clinical Response	Solithromycin Oral (N=426) n (%)	Moxifloxacin Oral (N=434) n (%)
Responder	273 (64.1)	277 (63.8)
Difference (95% CI)[a]	0.26 (-6.4, 6.9)	
Non-responder (including indeterminate)	153 (35.9)	157 (36.2)
Non-responder	128 (30.0)	133 (30.6)
Indeterminate	25 (5.9)	24 (5.5)

ECR=early clinical response; SFU=short term follow-up; ITT=intent-to-treat; CI=confidence interval
N=number of patients in the ITT population; n=number of patients in the specific category. Percentages were calculated as 100 x (n/N).
Note: Difference in responder rates is solithromycin minus moxifloxacin.
a. The confidence interval (CI) is calculated using an unadjusted continuity corrected Z-test.

6.4.3.4.3 Resolution of Baseline CABP Symptoms

In a further analysis, an outcome that required resolution of all baseline symptoms of CABP (cough, dyspnea, chest pain, and difficulty with sputum production) was examined. Resolution of all baseline symptoms of CABP on Day 4 (72 hours) at the EOT visit and at the SFU visit is presented in Table 40. Similar proportions of patients in each treatment group achieved resolution of baseline CABP symptoms at each assessment. As expected, even with effective antimicrobial therapy, complete CABP symptom resolution requires time.

Table 40 Study 300: Resolution of All Baseline Symptoms of CABP on Day 4, at EOT, and SFU in the ITT Population

Visit	Solithromycin Oral N=426 n/N1 (%)	Moxifloxacin Oral N=434 n/N1 (%)	Treatment Difference (95% CI)[a]
Day 4	7/408 (1.7)	11/417 (2.6)	-0.92 (-3.2, 1.3)
EOT	100/402 (24.9)	115/412 (27.9)	-3.04 (-9.3, 3.3)
SFU	219/394 (55.6)	232/404 (57.4)	-1.84 (-9.0, 5.3)

EOT=end of treatment; SFU=short-term follow-up visit.

N=number of patients in the ITT population; n=number of patients with resolution of all baseline symptoms of CABP at the specified visit; N1=number of patients with non-missing assessments of all baseline signs and symptoms at the specified visit. Percentages were calculated as 100 x (n/N1).

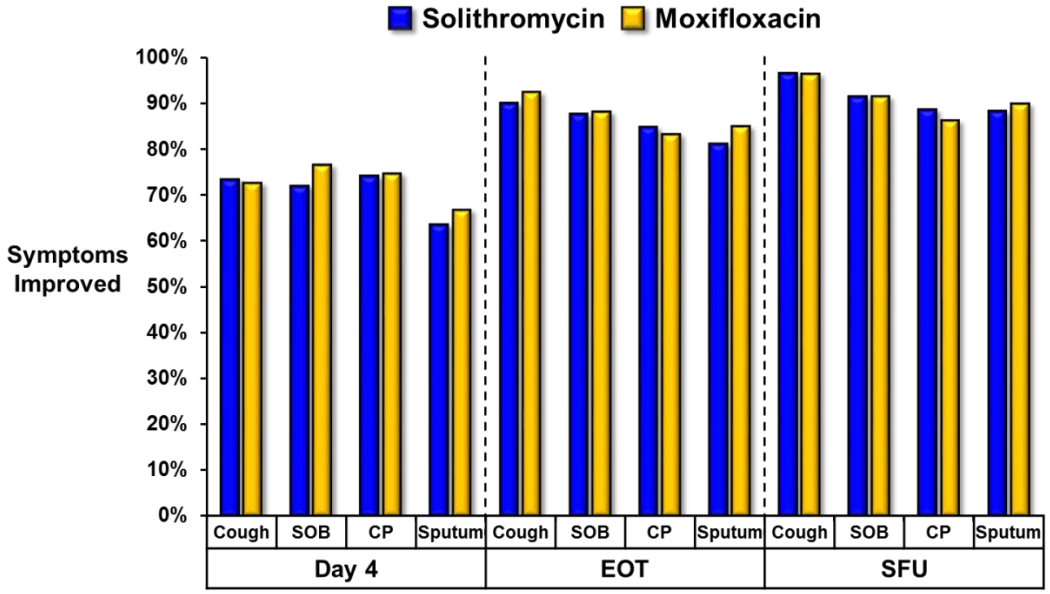
Note: Resolution was defined as absence of all baseline symptoms of CABP.

a. Difference in clinical success rates is solithromycin minus moxifloxacin; CIs were calculated using a continuity corrected Z-test

6.4.3.4.4 Rates of CABP Symptom Improvement by Study Drug and Visit

Figure 15 illustrates patient symptom improvement for the solithromycin and moxifloxacin treatment groups at the Day 4 (ECR), EOT, and SFU assessment time points. In both treatment groups, CABP symptoms showed similar improvement at each subsequent time point.

Figure 15 Study 300: Percentage of Patients with CABP Symptom Improvement Compared with Baseline at Day 4, EOT, and SFU in the ITT Population



SOB=shortness of breath; CP=Chest pain; EOT=end of treatment; SFU=short-term follow-up

6.5 Study 301: IV/Oral Solithromycin

6.5.1 Disposition of Patients

A total of 434 patients were randomized to solithromycin and 429 patients were randomized to moxifloxacin. One patient in the solithromycin group and 4 patients in the moxifloxacin group did not receive study drug; these patients were included in the ITT population but excluded from the Safety population. One patient was randomized to solithromycin but received moxifloxacin on Day 1 (and received no other study drug); this patient was included in the solithromycin group in all populations except the Safety population (Table 41).

The majority of patients completed the study (> 93% in each treatment group). More patients in the solithromycin group withdrew from the study due to withdrawn consent and AEs, primarily due to infusion site events.

Most patients in each treatment group transitioned to oral treatment during the study, and the timing and pattern of patients switching to oral therapy was similar in each group (Figure 21 in Section 7.1). Likewise, a similar percentage of patients in each treatment group remained on IV therapy for 7 days: 21.8% of solithromycin patients and 25.1% of moxifloxacin patients.

Table 41 Study 301: Patient Disposition in the ITT Population

	Solithromycin IV to Oral N=434 n (%)	Moxifloxacin IV to Oral N=429 n (%)
Patients completing the study	**407 (93.8)**	**408 (95.1)**
Patients prematurely withdrawing from study	**27 (6.2)**	**21 (4.9)**
Reason for premature withdrawal		
Lost to follow-up	0	0
Withdrew consent	15 (3.5)	8 (1.9)
Unwilling to comply with required protocol procedures	0	1 (0.2)
Death	5 (1.2)	7 (1.6)
Adverse event	5 (1.2)	1 (0.2)
Other	2 (0.5)	4 (0.9)
Patients prematurely discontinuing study drug	**46 (10.6)**	**38 (8.9)**
Reason for premature discontinuation		
Adverse event	20 (4.6)	16 (3.7)
Development of a clinically significant laboratory abnormality	1 (0.2)	2 (0.5)
Clinical failure	14 (3.2)	8 (1.9)
Study drug not taken	1 (0.2)	2 (0.5)[a]
Other[b]	10 (2.3)	10 (2.3)
Withdrew consent	8 (1.8)	7 (1.6)

ITT=intent-to-treat.

N=Number of patients in the ITT population; n=number of patients within a specific category. Percentages were calculated as 100 × (n/N).

a. 2 additional moxifloxacin patients did not take study drug as they withdrew consent from the study prior to the first dose.

b. The "other" category in the solithromycin group included withdrew consent, incorrect study drug given, and received other antibiotics, the "other" category in the moxifloxacin group included noncompliance with oral therapy, withdrew consent, confirmation of pulmonary tuberculosis, study drug not taken, clinical failure, and death.

6.5.2 Primary Efficacy Endpoint: Early Clinical Response (ECR)

In the ITT population, 79.3% of patients in the solithromycin group and 79.7% of patients in the moxifloxacin group were responders in the ECR assessment (treatment difference: -0.46; 95% CI: -6.1, 5.2; Table 42). The lower bound of the 95% CI for the treatment difference was greater than -10%, demonstrating that solithromycin was non-inferior to moxifloxacin. The most common reason for non-response in each group was failure to achieve improvement in ≥ 2 baseline symptoms of CABP (63.2% of solithromycin non-responders; 60.3% of moxifloxacin non-responders).

Table 42 Study 301: Early Clinical Response in the ECR in the ITT Population

Early Clinical Response	Solithromycin IV to Oral N=434 n (%)	Moxifloxacin IV to Oral N=429 n (%)
Responder	**344 (79.3)**	**342 (79.7)**
Difference (95% CI)[a]	-0.46 (-6.1, 5.2)	
Non-responder (including indeterminate)	90 (20.7)	87 (20.3)
Non-responder	76 (17.5)	78 (18.2)
Indeterminate	14 (3.2)	9 (2.1)
Reasons for nonresponse[b]		
Did not improve in ≥ 2 symptoms of CABP	48 (63.2)	47 (60.3)
Worsening of any symptom of CABP	12 (15.8)	22 (28.2)
Received a concomitant antibiotic for treatment of CABP prior to assessment of ECR	17 (22.4)	18 (23.1)
Died from any cause through the LFU visit	5 (6.6)	7 (9.0)

ECR=Early Clinical Response; ITT=intent-to-treat; LFU=Late Follow-up.

N=Number of patients in the ITT population; n=number of patients within a specific category. Percentages were calculated as 100 × (n/N).

a. Difference in clinical responder rates is solithromycin minus moxifloxacin; CI was calculated using an unadjusted continuity corrected Z-test

b. Percentage of non-responders

6.5.2.1 Sensitivity Analyses

For the primary efficacy outcome of ECR, sensitivity analyses were conducted to determine a CI adjusted for the randomization strata and to assess the effect of missing data on the treatment difference and CI. The adjusted CIs (adjusted for either the as randomized strata or the actual strata per the eCRF) were only slightly different from the unadjusted CIs, and the lower bound of the CI remained above -10% in all analyses (Table 43).

In another sensitivity analysis, if patients with missing data (i.e. indeterminate response) were considered responders rather than non-responders, the treatment difference remained the same as in the primary analysis, and the lower bound of the CI was above -10%. The multiple imputation analysis resulted in a treatment difference of 0.40 (-4.8, 5.7), showing that missing data had little impact on the efficacy results. As in Study 300, the primary outcome was not sensitive to variation in statistical methodology or the utilization of different methods for handling missing data.

Table 43 Study 301: ECR by As-randomized Strata, Strata per the eCRF, and Patients with Missing Data Considered Responders in the ITT Population

Sensitivity Analysis Early Clinical Response	Solithromycin IV to Oral N=434 n (%)	Moxifloxacin IV to Oral N=429 n (%)	Treatment Difference (95% CI)
As-randomized strata			
Responder	344 (79.3)	342 (79.7)	-0.46 (-5.9, 5.0)
Strata per the eCRF			
Responder	344 (79.3)	342 (79.7)	-0.46 (-5.9, 5.0)
Patients with missing data considered responders			
Responder	358 (82.5)	351 (81.8)	0.67 (-4.7, 6.0)
Multiple Imputation Analysis[a]			
Responder	(81.8)	(81.4)	0.40 (-4.8, 5.7)

CI=confidence interval; eCRF=electronic case report form; ITT=intent-to-treat.

N=Number of patients in the ITT population; n=number of patients within a specific category. Percentages are calculated as 100 × (n/N).

Note: Difference in clinical responder rates (solithromycin minus moxifloxacin). Adjusted CIs were calculated using the Miettinen and Nurminen method with adjustment for the stratification factors of geographic region and PORT risk class. Due to small numbers in the cells, adjustment for asthma/COPD could not be done and Europe and North America were combined into one region. Cochran-Mantel-Haenszel weights were used for the strata.

a. Markov chain Monte Carlo full data imputation used. 10 datasets created using geographic region, PORT risk class, asthma/chronic obstructive pulmonary disease, and receipt of prior antibiotics for CABP as predictive variables.

6.5.3 Additional Efficacy Endpoints

6.5.3.1 ECR with Improvement in Vital Signs in ITT Population

Similar percentages of patients in the solithromycin (42.6%) and moxifloxacin (38.9%) groups achieved ECR with the vital signs endpoint in Study 301 (treatment difference: 3.70; 95% CI: -3.1, 10.5) (Table 44). Tachypnea was the vital sign most often responsible for non-response in patients who were ECR responders but who failed to meet this endpoint (accounting for 95% and 92% of moxifloxacin and solithromycin patients, respectively, who met response criteria for ECR but not for this endpoint).

Table 44 Study 301: ECR with Inclusion of Improvement in Vital Signs in the ITT Population

Early Clinical Response	Solithromycin IV to Oral N=434 n (%)	Moxifloxacin IV to Oral N=429 n (%)
Responder	185 (42.6)	167 (38.9)
Difference (95% CI)[a]	3.70 (-3.1, 10.5)	
Non-responder (including Indeterminate)	249 (57.4)	262 (61.1)
Non-responder	235 (54.1)	253 (59.0)
Indeterminate	14 (3.2)	9 (2.1)

CI=confidence interval; ITT=intent-to-treat.
N=Number of patients in the ITT population; n=number of patients within a specific category. Percentages were calculated as 100 × (n/N).
a. Difference in clinical responder rates is solithromycin minus moxifloxacin; CIs were calculated using an unadjusted continuity corrected Z-test

6.5.3.2 ECR in mITT Population

In the evaluation of ECR in the mITT population of Study 301, the percentage of responders was 80.3% for solithromycin and 79.1% for moxifloxacin (treatment difference: 1.26; 95% CI: -8.1, 10.6; Table 45). Given that the lower bound of the 95% CI for the treatment difference was greater than -15%, solithromycin was non-inferior to moxifloxacin in this single study in the mITT population. The most common reason for non-response was failure to achieve improvement in ≥ 2 symptoms of CABP.

Table 45 Study 301: Early Clinical Response in the mITT Population

Early Clinical Response	Solithromycin IV to Oral N=173 n (%)	Moxifloxacin IV to Oral N=153 n (%)
Responder	139 (80.3)	121 (79.1)
Difference (95% CI)[a]	1.26 (-8.1, 10.6)	
Non-responder (include indeterminate)	34 (19.7)	32 (20.9)
Non-responder	28 (16.2)	30 (19.6)
Indeterminate	6 (3.5)	2 (1.3)
Reasons for nonresponse[b]		
Did not improve in ≥ 2 symptoms of CABP	21 (75.0)	18 (60.0)
Worsening of any symptom of CABP	3 (10.7)	8 (26.7)
Received a concomitant antibiotic for treatment of CABP prior to assessment of ECR	6 (21.4)	6 (20.0)
Died from any cause through the LFU visit	1 (3.6)	2 (6.7)

CI=confidence interval; ECR=early clinical response; LFU=late follow up; mITT=microbiological intent-to-treat.
N=Number of patients in the mITT population; n=number of patients within a specific category. Percentages are calculated as 100 × (n/N).
a. Difference in clinical responder rates is solithromycin minus moxifloxacin; CI was calculated using an unadjusted continuity corrected Z-test
b. Percentage of non-responders

6.5.3.3 Investigator Assessment of Clinical Response at SFU

As in Study 300, clinical success rates at SFU as determined by the investigator were high in both treatment groups in Study 301, although they were higher in the moxifloxacin treatment group. Solithromycin clinical success rates at SFU were nearly identical in each of the Phase 3 studies.

In the ITT population of Study 301, therapy for 84.6% of patients receiving solithromycin and 88.6% of patients receiving moxifloxacin was considered successful by investigators at the SFU visit (Table 46). EOT failures that were carried forward accounted for the majority of SFU failures (42 of 54 for solithromycin patients, and 31 of 35 for moxifloxacin patients). In the CE-SFU population, clinical success rates as assessed by the investigator were high for both groups, 86.4% for solithromycin and 92.5% for moxifloxacin. This 6.1% observed treatment difference is attributable to multiple factors. Ten patients in the solithromycin group compared with only 1 patient in the moxifloxacin group discontinued study drug due to an infusion site AE and subsequently received a non-study antibiotic. Five of the solithromycin failures were directly attributable to an interruption in IV study drug supply leading the investigator to select alternative antibiotic therapy (categorized by definition as failure), and occurred only in the solithromycin group. In addition, 18 solithromycin treatment successes were censored (vs. 9 for moxifloxacin) due to an out-of-window assessment. Collectively, these three parameters (effect of IV infusion pain, drug supply interruption, and analysis-window driven censoring of populations) influenced outcome rates.

Table 46 Study 301: Clinical Response at SFU in the ITT Population

Population Clinical Response at SFU	Solithromycin IV to Oral n (%)	Moxifloxacin IV to Oral n (%)
ITT	**N=434**	**N=429**
Success	367 (84.6)	380 (88.6)
Difference (95% CI)[a]	-4.02 (-8.8, 0.8)	
Failure (includes indeterminate)	**67 (15.4)**	**49 (11.4)**
Failure	54 (12.4)	35 (8.2)
Reasons for clinical failure[b]:		
Classified as failure at the EOT assessment and carried forward to SFU	42 (9.7)	31 (7.2)
Lack of resolution or worsening of baseline signs and symptoms and required additional antibacterial medication	17 (3.9)	10 (2.3)
Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication	9 (2.1)	9 (2.1)
Study drug discontinued due to an AE and required additional antibacterial medication	15 (3.5)	10 (2.3)
Death from any cause through EOT	3 (0.7)	4 (0.9)
Classified as failure from EOT through SFU	12 (2.8)	4 (0.9)
Development of new signs and symptoms, complications, or radiologic findings of CABP and required additional antibacterial medication	10 (2.3)[c]	3 (0.7)
Death from any cause from EOT to SFU	1 (0.2)	2 (0.2)[d]

Population Clinical Response at SFU	Solithromycin IV to Oral n (%)	Moxifloxacin IV to Oral n (%)
Indeterminate	**13 (3.0)**	**14 (3.3)**
Reasons for indeterminate clinical response:		
Classified as Indeterminate at the EOT assessment and considered indeterminate at SFU Assessment	11 (2.5)	11 (2.6)
Lost to follow-up prior to EOT assessment, or missed EOT visit	2 (0.5)	2 (0.5)
Other Reason	9 (2.1)	9 (2.1)
Classified as indeterminate at SFU	2 (0.5)	3 (0.7)
Lost to follow-up after EOT assessment, or missed SFU visit	0	0
Other Reason	2 (0.5)	3 (0.7)
CE-SFU	**N=391**	**N=388**
Success	**338 (86.4)**	**359 (92.5)**
Difference (95% CI)[a]	-6.08 (-10.6,-1.5)	
Failure	**53 (13.6)**	**29 (7.5)**

AE=adverse event; CE=clinically evaluable; CI=confidence interval; EOT=end of treatment; ITT=intent-to-treat SFU=short-term follow-up.

N=Number of patients in the ITT population; n=number of patients within a specific category. Percentages were calculated as 100 × (n/N).

a. Difference in clinical success rates is solithromycin minus moxifloxacin; CIs were calculated using a continuity corrected Z-test.
b. Reasons for failure are not mutually exclusive.
c. One additional patient in the solithromycin group did not have a reason for failure recorded on the eCRF.
d. One patient in the moxifloxacin group was a clinical failure at EOT for lack of resolution of CABP symptoms and died between EOT and SFU. This patient is counted only once in the classified as failure between EOT and SFU line.

6.5.3.4 Outcome at SFU Based on CABP Symptoms

Symptom-based efficacy outcomes in Study 301 were very similar in the solithromycin and moxifloxacin treatment groups.

6.5.3.4.1 Response at SFU Based on Major CABP Symptoms

Similar proportions of patients in the solithromycin (79.7%) and moxifloxacin (76.9%) groups achieved response at SFU based on analysis of the major CABP symptoms in the ITT population (Table 47). Response in the CE-SFU population were slightly higher than the ITT population and comparable between groups.

Table 47 Study 301: Response at SFU Based on Major Symptoms of CABP in the ITT and CE-SFU Populations

Population	Response at SFU Based on Major Symptoms of CABP	Solithromycin IV to Oral n (%)	Moxifloxacin IV to Oral n (%)
ITT	N	434	429
	Response	346 (79.7)	330 (76.9)
	Difference (95% CI)[a]	2.80 (-2.9, 8.5)	
	Failure	59 (13.6)	72 (16.8)
	Indeterminate	29 (6.7)	27 (6.3)
CE-SFU	N	391	388
	Response	317 (81.1)	310 (79.9)
	Difference (95% CI)[a]	1.18 (-4.7, 7.0)	
	Failure	56 (14.3)	65 (16.8)
	Indeterminate	18 (4.6)	13 (3.4)

ITT=intent-to-treat; CI=confidence interval; CE=clinical evaluation; SFU=short-term follow-up.
N=Number of patients in the ITT or CE-SFU population; n=number of patients within a specific category. Percentages were calculated as 100 × (n/N).
a. Difference in clinical success rates is solithromycin minus moxifloxacin; CIs were calculated using a continuity corrected Z-test

6.5.3.4.2 Sustained ECR

In the ITT population, sustained ECR (defined in Section 6.4.3.4.1) was achieved by 68.4% of patients in the solithromycin group and 67.6% of patients in the moxifloxacin group (Table 48).

Table 48 Study 301: Sustained ECR at the SFU Visit in the ITT Population

Sustained Early Clinical Response	Solithromycin IV to Oral (N=434) n (%)	Moxifloxacin IV to Oral (N=429) n (%)
Responder	297 (68.4)	290 (67.6)
Difference (95% CI)[a]	0.83 (-5.6, 7.3)	
Non-responder (including indeterminate)	137 (31.6)	139 (32.4)
Non-responder	117 (27.0)	125 (29.1)
Indeterminate	20 (4.6)	14 (3.3)

ECR=early clinical response; SFU=short term follow-up; ITT=intent-to-treat; CI=confidence interval.
N=Number of patients in the ITT population; n=number of patients within a specific category. Percentages were calculated as 100 × (n/N).
a. Difference in clinical success rates is solithromycin minus moxifloxacin; the confidence interval (CI) is calculated using an unadjusted continuity corrected Z-test.

6.5.3.4.3 Resolution of Baseline CABP Symptoms

Table 49 presents resolution of all baseline symptoms of CABP (cough, dyspnea, chest pain, and difficulty with sputum production) in the solithromycin and moxifloxacin groups on Day 4, at the EOT visit, and at the SFU visit. Slightly higher percentages of solithromycin patients achieved complete symptom resolution in the cardinal symptoms of CABP at each analysis time point.

Table 49 Study 301: Resolution of All Baseline Symptoms of CABP on Day 4, at EOT, and SFU in the ITT Population

Visit	Solithromycin IV to Oral N=434 n/N1 (%)	Moxifloxacin IV to Oral N=429 n/N1 (%)	Treatment Difference (95% CI)[a]
Day 4	23/404 (5.7)	7/405 (1.7)	4.00 (1.1, 5.8)
EOT	141/408 (34.6)	118/403 (29.3)	5.28 (-1.4, 11.9)
SFU	253/405 (62.5)	240/402 (59.7)	2.77 (-4.2, 9.7)

EOT=end of treatment; SFU=short-term follow-up visit.

N=number of patients in the ITT population; n=number of patients with resolution of all baseline symptoms of CABP at the specified visit; N1=number of patients with non-missing assessments of all baseline signs and symptoms at the specified visit. Percentages were calculated as 100 x (n/N1).

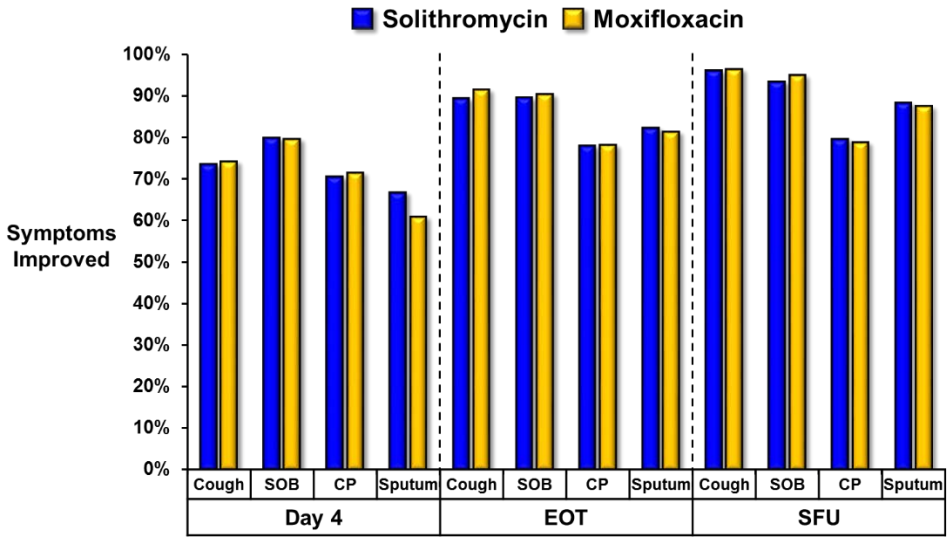
Note: Resolution was defined as absence of all baseline symptoms of CABP.

a. Difference in clinical success rates is solithromycin minus moxifloxacin; CIs were calculated using a continuity corrected Z-test

6.5.3.4.4 CABP Symptom Improvement by Visit

Figure 16 shows patient symptom improvement for the solithromycin and moxifloxacin treatment groups at the Day 4 (ECR), EOT, and SFU assessment time points. In both treatment groups, CABP symptoms showed improvement at each time point. As in Study 300, the rates of symptom improvement were similar between treatment groups at each time point.

Figure 16 Study 301: Percentage of Patients with CABP Symptom Improvement Compared with Baseline at Day 4, EOT, and SFU in the ITT Population



CP=Chest pain; EOT=end of treatment; SFU=short-term follow-up; SOB=shortness of breath

6.6 Outcomes from Integrated Analysis of Studies 300 and 301

Data from Studies 300 and 301 were pooled for pathogen specific and subgroup analyses, as the design of the protocols, including comparator drug, inclusion/exclusion criteria, clinical assessment time points, and efficacy and safety outcome measures, were nearly identical.

6.6.1 Outcomes by Pathogen

At a meeting held to discuss analysis and summarization of data for the solithromycin NDA, FDA indicated that, while molecular diagnostics are appropriate for inclusion of patients in the mITT population for efficacy analyses at a population level, more traditional, culture-based diagnoses are preferred for pathogen-specific analyses (i.e. the mITT-2 and ME-2 populations) to provide a more definitive diagnosis as well as to ensure a high percentage of accompanying susceptibility data. An exception was made for *L. pneumophila,* for which few culture-based diagnoses were made during the trials and for which UAT is a well-established definitive means of diagnosis.

Analyses are presented by target baseline pathogen for the outcomes of ECR in the mITT-2 population, as a parallel assessment of the primary endpoint for the Phase 3 trials, and investigator assessment of clinical success at the SFU visit in the ME-SFU-2 population (Table 50 and Table 51). Appendix 11.6 presents all pathogen outcomes and results by study. Success rates by pathogen were high and comparable between the solithromycin and moxifloxacin groups.

Table 50 By-Pathogen ECR Rates - Pooled Phase 3 Studies in the mITT-2 Population

Target Baseline CABP Pathogens	Pooled Phase 3 Studies	
	Solithromycin (N=222)	Moxifloxacin (N=196)
S. pneumoniae	42/53 (79.2)	51/63 (81.0)
Macrolide-resistant	12/14 (85.7)	12/15 (80.0)
S. aureus (MSSA)	23/34 (67.6)	16/21 (76.2)
H. influenzae	47/55 (85.5)	38/46 (82.6)
M. catarrhalis	14/15 (93.3)	7/7 (100)
M. pneumoniae	34/39 (87.2)	32/40 (80.0)
L. pneumophila	5/8 (62.5)[a]	2/2 (100)[a]

MSSA=methicillin-susceptible *S. aureus*

a. When serological diagnoses for *L. pneumophila* are included, ECR responder rates were 77.2% (61/79) vs. 80.0% (64/80) for solithromycin and moxifloxacin, respectively.

Table 51 By-Pathogen Clinical Success Rates at SFU - Pooled Phase 3 Studies in the ME-SFU-2 Population

Target Baseline CABP Pathogens	Pooled Phase 3 Studies	
	Solithromycin (N=207)	Moxifloxacin (N=183)
S. pneumoniae	41/49 (83.7)	53/60 (88.3)
Macrolide-resistant	13/13 (100.0)	13/14 (92.9)
S. aureus (MSSA)	27/33 (81.8)	18/21 (85.7)
H. influenzae	42/50 (84.0)	40/45 (88.9)
M. catarrhalis	13/14 (92.9)	6/7 (85.7)
M. pneumoniae	33/37 (89.2)	34/36 (94.4)
L. pneumophila	7/8 (87.5)[a]	2/2 (100.0)[a]

MSSA=methicillin-susceptible *S. aureus*

a. When serological diagnoses are included, success rates between solithromycin and moxifloxacin patients were 89.7% (70/78) vs. 93.3% (70/75), respectively.

S. pneumoniae

Patients with *S. pneumoniae* had similar ECR rates in the pooled analyses of solithromycin- and moxifloxacin patients (79.2% vs. 81.0% in the mITT-2 population, respectively). In the pooled ME-SFU-2 population at SFU, there were 8 failures in the solithromycin group (41/49, 83.7%) and 7 failures in the moxifloxacin group (53/60, 88.3%). Of note, 2 patients in the solithromycin group were responders for ECR, but discontinued study drug after the ECR assessment due to non-efficacy related AEs and therefore were considered failures at the SFU visit.

Among solithromycin patients with macrolide-resistant *S. pneumoniae*, solithromycin MICs were ≤ 0.5 µg/mL and solithromycin success rates were high for both ECR and investigator assessment

of clinical success at SFU (85.7% [12/14] at ECR and 100% [13/13] at clinical success at SFU) in this resistant subpopulation.

Outcomes in patients with pneumococcal bacteremia are discussed in Section 6.6.2.

MSSA

In both treatment groups, ECR responder rates were lower with MSSA compared to other target CABP pathogens. Similar observations of lower success rates with *S. aureus* compared to other pathogens were also observed with ceftaroline and ceftriaxone in the FOCUS 1&2 trials (Critchley 2011). At the SFU visit, clinical success rates were more comparable to those observed with other pathogens (81.8% for solithromycin and 85.7% for moxifloxacin).

H. influenzae

Solithromycin patients with *H. influenzae* had comparable ECR responder rates to those treated with moxifloxacin (85.5% vs. 82.6%, respectively). Comparable rates were also observed in clinical success at the SFU visit (84.0% vs. 88.9%, respectively).

Solithromycin, similar to other macrolides, has higher MICs against *H. influenzae* when compared to other common CABP pathogens. Despite intermediate activity in vitro, macrolides have been used to treat CABP due to *H. influenzae*, likely due to the high concentrations achieved at the site of infection (i.e. the lungs). The highest solithromycin MIC observed for *H. influenzae* in the trials was 4 µg/mL. All 5 solithromycin patients with *H. influenzae* with an MIC of 4 µg/mL were responders for ECR and clinical successes at SFU. These outcomes, coupled with univariable PK/PD subgroup analyses for *H. influenzae* using clinical data (Section 6.7), suggest that the exposures achieved with the solithromycin dosing regimen are sufficient for treating patients with *H. influenzae* despite higher MICs.

M. catarrhalis

Both solithromycin and moxifloxacin performed well in patients with CABP due to *M. catarrhalis.* ECR responder rates were 93.3% vs. 100%, and clinical success rates at SFU were 92.9% vs. 85.7% for solithromycin vs. moxifloxacin patients, respectively.

M. pneumoniae

ECR responder rates in solithromycin patients with *M. pneumoniae* compared to moxifloxacin patients were 87.2% vs. 80.0%, respectively. At the SFU visit, clinical success rates were 89.2% and 94.4%, respectively.

L. pneumophila

The number of patients with a *L. pneumophila* diagnosis in the mITT-2 and ME-SFU-2 populations was small (8 solithromycin patients and 2 moxifloxacin patients). For the assessment of ECR, there were 3 non-responders in the solithromycin group and none in the moxifloxacin group. Of the 3 non-responders, 1 was indeterminate for ECR and all 3 were considered a clinical success at

SFU by the investigator. At SFU, there was 1 failure in the solithromycin group (87.5% [7/8] and none in the moxifloxacin group (100% [2/2]).

The mITT-2 and ME-SFU-2 populations do not include diagnosis by serology. When serological diagnoses are also considered for *L. pneumophila*, ECR responder rates were 77.2% (61/79) vs. 80.0% (64/80), and clinical success rates at SFU were 89.7% (70/78) vs. 93.3% (70/75) in the solithromycin and moxifloxacin arms, respectively.

6.6.2 Outcomes in Patients with Bacteremia

Twenty patients in the solithromycin group and 21 patients in the moxifloxacin group had bacteremia identified in the Phase 3 studies. In each treatment group, *S. pneumoniae* was the most frequent pathogen isolated from blood specimens. ECR and investigator assessment of clinical success at SFU in patients with bacteremia are provided in Table 52.

Table 52 ECR and Clinical Success at SFU by Pathogen in Patients with Bacteremia - Pooled Phase 3 Studies in the mITT-2 Population

	Pooled Phase 3 Studies			
	Early Clinical Response		Investigator Assessment of Clinical Success at SFU	
Baseline Pathogens	Solithromycin (N=20)	Moxifloxacin (N=21)	Solithromycin (N=20)	Moxifloxacin (N=21)
All Bacteremic patients	13/20 (65.0)	14/21 (66.7)	14/20 (70.0)	14/21 (66.7)
S. pneumoniae	8/12 (66.7)	13/16 (81.3)	8/12 (66.7)	12/16 (75.0)
S. aureus (MSSA)	1/3 (33.3)	1/1 (100)	2/3 (66.7)	1/1 (100)
H. influenzae	2/2 (100)	-	1/2 (50.0)	-
E. coli	0/1 (0)	-	1/1 (100)	-
K. pneumoniae	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)
M. morganii	-	0/1 (0)	-	0/1 (0)
P. multocida	1/1 (100)	-	1/1 (100)	-
P. aeruginosa	-	0/1 (0)	-	0/1 (0)
Salmonella spp.	-	0/1 (0)	-	0/1 (0)

MSSA=methicillin-susceptible *S. aureus*; SFU=short-term follow-up

In CABP clinical trials, outcomes in cases of pneumococcal pneumonia with bacteremia provide a snapshot of efficacy that is of particular interest, given the certainty of the diagnosis, the severity of the disease, and the high incidence of pneumococcus (with or without bacteremia) as a CABP pathogen. Pneumococcal bacteremia was identified in 28 patients (12 solithromycin patients and 16 moxifloxacin patients) from the pooled study population. Treatment was considered unsuccessful at SFU in 4 patients from each group. No patient among these 8 had persistent bacteremia, nor was pneumococcus re-isolated in follow up from sputum cultures. Narratives for these patients are in Appendix 11.6.1. A review of data from all pneumococcal bacteremia cases shows comparable responses in WBC count and fever curve in each treatment arm, as shown in Figure 17 and Figure 18.

Figure 17 Pneumococcal Bacteremia Patients: WBC Counts by Study Visit

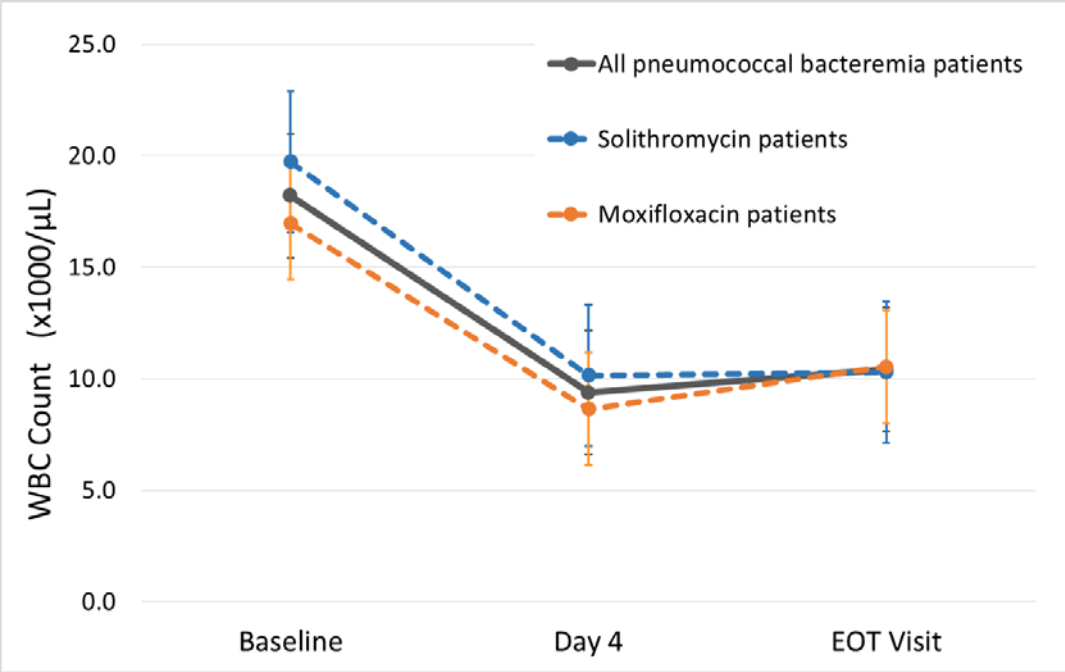
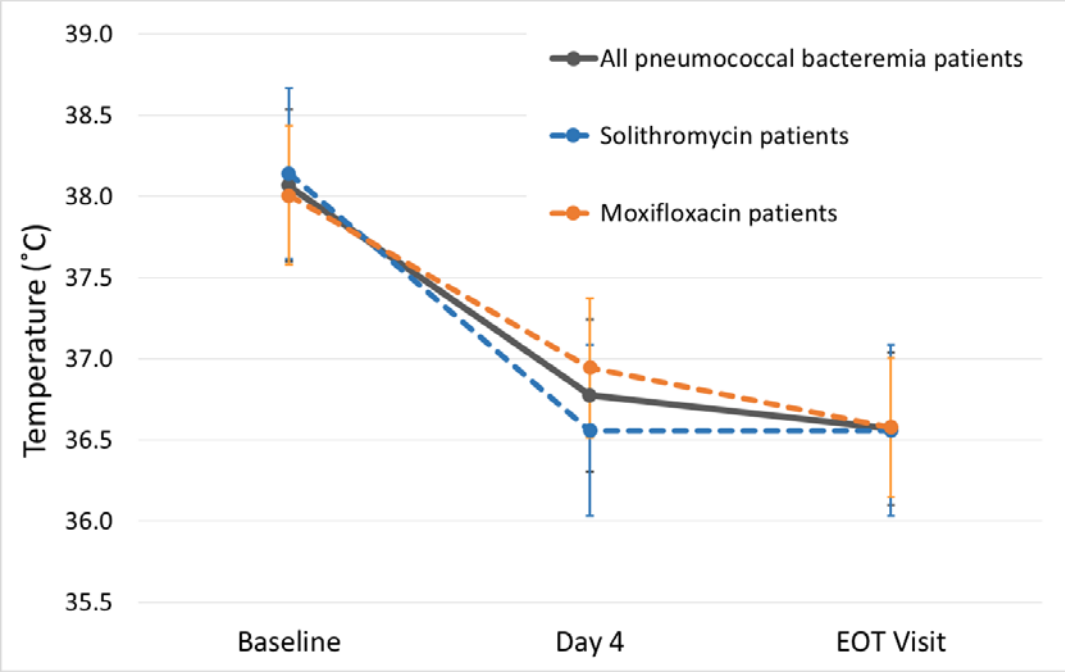


Figure 18 Pneumococcal Bacteremia Patients: Body Temperature by Study Visit



There were few staphylococcal bacteremias in the trial. For the assessment of ECR, 1 of 3 staphylococcal bacteremia patients treated with solithromycin were responders vs. 1 of 1 patients treated with moxifloxacin. In the solithromycin group, 2 of 3 patients with *S. aureus* bacteremia were classified by the investigator as clinical successes at SFU. The single solithromycin failure at SFU was a patient who was a clinical success at EOT but withdrew consent prior to SFU and was therefore counted as a failure (due to an indeterminate outcome).

The 2 patients with *H. influenzae* bacteremia in the solithromycin group were both ECR responders. The single *H. influenzae* failure at SFU withdrew consent on Day 4 (following the ECR responder assessment) and therefore was counted as a failure due to an indeterminate outcome at SFU.

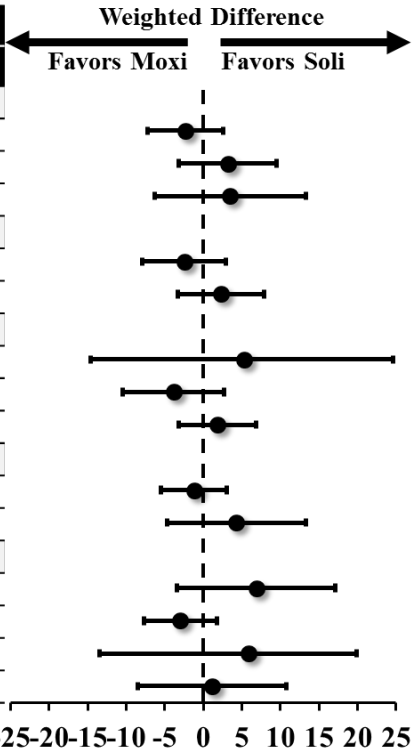
Among patients with other Gram-negative pathogens, 2 of 3 patients were ECR responders, and 3 of 3 patients were clinical successes at SFU in the solithromycin group. In the moxifloxacin group, 0 out of 4 patients were ECR responders, and 1 out of 4 patients were clinical successes at SFU.

6.6.3 ECR by Demographic and Disease Severity Subpopulations

Pooled efficacy analyses of ECR were conducted utilizing demographic subpopulations (age, gender, BMI, race and geographic region), baseline disease severity subpopulations (PORT Risk Class, SIRS criteria, history of asthma or COPD), and prior antibiotic use subgroups (Figure 19 and Figure 20) and demonstrate consistent solithromycin efficacy across subpopulations. In patients from North America (comprised mostly of patients from the US), 72.8% and 66.0% of solithromycin and moxifloxacin patients, respectively, were responders. Solithromycin responder rates were similar to moxifloxacin in patients with more severe disease and risk factors (PORT Risk Class III/IV and concurrent asthma and/or COPD). Responder rates were comparable between treatment groups for patients receiving and not receiving a prior antibiotic, and were slightly higher in patients who received a prior antibiotic.

Figure 19 ECR Subpopulation Analyses by Demographic Characteristics and Geographic Region - Pooled Phase 3 Studies in the ITT Population

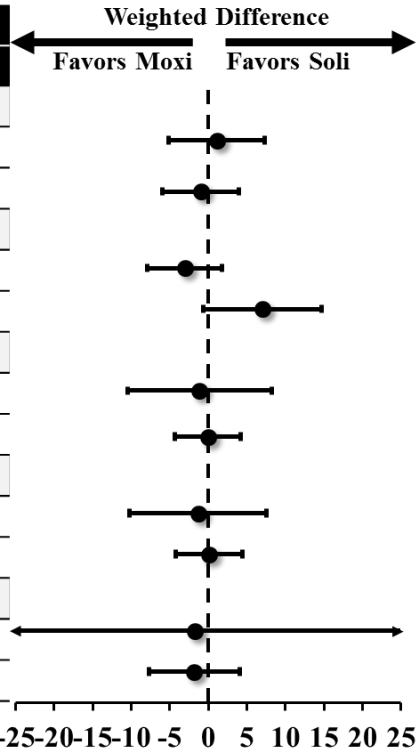
Subgroup	Solithromycin n/N	Solithromycin %	Moxifloxacin n/N	Moxifloxacin %
Age				
<65 years	407/517	78.7	426/526	81.0
≥ 65 years	269/342	78.7	252/334	75.4
≥ 75 years	115/145	79.3	106/140	75.7
Gender				
Male	337/439	76.8	367/463	79.3
Female	339/420	80.7	311/397	78.3
BMI				
Underweight	29/38	76.3	27/37	73.0
Normal Weight	234/300	78.0	236/288	81.9
Overweight	412/520	79.2	412/532	77.4
Race				
White	541/690	78.4	555/698	79.5
Non-White	135/169	79.9	123/162	75.9
Geographic Region				
North America	110/151	72.8	103/156	66.0
Europe	420/523	80.3	418/502	83.3
Latin America	42/57	73.7	48/65	73.8
Rest of World	104/128	81.3	109/137	79.6



Differences in clinical responder rates (solithromycin minus moxifloxacin) are weighted for study, CIs were calculated using the Miettinen and Nurminen method with adjustment for the stratification factor of study. Stratum weights were the inverse variance of each effect size

Figure 20 ECR Subpopulation Analyses by Disease Severity - Pooled Phase 3 Studies in the ITT Population

Subgroup	Solithromycin n/N	Solithromycin %	Moxifloxacin n/N	Moxifloxacin %
PORT Risk Class				
PORT Class II	256/315	81.3	254/317	80.1
PORT Class III / IV	420/544	77.2	424/543	78.1
SIRS Criteria				
Yes	420/544	77.2	445/555	80.2
No	191/232	82.3	156/207	75.4
History of COPD or Asthma				
Yes	119/157	75.8	119/156	76.3
No	557/702	79.3	559/704	79.4
Prior Antibiotic Use				
Yes	124/155	80.0	125/154	81.2
No	552/704	78.4	553/706	78.3
Bacteremia (mITT)				
Yes	13/20	65.0	14/21	66.7
No	302/388	77.8	285/356	79.6



Differences in in clinical responder rates (solithromycin minus moxifloxacin) are weighted for study, CIs were calculated using the Miettinen and Nurminen method with adjustment for the stratification factor of study. Stratum weights were the inverse variance of each effect size.

6.7 PK/PD Efficacy Analyses

PK/PD analyses for efficacy were based on data from patients enrolled in Studies 300 and 301 with sufficient PK data in both the ME and ME-2 populations. PK/PD analyses for efficacy were also examined among subpopulations of patients with *S. pneumoniae* and *H. influenzae* at baseline.

Results of the univariable PK/PD analyses for efficacy based on the ME and the ME-2 analysis populations and the subpopulations of patients with *S. pneumoniae* or *H. influenzae* failed to reveal statistically significant relationships between free-drug plasma AUC:MIC ratio and the efficacy endpoints evaluated. The high percentages of success in ECR and at SFU and the distribution of $AUC_{0\text{-}24}$:MIC ratios observed relative to the targets suggest that patients in the Phase 3 trials achieved solithromycin exposures on the plateau of the PK/PD relationships for efficacy.

7 SAFETY ACROSS DEVELOPMENT

7.1 Summary

- More than 2000 individuals have received solithromycin in clinical trials as of July 31, 2016, including 920 patients with CABP in the Phase 2 study (n=64) and in the Phase 3 studies (n=856).
- In the pooled Phase 3 studies, the overall incidence of AEs was higher in the solithromycin group (44%) compared with the moxifloxacin group (35%), this difference was due to a higher incidence of infusion site events in the IV to oral Study 301. Infusion site events are common to the macrolide class, but are not a known issue for fluoroquinolones.
- Excluding infusion site events, the incidence of TEAEs was comparable between solithromycin (35.5%) and moxifloxacin (34.3%). The most common non-infusion related AEs with solithromycin were diarrhea, headache, nausea, and dizziness, most of which were of mild severity.
- No *C. difficile*-associated diarrhea was observed in any solithromycin patient, while 3 cases were reported in moxifloxacin patients.
- AEs leading to discontinuation of study drug were reported for 5% of solithromycin patients and 3% of moxifloxacin patients. More solithromycin patients discontinued due to infusion events (10 vs. 1) and more moxifloxacin patients discontinued due to rashes (3 vs. 0).
- The incidence of SAEs was 7% in the solithromycin group and 6% for moxifloxacin. Most of the SAEs were unrelated to study drug and attributable to underlying respiratory or cardiac diseases.
- Eleven (11) deaths occurred in solithromycin patients, and 13 deaths occurred in moxifloxacin patients.
- Solithromycin was associated with reversible elevations of liver transaminases more frequently than moxifloxacin. An exposure response analysis showed a relationship between solithromycin plasma concentrations and ALT elevations. There were few liver-related AEs in either treatment group and no Hy's Law cases observed.
- DILIsym mechanistic modeling of high-risk populations predicts reversible dose-dependent liver enzyme elevation under the 5- and 7-day, oral and IV to oral solithromycin CABP dosing regimens, with no Hy's Law cases.
- Solithromycin was not associated with the type of macrolide-atypical AEs that have been a concern for telithromycin (severe exacerbation of myasthenia gravis, vision abnormalities, loss of consciousness, or idiosyncratic hepatic failure).
- A thorough QT study showed that solithromycin does not prolong the QT interval. In the Phase 3 studies, QT prolongation and cardiac safety events were observed more frequently with moxifloxacin than solithromycin.

7.2 Extent of Exposure

Over 2000 individuals have been exposed to solithromycin as of July 31, 2016.

The primary source of safety data is the two Phase 3 studies in patients with CABP; 856 patients who received solithromycin are in this Safety population.

An additional group pooled for safety analysis in CABP patients includes the data from the Phase 2 oral CABP study (64 solithromycin patients) plus the Phase 3 data; 920 patients are in this group pooled for safety analyses.

Phase 1 data from completed studies in 554 healthy adult subjects with systemic exposure were pooled for analysis.

The CABP and healthy subject groups pooled for analysis include 1474 unique individuals who received solithromycin (Table 53).

Table 53 Exposure to Solithromycin or Comparator in Studies Integrated for Safety Analyses

Studies	Solithromycin	Comparator
Phase 3 CABP		
	856	858
All CABP (Phase 2 + Phase 3)		
	920	926
Phase 1 Non-therapeutic trials in healthy adult subjects		
Oral Clinical Pharmacology	188	38
IV Clinical Pharmacology	270	138
Oral Biopharmaceutics	96	0
TOTAL	**1474**	**1102**

Studies that included safety data that were fully assessed and reported in the NDA but not incorporated into one of the pooled analysis groups are collectively referred to as the "non-integrated studies." These included ongoing studies or completed non-CABP studies. As of July 31, 2016, 600 individuals have received solithromycin in these trials (approximately 350 of whom received a single dose).

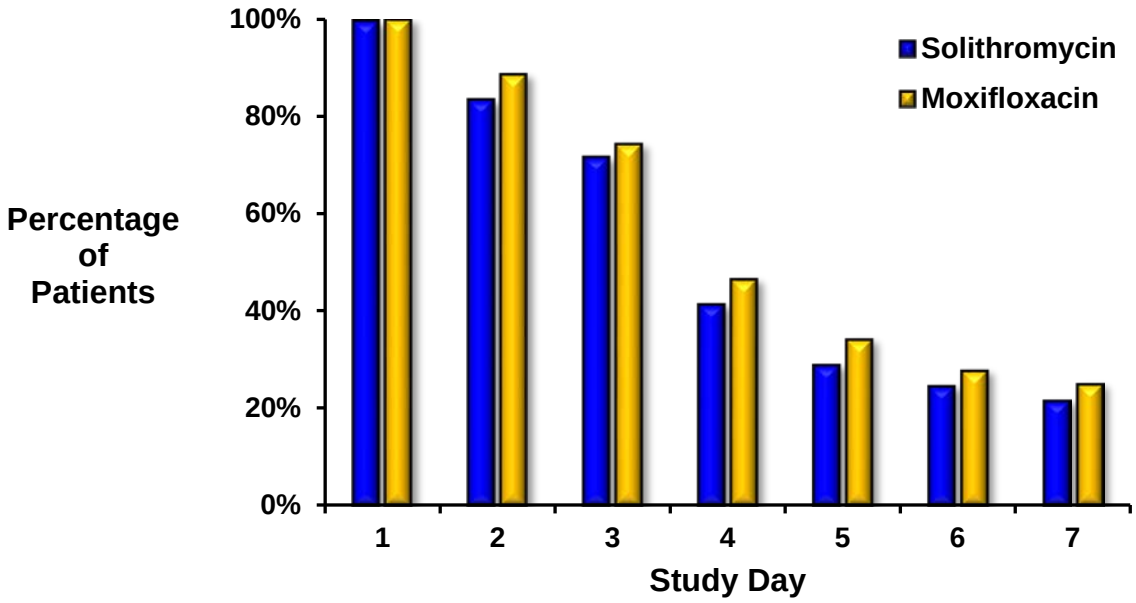
In both Phase 3 studies, compliance with study drug administration was high (>98% across treatment groups in both trials).

In Study 300, patients randomized to solithromycin received 5 days of active drug, followed by 2 days of placebo. Moxifloxacin patients received 7 days of active drug. Mean exposure to study drug was comparable for solithromycin (6.7 days) and moxifloxacin (6.8 days).

In Study 301, mean exposure to study drug was comparable in the solithromycin (6.6 days) and moxifloxacin (6.7 days) groups. As shown in Figure 21, the overall pattern of transition from IV to oral therapy in Study 301 was similar in both treatment groups. Most patients transitioned to oral therapy, with the majority of patients starting oral therapy between Days 2 and 5. Similar

percentages of patients in each treatment group remained on IV therapy for 7 days: 21.8% of solithromycin patients and 25.1% of moxifloxacin patients.

Figure 21 Intravenous Study Drug Exposure by Day – Study 301



Denominator is total number of patients enrolled in the treatment group.

7.3 Treatment-emergent Adverse Events

Table 54 presents a summary of TEAEs in the Phase 3 studies. The overall incidence of TEAEs was higher in the solithromycin group (44.2%) compared with the moxifloxacin group (35.2%). This difference was almost entirely due to a higher incidence of infusion site events observed in the IV to oral Study 301. Excluding IV infusion site events, the overall TEAE incidence was similar between the solithromycin (35.5%) and moxifloxacin (34.3%) groups. The incidence of SAEs was similar between treatment groups in the pooled Phase 3 studies (6.8% solithromycin, 5.8% moxifloxacin).

Table 54 Summary of TEAEs in Phase 3 CABP Studies

	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral (N=424) n (%)	Moxi Oral (N=432) n (%)	Soli IV to Oral (N=432) n (%)	Moxi IV to Oral (N=426) n (%)	Soli Pooled (N=856) n (%)	Moxi Pooled (N=858) n (%)
TEAEs	155 (36.6)	154 (35.6)	223 (51.6)	148 (34.7)	378 (44.2)	302 (35.2)
Excluding IV infusion site events	155 (36.6)	154 (35.6)	149 (34.5)	140 (32.9)	304 (35.5)	294 (34.3)
TEAEs leading to premature discontinuation of drug	16 (3.8)	13 (3.0)	25 (5.8)	16 (3.8)	41 (4.8)	29 (3.4)
Excluding IV infusion site events	16 (3.8)	13 (3.0)	16 (3.7)	16 (3.8)	32 (3.7)	29 (3.4)
Severe TEAEs	21 (5.0)	21 (4.9)	28 (6.5)	18 (4.2)	49 (5.7)	39 (4.5)
Excluding IV infusion site events	21 (5.0)	21 (4.9)	21 (4.9)	18 (4.2)	42 (4.9)	39 (4.5)
Serious TEAEs (SAEs)	28 (6.6) [a]	27 (6.3)	30 (6.9)	23 (5.4)	58 (6.8) [a]	50 (5.8)
SAEs leading to death	6 (1.4)	6 (1.4)	5 (1.2)	7 (1.6)	11 (1.3)	13 (1.5)

TEAE=treatment-emergent adverse event

a. An additional SAE in the solithromycin group in Study 300 is not included in the dataset.

7.3.1 Common TEAEs

Infusion site TEAEs were the most frequently reported TEAEs for solithromycin and reported with a notably higher incidence than moxifloxacin (31.3% vs 5.4%) (Table 55). The most commonly reported TEAEs excluding infusion site events in patients receiving solithromycin were diarrhea (4.3%), headache (4.0%), nausea (3.4%), and dizziness (2.3%). In patients receiving moxifloxacin, the most commonly reported TEAEs were diarrhea (6.2%), headache (3.4%), nausea (2.8%), and hypertension (1.7%).

C. difficile-associated diarrhea was not observed in any solithromycin patients, but was reported in 3 moxifloxacin patients. One episode of peripheral neuropathy (bilateral hand paresthesia) was observed in a moxifloxacin patient that did not resolve during 6 months of follow-up.

Table 55 Summary of Most Frequently Reported (≥ 2%) TEAEs Phase 3 Studies

	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral N=424 n (%)	Moxi Oral N=432 n (%)	Soli IV to Oral N=432 n (%)	Moxi IV to Oral N=426 n (%)	Soli Pooled N=856 n (%)	Moxi Pooled N=858 n (%)
Patients with ≥ 1 TEAE	155 (36.6)	154 (35.6)	223 (51.6)	148 (34.7)	378 (44.2)	302 (35.2)
Patients with ≥ 1 TEAE (excluding infusion site events)	155 (36.6)	154 (35.6)	149 (34.5)	140 (32.9)	304 (35.5)	294 (34.3)
Preferred Term (Excluding Infusion Site Events), n (%)						
Diarrhea	18 (4.2)	28 (6.5)	19 (4.4)	25 (5.9)	37 (4.3)	53 (6.2)
Headache	19 (4.5)	11 (2.5)	15 (3.5)	18 (4.2)	34 (4.0)	29 (3.4)
Nausea	15 (3.5)	17 (3.9)	14 (3.2)	7 (1.6)	29 (3.4)	24 (2.8)
Dizziness	9 (2.1)	7 (1.6)	11 (2.5)	5 (1.2)	20 (2.3)	12 (1.4)
Pneumonia	7 (1.7)	5 (1.2)	11 (2.5)	5 (1.2)	18 (2.1)	10 (1.2)
Vomiting	10 (2.4)	10 (2.3)	4 (0.9)	3 (0.7)	14 (1.6)	13 (1.5)
Hypokalemia	2 (0.5)	3 (0.7)	11 (2.5)	9 (2.1)	13 (1.5)	12 (1.4)
Hypertension	6 (1.4)	5 (1.2)	6 (1.4)	10 (2.3)	12 (1.4)	15 (1.7)
Insomnia	2 (0.5)	4 (0.9)	9 (2.1)	5 (1.2)	11 (1.3)	9 (1.0)
Infusion Site Preferred Terms, n (%)			135 (31.3)	23 (5.4)		
Infusion site pain	-	-	45 (10.4)	6 (1.4)	-	-
Infusion site phlebitis	-	-	43 (10.0)	4 (0.9)	-	-
Infusion related reaction	-	-	28 (6.5)	1 (0.2)	-	-
Infusion site erythema	-	-	19 (4.4)	2 (0.5)	-	-
Infusion site thrombosis	-	-	9 (2.1)	7 (1.6)	-	-
Infusion site paresthesia	-	-	9 (2.1)	0	-	-

TEAE=treatment-emergent adverse event

7.3.2 Severity of TEAEs

The majority of patients with TEAEs in the Phase 3 studies experienced events of mild or moderate severity (Table 56). Severe TEAEs occurred in 5.7% of solithromycin patients and 4.5% of moxifloxacin patients. Other than infusion site events (8 solithromycin patients), the incidence of any specific severe TEAE was similar between solithromycin and moxifloxacin (4.9% vs. 4.5%, respectively) (Table 54).

The infusion site events in solithromycin patients were generally mild (83.3%) or moderate (14.0%), with few severe events (2.7%). These events account for the differences between treatment groups shown in Table 56. Infusion site pain generally resolved the same day as onset (> 85% of events), and phlebitis events had a mean duration of 6 days. All of these events resolved in both treatment groups.

Table 56 Summary of Overall TEAEs by Severity in Pooled Phase 3 Solithromycin Studies

	Pooled Phase 3 Studies	
	Solithromycin (N=856) n (%)	**Moxifloxacin (N=858) n (%)**
Patients with ≥ 1 TEAE	**378 (44.2)**	**302 (35.2)**
Mild	207 (24.2)	160 (18.6)
Moderate	122 (14.3)	103 (12.0)
Severe	49 (5.7)	39 (4.5)

TEAE=treatment-emergent adverse event

7.4 Adverse Events Leading to Discontinuation of Study Drug

In the Phase 3 trials, TEAEs leading to discontinuation of study drug occurred in 41 (4.8%) solithromycin patients and 29 (3.4%) moxifloxacin patients (Table 57). The most frequently reported TEAEs resulting in premature discontinuation of study drug for solithromycin patients were infusion site events and (worsening) pneumonia; most other preferred terms were reported in only a single solithromycin or moxifloxacin patient. Three moxifloxacin patients discontinued due to an AE of rash.

The incidence of non-infusion site TEAEs leading to premature discontinuation of study drug was similar between solithromycin (32 patients; 3.7%) and moxifloxacin (29 patients; 3.4%). The incidence of premature discontinuation of study drug or withdrawal from the study due to these events was relatively low (10 solithromycin patients and 1 moxifloxacin patient).

Table 57 Summary of TEAEs Leading to Premature Discontinuation of Study Drug in ≥ 2 Patients by Preferred Term in the Phase 3 Studies

	Study 300		Study 301		Pooled Phase 3 Studies	
Preferred Term by SOC	**Soli Oral N=424 n (%)**	**Moxi Oral N=432 n (%)**	**Soli IV to Oral N=432 n (%)**	**Moxi IV to Oral N=426 n (%)**	**Soli Pooled N=856 n (%)**	**Moxi Pooled N=858 n (%)**
Patients with ≥ 1 TEAE leading to premature discontinuation of study drug	16 (3.8)	13 (3.0)	25 (5.8)	16 (3.8)	41 (4.8)	29 (3.4)
Pneumonia	2 (0.5)	0	3 (0.7)	1 (0.2)	5 (0.6)	1 (0.1)
Infusion site pain	0	0	3 (0.7)	0	3 (0.4)	0
Infusion related reaction	0	0	3 (0.7)	0	3 (0.4)	0
Rash	0	0	0	3 (0.7)	0	3 (0.3)
Nausea	2 (0.5)	2 (0.5)	0	0	2 (0.2)	2 (0.2)
Infusion site phlebitis	0	0	2 (0.5)	0	2 (0.2)	0
Empyema	1 (0.2)	0	1 (0.2)	0	2 (0.2)	0
Atrial fibrillation	1 (0.2)	0	0	2 (0.5)	1 (0.1)	2 (0.2)
Acute respiratory failure	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.1)	2 (0.2)
Diarrhea	0	2 (0.5)	0	0	0	2 (0.2)

Preferred Term by SOC	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral N=424 n (%)	Moxi Oral N=432 n (%)	Soli IV to Oral N=432 n (%)	Moxi IV to Oral N=426 n (%)	Soli Pooled N=856 n (%)	Moxi Pooled N=858 n (%)
Neutropenia	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)
Pulmonary tuberculosis	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)
Pruritus	0	0	0	2 (0.5)	0	2 (0.2)

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

7.5 Serious Adverse Events

The incidence of SAEs was similar between solithromycin (6.8%) and moxifloxacin (5.8%) patients in the Phase 3 trials. Most of the SAEs were unrelated to study drug and attributable to underlying respiratory or cardiac diseases. The most common (occurring in ≥ 2 patients in either treatment group) are shown in Table 58. Three SAEs of allergic reactions occurred in Study 301: urticaria (1 solithromycin patient), anaphylactic reaction (1 patient in each treatment group).

Table 58 Serious Adverse Events by Preferred Term in ≥ 2 Patients in the Phase 3 Studies

MedDRA Preferred term	Pooled Phase 3 Studies	
	Solithromycin (N=856) n (%)	Moxifloxacin (N=858) n (%)
Patients with an SAE	**58 (6.8)**	**50 (5.8)**
Pneumonia	13 (1.5)	6 (0.7)
Respiratory failure	3 (0.4)	3 (0.3)
Pleural effusion	3 (0.4)	1 (0.1)
Acute respiratory failure	2 (0.2)	6 (0.7)
Empyema	2 (0.2)	2 (0.2)
COPD	2 (0.2)	2 (0.2)
Cardiac failure	2 (0.2)	2 (0.2)
Myocardial infarction	2 (0.2)	1 (0.1)
Pulmonary tuberculosis	2 (0.2)	1 (0.1)
Septic shock	2 (0.2)	1 (0.1)
Cardiac arrest	2 (0.2)	1 (0.1)
Acute myocardial infarction	2 (0.2)	0
Cerebrovascular accident	2 (0.2)	0
Pulmonary embolism	1 (0.1)	2 (0.2)
Atrial fibrillation	1 (0.1)	2 (0.2)
Deep vein thrombosis	1 (0.1)	2 (0.2)
Cardiac failure congestive	0	3 (0.3)
Lung neoplasm malignant	0	2 (0.2)

SAE=serious adverse event

Non-fatal SAEs that were reported in Studies 200, 300, and 301 are listed in Appendix 11.7. No SAEs occurred in healthy subjects in the Phase 1 studies. As of July 31, 2016, 10 SAEs were reported in 9 individuals in the non-integrated studies; these SAEs are presented in Appendix 11.7, Table 71.

7.6 Mortality

In the Phase 3 CABP studies, 11 deaths occurred in the solithromycin group and 13 deaths occurred in the moxifloxacin group (Table 54); one additional death occurred in the Phase 2 CABP study in the levofloxacin group and none in the solithromycin group. Most deaths in each treatment group appeared to be attributable to underlying respiratory or cardiac diseases in patients presenting with multiple comorbidities and risk factors. No TEAEs resulting in death were considered related to study drug by any investigator. Narratives for these patients are provided in Appendix 11.8.2.

7.7 Safety Topics of Special Interest

Safety topics of special interest that were evaluated across the development program included hepatic safety, cardiovascular safety, visual disturbances, loss of consciousness and exacerbation of myasthenia gravis. Most of the data on these topics comes from the Phase 3 CABP studies; however, relevant safety data from other studies is also discussed. A discussion of the differentiation of solithromycin from telithromycin for the AEs that were of particular concern with that molecule follows in Section 7.7.4.

7.7.1 Hepatic Safety

Antibiotics are one of the most common causes of drug induced liver injury, due in part to the large number of people exposed to antibiotics as well as the high doses that are administered relative to many other types of drugs. Overall, however, the frequency of serious hepatotoxicity associated with antibiotic use is low (estimated <5 per 100,000 people) (National Institutes of Health LiverTox® website).

Macrolides as a class are associated with a relatively low risk of hepatotoxicity. Other antibiotics such as amoxicillin/clavulanic acid, which is broadly prescribed and generally considered very safe, have a higher risk of hepatotoxicity than most macrolides (Leitner 2010). The most common hepatotoxic effect of macrolides is a transient and asymptomatic elevation in serum aminotransferase levels. This effect has been demonstrated with all four macrolide antibiotics currently on the market (erythromycin, clarithromycin, azithromycin and telithromycin).

For erythromycin, azithromycin, and clarithromycin, this risk seems to be very low. Telithromycin, however, has been linked to severe forms of acute, clinically apparent hepatotoxicity at a rate believed to be significantly higher than the other macrolides. The cause of hepatotoxicity from telithromycin is unknown, but the short latency period and abrupt onset of injury seen in patients suggests rapid onset hypersensitivity as a plausible cause (Brinker 2009).

7.7.1.1 Liver-related TEAEs

Liver-related AEs were reported with comparable incidence for solithromycin patients vs. moxifloxacin patients (2.1% vs. 2.0%; Table 59) in the Phase 3 studies. The most frequently reported events were asymptomatic elevations in hepatic transaminases. Excluding AEs due to laboratory abnormalities, the number of liver related events was low in both groups: 2 in the solithromycin group (both hepatomegaly) and 3 in the moxifloxacin group (ascites, hepatosplenomegaly, and abnormal feces). The three cases with hepatomegaly (2 with hepatomegaly, 1 with hepatosplenomegaly) were reported from a single site and were not associated with elevations of liver safety laboratory parameters.

Table 59 Summary of Liver Related and Biliary System Related TEAEs of Special Interest in Pooled Phase 3 Studies

Liver Related Adverse Event Term	Solithromycin Pooled N=856 n (%)	Moxifloxacin Pooled N=858 n (%)
Patients with liver- or biliary-system related investigations, signs, and symptoms events of special interest[a]	18 (2.1)	17 (2.0)
Hepatic safety laboratory parameter abnormality[b]	16 (1.9)	14 (1.6)
Hepatic enzyme increased	7 (0.8)	4 (0.5)
Elevated ALT	5 (0.6)	8 (0.9)
Elevated AST	4 (0.5)	4 (0.5)
Elevated ALT & AST (transaminases)	2 (0.2)	2 (0.2)
Elevated Alkaline phosphatase	1 (0.1)	1 (0.1)
Liver function tests abnormal	2 (0.2)	1 (0.1)
Ascites	0	1 (0.1)
Hepatomegaly	2 (0.2)	0
Hepatosplenomegaly	0	1 (0.1)
Abnormal faeces	0	1 (0.1)

a. Includes all AEs captured by MedDRA SMQ liver related investigations, signs, and symptoms.
b. All elevated hepatic safety lab parameter AEs among solithromycin patients were asymptomatic.

7.7.1.2 Liver Safety Laboratory Parameters

ALT and AST elevations >ULN were noted at baseline (prior to first dose) in 15.1% and 17.9%, respectively, of solithromycin patients in the pooled Phase 3 CABP studies.

ALT and AST elevations >3×ULN and >5×ULN occurred more frequently with solithromycin than moxifloxacin (Table 60) in the Phase 3 studies. Elevations to >10×ULN were infrequent and comparable (4 solithromycin patients, 3 moxifloxacin patients). Peak elevations in ALT and AST in solithromycin patients were generally observed on Day 4. These elevations were typically asymptomatic, not associated with bilirubin elevation, and resolved rapidly (in many cases during continued study drug dosing). Notable alkaline phosphatase (ALP) and bilirubin elevations occurred infrequently.

Table 60 Frequency of Liver-Related Laboratory Assessments >3×ULN, >5×ULN, and >10×ULN at Any Post-Baseline Study Visit

Parameter (unit)	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral N=424 n (%)	Moxi Oral N=432 n (%)	Soli IV to Oral N=432 n (%)	Moxi IV to Oral N=426 n (%)	Soli Pooled N=856 n (%)	Moxi Pooled 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)
AST (U/L), n/N1						
>3×ULN	10/406 (2.5)	8/416 (1.9)	20/416 (4.8)	10/409 (2.4)	30/822 (3.6)	18/825 (2.2)
>5×ULN	4/406 (1.0)	4/416 (1.0)	9/416 (2.2)	2/409 (0.5)	13/822 (1.6)	6/825 (0.7)
>10×ULN	2/406 (0.5)	2/416 (0.5)	2/416 (0.5)	0/409	4/822 (0.5)	2/825 (0.2)
ALP (U/L), n/N1						
>3×ULN	7/411 (1.7)	2/423 (0.5)	1/417 (0.2)	1/415 (0.2)	8/828 (1.0)	3/838 (0.4)
>5×ULN	3/411 (0.7)	1/423 (0.2)	1/417 (0.2)	0/415	4/828 (0.5)	1/838 (0.1)
>10× ULN	0/411	0/423	1/417 (0.2)	0/415	1/828 (0.1)	0/838
Direct Bilirubin (mg/dL), n/N1						
>3×ULN	2/402 (0.5)	1/412 (0.2)	1/413 (0.2)	2/407 (0.5)	3/815 (0.4)	3/819 (0.4)
>5×ULN	0/402	0/412	1/413 (0.2)	1/407 (0.2)	1/815 (0.1)	1/819 (0.1)
>10×ULN	0/402	0/412	0/413	1/407 (0.2)	0/815	1/819 (0.1)
Total Bilirubin (mg/dL), n/N1						
>3×ULN	1/412 (0.2)	0/422	0/416	1/413 (0.2)	1/828 (0.1)	1/835 (0.1)
>5×ULN	0/412	0/422	0/416	0/413	0/828	0/835
>10×ULN	0/412	0/422	0/416	0/413	0/828	0/835

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; ULN=upper limit of normal

N = Number of patients in the Safety Population. N1 = Number of patients with a post-baseline lab value for the specified parameter. n = Number of patients with a post-baseline value > 3×ULN, > 5×ULN, or > 10×ULN at any post-baseline visit.

Note: Baseline is defined as the last assessment prior to the first dose of study drug. Worst, or most severe, laboratory results during the study are included in the table. Patients can appear in the table only once per parameter.

Treatment-emergent transaminase elevations occurred more frequently among patients in whom these parameters were elevated at baseline. Among solithromycin patients who had baseline ALT or AST values within the normal range, ALT elevation to > 3×ULN occurred in 4.7% of patients and AST elevation to > 3×ULN in 1.6%.

7.7.1.3 CABP Patients with Underlying Liver Disease

Underlying liver disease in the Phase 3 studies was defined by the following parameters: a known diagnosis of cirrhosis, a new diagnosis of cirrhosis; or chronic Hepatitis B or C virus infection identified at baseline (+HBsAg or +HCV RNA).

The incidence of TEAEs was similar in patients with underlying liver disease in both treatment groups compared to patients without underlying liver disease (Table 61). The incidence of SAEs was higher in patients with underlying liver disease in both treatment groups compared to patients without underlying liver disease. No specific SAE term was reported for more than 1 patient, consistent with the absence of any particular safety signal in this group.

Table 61 Summary of TEAEs (Excluding Infusion Site Events) and SAEs by Underlying Liver Disease (Yes/No) in the Pooled Phase 3 Studies

	Solithromycin		Moxifloxacin	
	N	n (%)	N	n (%)
Any TEAE				
Underlying Liver Disease - No	814	291 (35.7)	805	280 (34.8)
Underlying Liver Disease - Yes	42	13 (31.0)	53	14 (26.4)
Any SAE				
Underlying Liver Disease - No	814	53 (6.5)	805	45 (5.6)
Underlying Liver Disease - Yes	42	5 (11.9)	53	5 (9.4)

TEAE=treatment-emergent adverse event; SAE=serious adverse event
N=Number of patients in the subgroup; n=number of patients.

7.7.1.4 eDISH Plots and Hy's Law

Hy's Law defines a constellation of laboratory and clinical findings that are predictive of severe drug-induced liver injury. Hy's Law 'cases' meet the following criteria:

1. elevation of ALT or AST to >3×ULN observed concurrently with a bilirubin value >2×ULN;
2. no laboratory evidence of cholestasis as a basis for the elevated bilirubin (serum ALP level <2×ULN);
3. other reasons for the elevation of the aminotransferase and bilirubin (e.g. viral hepatitis, previous liver disease or another drug capable of causing liver injury) have been ruled out, leaving DILI as the probable cause.

Patients meeting Hy's Law transaminase and bilirubin laboratory criteria are found in the right upper quadrant of drug-induced serious hepatotoxicity (eDISH) plots.

Figure 22 is an eDISH plot with highest ALT or AST values for each individual vs. the highest total bilirubin levels for that individual in the solithromycin development program. This includes data from all adult Cempra Phase 1, 2 and 3 studies available as of July 31, 2016 (1526 solithromycin patients, 1109 moxifloxacin or other control patients, and 61 patients who received both treatments in crossover studies). Measured parameters are all post-baseline (following drug or control exposure) and are not required to occur simultaneously. For this figure, 3×ULN for transaminase values and 2×ULN for total bilirubin values defines the quadrants.

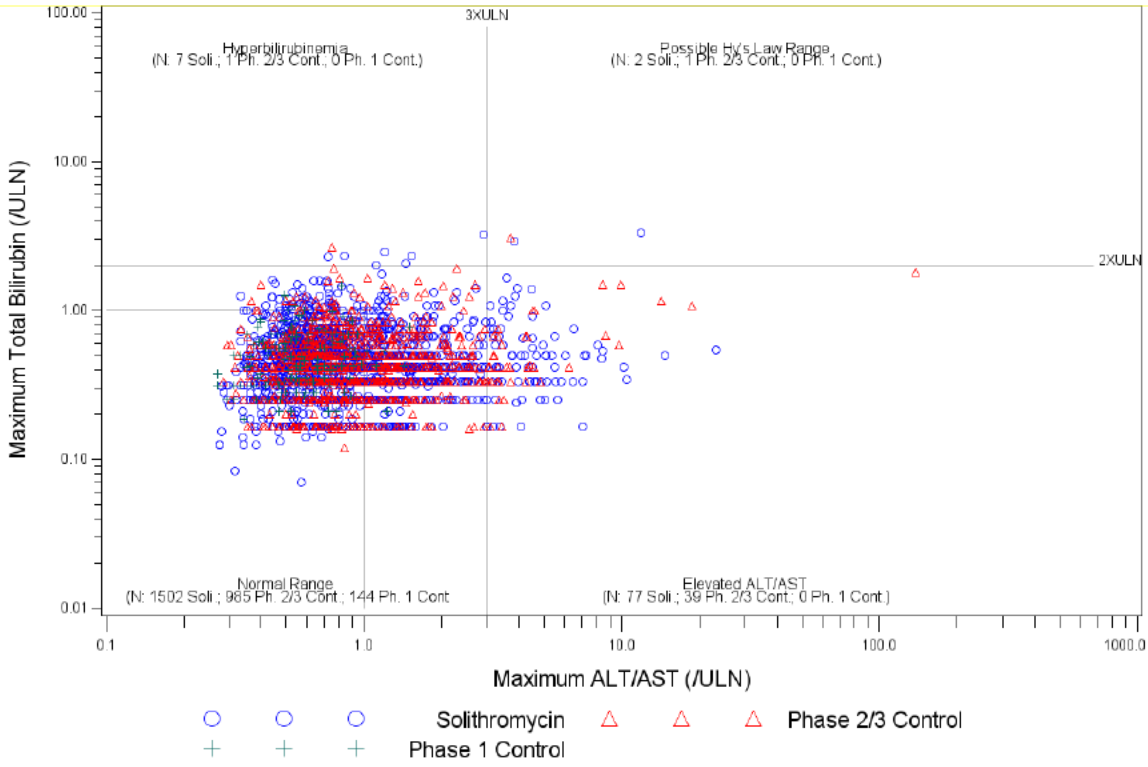
Three patients fall in the right upper quadrant of this figure, meeting Hy's Law laboratory criteria, with an ALT or AST value >3×ULN and a bilirubin value >2×ULN post-baseline (1 moxifloxacin patient in Study 301; 1 solithromycin patient in Study 301; and 1 solithromycin patient in Study 204, an exploratory study of the effect of solithromycin on airway inflammation in patients

with COPD). A fourth patient (1 solithromycin patient in Study 300) (plotted just to the left of the 3×ULN vertical line, in the left upper quadrant of the figure) met Hy's Law laboratory criteria at baseline (prior to study drug exposure), but not during follow-up at the research site (through Day 7). During a subsequent (and end-of-life) admission to another hospital, laboratory data met Hy's Law criteria. Narratives for each of these patients are presented in Appendix 11.8.1.

Six solithromycin patients and 1 moxifloxacin patient fall in the left upper quadrant of this figure (total bilirubin value >2×ULN). Five of the 6 solithromycin patients had elevated total bilirubin at baseline (cirrhosis or Gilbert Syndrome) and 1 had obstruction due to a gallstone (an SAE).

An expert panel of independent hepatologists (comprised of Dr. Paul Watkins, Dr. Leonard Seeff, and Dr. James Freston) reviewed each of these patient profiles, and concluded that none were Hy's Law cases.

Figure 22 eDISH Plot: Maximum of ALT or AST (Highest Level of Either Aminotransferase Value) vs. Total Bilirubin (2.0×ULN threshold) (All Studies)



7.7.1.5 DILIsym Analysis

DILIsym is a computational model of drug-induced liver injury that integrates estimates of drug-specific mechanistic liver injury parameters with exposure data to determine drug-candidate DILI risk.

DILIsym predicts dose-dependent liver enzyme elevations under the 5- and 7-day, oral and IV to oral solithromycin CABP dosing regimens and the modeled oral erythromycin regimen. These elevations closely matched observed clinical data and are predicted to resolve upon conclusion of therapy in the simulations with both molecules. Importantly, DILIsym predicts that no Hy's Law cases will occur with the solithromycin CABP dosing regimens.

ALT elevation can be correlated with hepatocyte loss, with clinically relevant decline in liver function believed to occur when more than 25% of a person's hepatocytes are lost or compromised. DILIsym predicts that 99.9% of simulated individuals will have ALT elevation profiles consistent with loss or compromise of no more than 3% of hepatocytes. The greatest model-predicted hepatocyte loss following solithromycin exposure was 9% in an outlier high ALT patient. The comparable figure for modeled erythromycin exposure under DILIsym was 15% hepatocyte loss.

Collectively, the clinical and DILIsym data indicate that oral or IV solithromycin can be administered for up to 7 days for treatment of CABP with a hepatic safety profile comparable to the older macrolide antibiotics.

7.7.1.6 ALT Increases in Long Term Dosing Studies

7.7.1.6.1 COPD Pilot Study

Study 204 is an exploratory randomized controlled evaluation of the effect of solithromycin on airway inflammation in patients with COPD and is being conducted at a single site in the United Kingdom. In the first dosing cohort, patients received 400 mg of solithromycin or placebo for 28 days and, following a 4-week washout, crossed over to the other regimen for 28 days. Four patients received solithromycin.

Three patients receiving solithromycin experienced ALT elevation to > 3×ULN. An episode of cholestatic hepatitis was diagnosed in one patient on Day 23 of dosing. A narrative for this patient is presented in Appendix 11.8.1. No additional patients are being enrolled, pending a protocol amendment after determining the appropriate dose for long term treatment.

7.7.1.6.2 NASH Pilot Study

Study 205 is an ongoing single-center, open label proof of principle study being conducted in the US to evaluate the efficacy and safety of a three month course of oral solithromycin for the treatment of NASH in patients without cirrhosis. The current dosing schedule is 200 mg QD for 7 days, followed by 200 mg three times weekly.

Six patients have been enrolled and have received solithromycin. One patient (who was receiving 200 mg daily) developed ALT and AST elevations > 3×ULN, without associated symptoms or bilirubin elevation, on the 29th day of dosing. A narrative for this patient is provided in Appendix 11.8.3.

7.7.2 Cardiovascular Safety

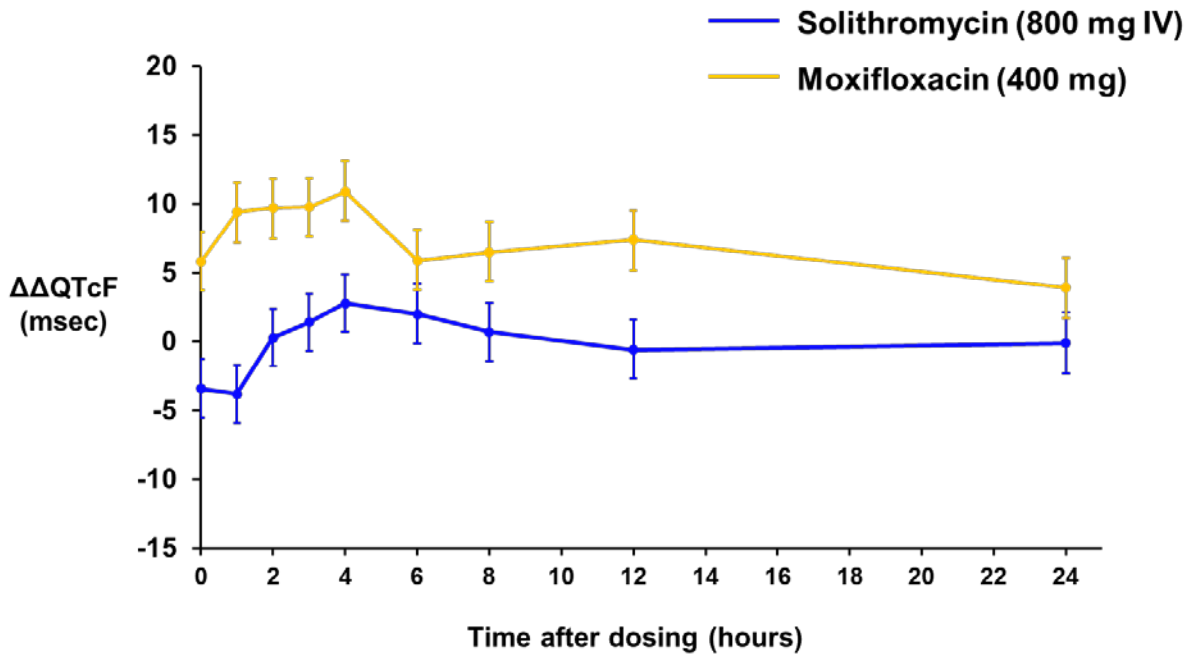
Macrolides have been associated with QT prolongation and risk for torsades de pointes. In March 2013, the FDA warned the public that azithromycin may cause fatal heart rhythm disturbances,

particularly in patients with known risk factors such as QT interval prolongation, hypokalemia, hypomagnesemia, bradycardia, or use of certain antiarrhythmic agents, including class IA (e.g. quinidine and procainamide) and class III (e.g. dofetilide, amiodarone, and sotalol) drugs that can prolong the QT interval.

7.7.2.1 QT Findings

In contrast to older macrolides, solithromycin does not appear to be associated with QT prolongation. A thorough QT study of solithromycin was negative, showing that solithromycin does not have a propensity to prolong the QT interval in a clinically significant manner in healthy subjects. The thorough QT study was a randomized, placebo- and active-controlled, 3-way crossover study of ECG effects of a supratherapeutic exposure. Subjects (48 healthy adults) were administered an infusion of 800 mg IV solithromycin over 40 minutes (400 mg infused over 60 minutes is the proposed clinical dose). The change-from-baseline QTcF was similar after dosing with solithromycin and placebo, and the resulting placebo-corrected QTcF change from baseline (ΔΔQTcF) for solithromycin was small (<3.0 msec) at all time points (Figure 23). Dosing with moxifloxacin prolonged the QTcF, confirming the study's assay sensitivity to detect drug effects. Both modeled and observed data from the study showed that solithromycin is associated with a decrease from baseline in placebo-adjusted QTcF at higher exposures.

Figure 23 Solithromycin and Moxifloxacin Placebo-Adjusted QTcF Change from Baseline (ΔΔQTcF)



In the Phase 3 CABP studies, mean changes from baseline in QTcF interval were 5.6 and 13.7 msec on Day 4 for the solithromycin and moxifloxacin groups, respectively, with non-overlapping 90% CIs (Table 62). At EOT, mean changes from baseline in QTcF interval were 5.5 and 11.0 msec for the solithromycin and moxifloxacin groups, respectively. Four patients treated with solithromycin and 5 treated with moxifloxacin had a new QTc increase >500 msec. Among the 4 patients who

received solithromycin, 3 had an isolated increase on Day 4 and in the fourth the QTc met this threshold only on Day 7. All four episodes were associated with electrolyte abnormalities or acute cardiac ischemia.

Table 62 Summary of QTcF Parameters in Phase 3 Studies

QTcF Parameters	Study 300		Study 301		Pooled Phase 3	
	Soli Oral	Moxi Oral	Soli IV to Oral	Moxi IV to Oral	Soli Pooled	Moxi Pooled
Mean QTcF at Baseline, msec (N)	406.2 (N=401)	405.3 (N=412)	404.7 (N=405)	407.8 (N=409)	405.4 (N=806)	406.6 (N=821)
Mean QTcF Change from Baseline at Day 4, msec (N)	4.0 (N=373)	14.7 (N=384)	7.1 (N=373)	12.6 (N=380)	5.6 (N=746)	13.7 (N=764)
90% confidence intervals (lower bound, upper bound)	(2.03, 5.99)	(12.64, 16.83)	(4.98, 9.26)	(10.35, 14.81)	(4.07, 7.07)	(12.17, 15.14)
Mean QTcF Change from Baseline at EOT, msec (N)	4.5 (N=374)	12.2 (N=392)	6.5 (N=379)	9.7 (N=380)	5.5 (N=753)	11.0 (N=772)
90% confidence intervals (lower bound, upper bound)	(2.25, 6.70)	(10.22, 14.25)	(4.35, 8.63)	(7.21, 12.17)	(3.91, 7.06)	(9.40, 12.52)
Treatment-emergent QTcF >500 msec, n/N (%)	1/387 (0.3)	1/400 (0.3)	3/386 (0.8)	4/397 (1.0)	4/773 (0.5)	5/797 (0.6)
Treatment-emergent Increase in QTcF of >30 msec, n/N (%)	66/387 (17.1)	122/400 (30.5)	63/386 (16.3)	101/397 (25.4)	129/773 (16.7)	223/797 (28.0)
Treatment-emergent Increase in QTcF of >60 msec, n/N (%)	9/387 (2.3)	23/400 (5.8)	16/386 (4.1)	25/397 (6.3)	25/773 (3.2)	48/797 (6.0)

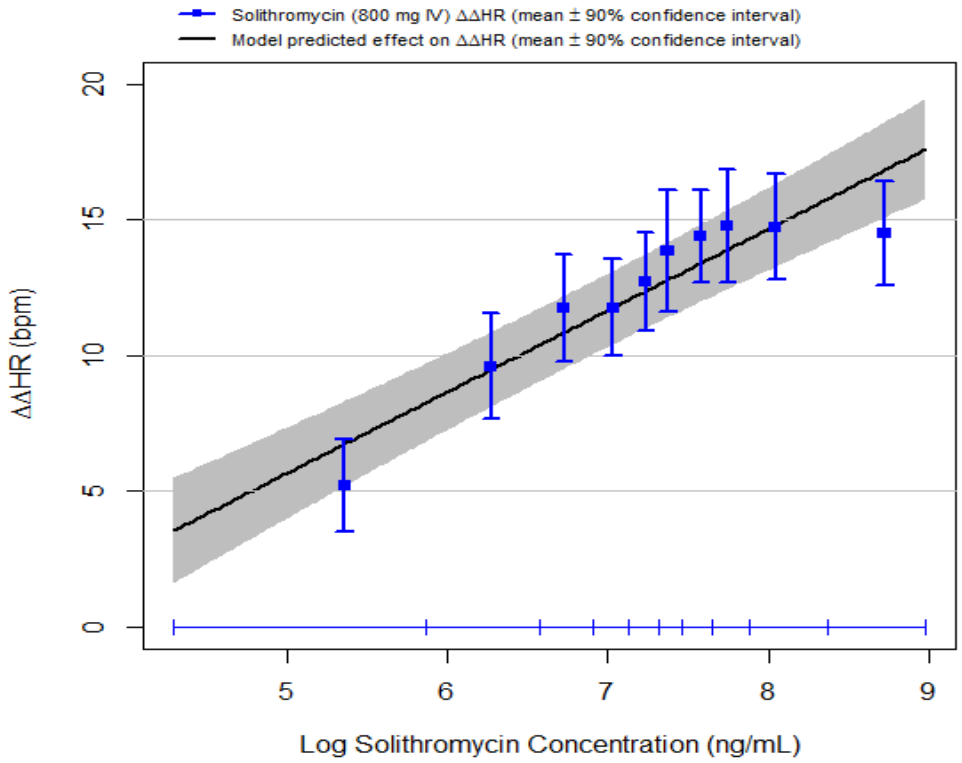
EOT=End of Treatment visit, IV=intravenous, msec=millisecond

7.7.2.2 Heart Rate

The thorough QT study showed that supratherapeutic plasma concentrations increased heart rate in healthy subjects; the placebo-adjusted mean change-from-baseline ECG heart rate peaked at 15 bpm immediately after the end of the infusion and remained above 12 bpm for the first 8 hours, after which it declined.

A concentration-effect analysis showed that the increase in heart rate was concentration-dependent and appeared to plateau with a maximum effect of approximately 15 bpm with frequent assessment of vital signs. There were no antecedent episodes of hypotension or evidence of loss of vascular tone as an explanation for the tachycardia occurring as a physiologic reflex phenomenon. There was no evidence of PR interval shortening in association with the increase in heart rate, providing additional evidence that the observed tachycardia was not an autonomic reflex event in response to changes in vascular tone.

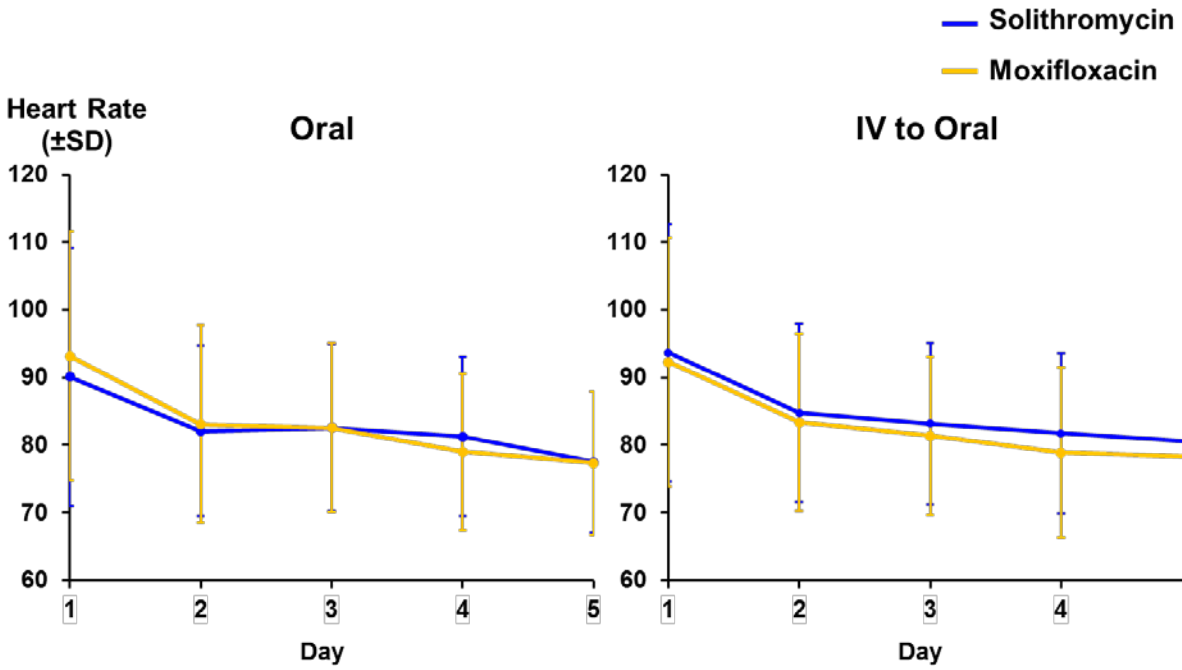
Figure 24 Goodness-of-fit Plot for Observed and Predicted Relation between Solithromycin Plasma Levels and ΔΔHR



Blue squares with vertical bars denote the observed mean ΔΔHR with 90% CI displayed at the median plasma concentration within each decile. The solid black line with gray shaded area denotes the model-predicted mean ΔΔHR with 90% CI. The horizontal blue lines with notches show the range of plasma concentrations divided into deciles for solithromycin (800 mg IV).

In contrast, in both Phase 3 CABP studies the overall mean heart rate decreased from baseline at each post-baseline time point in both treatment arms. In Study 300 (oral), the mean decreases in heart rate in solithromycin patients ranged from 8 bpm (Day 4) to 10.7 bpm (SFU) while those in moxifloxacin patients ranged from 14.1 bpm (Day 4) to 15 bpm (SFU). In Study 301 (IV to oral), a robust set of vital sign data was collected in hospitalized patients, including 4 hours after the first dose and daily while hospitalized (Figure 25). Similar trends in heart rate decrease as in Study 300 were observed in Study 301. These trends are attributable to improvement in the underlying infection, as patients with pneumonia often present with tachycardia at baseline due to some combination of hypoxia, fever, anemia and physiologic stress. The incidence of potentially clinically significant fluctuations in heart rate at each study visit was low (<1.0%) and occurred in a similar percentage of patients receiving solithromycin and moxifloxacin in the pooled Phase 3 CABP studies.

Figure 25 Mean Change in Heart Rate from Baseline by Treatment Group in Pooled Phase 3 Studies



Three in vitro studies have investigated inhibition of channels and receptors by solithromycin that may have contributed to the observation that solithromycin can increase heart rate. No potential mechanism for this effect has been identified to date. Human Nav1.5 and Cav1.2 ion channels, which impact repolarization and cardiac conduction, were not inhibited by solithromycin. Solithromycin did not have any significant effect on human HCN4 channel currents, the sino-atrial node pacemaker channel which regulates heart rhythm. Solithromycin did not inhibit a panel of receptors that can affect heart rate: adenosine (A_1), adrenergic (α_{1A}, α_{1B}, β_1, β_2), endothelin (ET_A, ET_B), histamine (H_2), muscarinic (M_2), serotonin (5-HT_{4e}) and the norepinephrine transporter.

7.7.2.3 Cardiac TEAEs

Cardiac AEs from the pooled Phase 3 studies are presented in Table 63 in descending order of frequency. All AEs in the System Organ Class (SOC) of Cardiac Disorders were included along with 3 preferred terms (prolonged QT, Troponin increased, Troponin T increased) in the Investigations SOC. Cardiac AEs were more frequently reported in moxifloxacin patients (4.7%) compared with solithromycin patients (3.0%). The largest differences between treatment groups for individual preferred terms were observed in the 3 most commonly reported preferred terms for moxifloxacin patients: atrial fibrillation (7 vs. 3 solithromycin patients), QT prolonged (6 vs. 3 solithromycin patients), and cardiac failure congestive (5 vs. 0 solithromycin patients).

Table 63 Cardiac Adverse Events in Pooled Phase 3 Studies

Preferred Term	Pooled Phase 3 Studies	
	Solithromycin Pooled (N=856) n (%)	Moxifloxacin Pooled (N=858) n (%)
Patients with any cardiac adverse event[a]	26 (3.0)	40 (4.7)
Atrial fibrillation	3 (0.4)	7 (0.8)
QT prolonged	3 (0.4)	6 (0.7)
Cardiac failure congestive	0	5 (0.6)
Myocardial ischaemia	1 (0.1)	4 (0.5)
Cardiac failure	3 (0.4)	3 (0.3)
Tachycardia	3 (0.4)	3 (0.3)
Tricuspid valve incompetence	0	3 (0.3)
Myocardial infarction	2 (0.2)	2 (0.2)
Acute myocardial infarction	2 (0.2)	1 (0.1)
Cardiac arrest	2 (0.2)	1 (0.1)
Mitral valve incompetence	1 (0.1)	2 (0.2)
Extrasystoles	2 (0.2)	0
Aortic valve incompetence	0	2 (0.2)
Angina pectoris	1 (0.1)	0
Cardiovascular insufficiency	1 (0.1)	1 (0.1)
Pericardial effusion	1 (0.1)	1 (0.1)
Sinus bradycardia	1 (0.1)	1 (0.1)
Sinus tachycardia	1 (0.1)	1 (0.1)
Troponin increased	1 (0.1)	1 (0.1)
Troponin T increased	0	1 (0.1)
Acute coronary syndrome	0	1 (0.1)
Atrial flutter	0	1 (0.1)
Atrioventricular block first degree	0	1 (0.1)
Bradycardia	0	1 (0.1)
Bundle branch block right	0	1 (0.1)
Cardiac failure acute	0	1 (0.1)
Cor pulmonale	0	1 (0.1)
Palpitations	0	1 (0.1)
Supraventricular tachycardia	0	1 (0.1)
Ventricular failure	0	1 (0.1)
Ventricular fibrillation	0	1 (0.1)

a. Includes all AEs in the Cardiac Disorders System Organ Class and 3 AEs (prolonged QT, Troponin increased, Troponin T increased) in the Investigations System Organ Class.

Four cardiac AESIs, based on both broad and narrow Standardized MedDRA Queries (SMQs), were investigated in the pooled Phase 3 studies. Overall rates of cardiac AEs and cardiac AESIs were lower in solithromycin patients compared with moxifloxacin patients in the pooled Phase 3 CABP studies. The AESIs included cardiac failure (MedDRA SMQ), tachyarrhythmias (including

supraventricular and ventricular tachyarrhythmias) (MedDRA SMQ), ischemic heart disease (MedDRA SMQ), and torsade de pointes/QT prolongation (MedDRA SMQ). Events in the four cardiovascular SMQs were as follows for solithromycin vs. moxifloxacin, respectively: cardiac failure events (1.3% vs. 2.1%), tachyarrhythmias (0.6% vs. 1.2%), ischemic heart disease (0.9% in both groups), and torsade de pointes/QT prolongation (0.7% vs. 1.0%) (no case of torsade de pointes was observed with either drug, in either study) (Figure 7).

7.7.3 Analysis of Adverse Events Associated with Telithromycin

Telithromycin has been associated with several AEs that are not expected with a macrolide antibiotic, including visual disturbances, loss of consciousness, severe exacerbation of myasthenia gravis, and rarely, idiosyncratic hepatic failure. The incidence and severity of these AEs may be related specifically to the structural characteristics and metabolism of telithromycin, which can result in antagonism of specific nACh receptor subtypes by the parent molecule and/or its metabolites. Solithromycin is differentiated from telithromycin in terms of structure, metabolism, and nACh receptor antagonism (Section 7.7.4).

The solithromycin safety database was analyzed for events of special interest based on the telithromycin safety signals. These analyses do not suggest an association of solithromycin with the types of safety events previously observed with telithromycin. The observation of exposure-related hepatic transaminase elevation in solithromycin patients is distinct from the acute and severe episodes of liver failure that were reported with telithromycin. Hepatic safety of solithromycin is discussed in Section 7.7.1, and the other AESIs are discussed below, based on data from the pooled Phase 3 studies.

7.7.3.1 Visual Disturbances

Vision disorder AESIs were reported in very few patients (Figure 7). Only one patient in the solithromycin group experienced an AE related to visual disturbances (‘black spots in eyes’).

7.7.3.2 Loss of Consciousness

No patients experienced spontaneous loss of consciousness, syncope, or fainting while on study drug. Dizziness occurred in 20 patients (2.3%) in the solithromycin group and 12 patients (1.4%) in the moxifloxacin group. None of these events was associated with fainting or syncope, or loss of consciousness, and none were associated with concurrent events of tachycardia, hypotension, or arrhythmia.

7.7.3.3 Exacerbation of Myasthenia Gravis

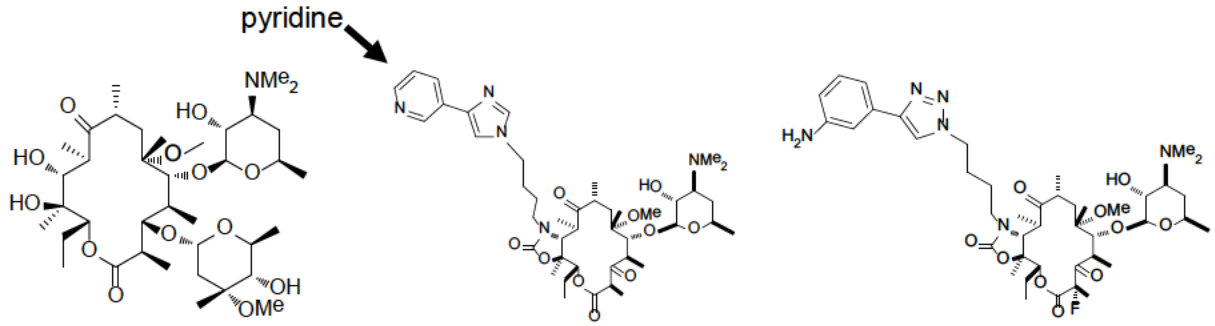
While a known history of myasthenia gravis was an enrollment exclusion criterion no patients experienced a new diagnosis of myasthenia gravis or exacerbation of myasthenia gravis.

7.7.4 Biochemical and Physiologic Differentiation of Solithromycin from Telithromycin

Telithromycin, the first ketolide, has been associated with some adverse reactions that were considered unusual for macrolides. These included blurred vision, loss of consciousness, rapid

progression of exacerbations of myasthenia gravis, and instances of idiosyncratic hepatic failure that were rare but possibly more common than with the older macrolides (erythromycin, azithromycin, and clarithromycin). The pyridine in the side chain is a distinctive feature of telithromycin, and is not present in the older macrolides or in solithromycin (Figure 26).

Figure 26 Chemical Structures of Clarithromycin, Telithromycin and Solithromycin



Clarithromycin Telithromycin Solithromycin

Because pyridine analogs have been known to interact with nACh receptors and evoke adverse reactions similar to the macrolide-atypical adverse reactions associated with telithromycin, it was hypothesized that these events could be associated with inhibition of nACh receptors. Therefore, telithromycin, clarithromycin, azithromycin, and solithromycin were tested against a variety of nACh receptors expressed in *Xenopus laevis* oocytes to determine the degree of inhibition (Bertrand 2010).

Telithromycin and/or its metabolites significantly inhibited the α3β4, α7, α3β2, α1β1δε, and α4β2 nACh receptors in these experiments. The cleaved side chain of telithromycin, which contains the pyridine moiety, also inhibited these receptors. While the intact telithromycin molecule does not effectively penetrate the blood-brain barrier, the side chain may be able to do so. Solithromycin and the older macrolides did not demonstrate the same profile of inhibition of the nACh receptors.

The visual disturbances associated with telithromycin can be attributed to inhibition of the α3β4 and α7 receptors that regulate visual accommodation and are found in the ciliary ganglion of the eye. Similarly, inhibition of the α4β2 receptor in the cortical region of the brain could be associated with loss of consciousness. Blockade of both the presynaptic neural muscle end plate receptor α3β2 and the postsynaptic neuromuscular junction receptor α1β1δε could result in the severe exacerbations of myasthenia gravis observed with telithromycin.

Inhibition of α7 receptors on targets of the vagally-mediated anti-inflammatory reflex (in particular on macrophages), whose activation by acetylcholine decreases release of TNF-α and other inflammatory cytokines, offers a potential explanation for the rare cases of serious hepatocellular injury that were observed (through inhibition of negative feedback control of macrophage proinflammatory mediator release).

Further support for the pyridine/nACh receptor inhibition hypothesis for visual disturbances is provided by studies conducted with voriconazole, an azole antifungal agent associated with visual disturbances, which also blocks α3β4 nACh receptors. Voriconazole contains a free heterocyclic nitrogen in its pyrimidine moiety. Conversely, fluconazole, which does not contain a free heterocyclic nitrogen and is not associated with visual disturbances, does not block these receptors.

Studies of the mode of inhibitory action of telithromycin at the α3β4 and α7 receptors indicate that telithromycin is acting by a dual mechanism, by competitive inhibition in the orthosteric ligand binding site and by a non-competitive inhibition at high ACh concentrations that is probably caused by an open channel blocker effect. Progesterone is known to sensitize these receptors (Valera 1992) and this could account for the more frequent occurrence of visual effects in young women receiving telithromycin.

8 PROPOSED INDICATION AND DOSING

The proposed indication, in patients 18 years of age and older, is as follows:

> Solithromycin is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative bacteria: *Streptococcus pneumoniae* (including penicillin-resistant isolates, macrolide-resistant isolates, multi-drug-resistant isolates, and cases with concurrent bacteremia), *Haemophilus influenzae* (including beta-lactamase producing isolates*), Moraxella catarrhalis*, *Staphylococcus aureus* (methicillin-susceptible [MSSA]), and the atypical bacterial pathogens *Legionella pneumophila* and *Mycoplasma pneumoniae*.

Dosing recommendations for patients with $CL_{CR} \geq 30$ mL/minute are as follows:

> The oral dosing regimen is 800 mg given as a single dose on day 1 followed by 400 mg QD for 4 days, for a total of 5 days of treatment. The IV regimen is 400 mg IV QD, infused over 60 minutes, for a total of 7 days of treatment. For patients who transition from IV to oral dosing, a single 800 mg dose is administered the first day of oral dosing, followed by 400 mg QD through the completion of a 7 day treatment course.

Dosing adjustment is recommended for patients with $CL_{CR} < 30$ mL/minute, as follows:

> The oral dosing regimen is 800 mg given as a single dose on day 1 followed by 200 mg QD for 4 days, for a total of 5 days of treatment. The IV regimen is 400 mg IV infused over 60 minutes on the first day, followed by 200 mg IV QD for a total of 7 days. For patients who transition from IV to oral dosing, a single 400 mg dose is administered the first day of oral dosing, followed by 200 mg QD through the completion of a 7 day treatment course.

Solithromycin will be available as 200 mg capsules for oral administration and in a 400 mg vial for reconstitution and dilution into 0.9% NaCl for IV administration.

9 BENEFIT RISK DISCUSSION

Data from the comprehensive clinical development program demonstrate the efficacy and safety of solithromycin for the treatment of adult patients with CABP. Macrolide-resistant pneumococci are now so widespread and clinically impactful in the US that empiric therapy with a macrolide alone can no longer be recommended for CABP. As a result, physicians employ treatment strategies that rely on the use of fluoroquinolones or combination treatments (typically a β-lactam with a macrolide). While these strategies are effective, the increasing use of fluoroquinolones and treatment with multiple antibiotics may have potential long-term safety consequences in some patients and worsen the problem of antibiotic resistance.

Solithromycin offers a monotherapy treatment regimen with both IV and oral formulations for CABP, with less antibiotic class-associated risk for *C. difficile* overgrowth than fluoroquinolones, and offers a strategy to avoid rare but potentially serious quinolone adverse effects. The IV formulation of solithromycin enables clinicians in urgent care and hospital settings to treat CABP with a formulation that will quickly achieve therapeutic exposures, with the option of transition to the same oral drug in appropriate patients.

Solithromycin was shown to be effective in the treatment of CABP in oral and IV to oral treatment regimens. In two pivotal Phase 3 studies, solithromycin was non-inferior to moxifloxacin for the primary outcome of ECR. These efficacy findings were substantiated by similar outcomes across pooled subpopulations for demographics, disease severity, and geographic region. By-pathogen ECR rates and clinical success rates at SFU for target CABP pathogens were also comparable to those observed for moxifloxacin.

More than 2000 subjects and patients have been exposed to solithromycin, and 920 adult patients have received solithromycin for up to 7 days for treatment of CABP. Solithromycin demonstrated a safety profile acceptable for treatment of patients with CABP. The profile of solithromycin was typical of macrolide antibiotics, including asymptomatic transaminase elevations and infusion related AEs. Unlike other macrolides, a thorough QT study of solithromycin was negative.

The data demonstrate that solithromycin will be a safe and effective new option for empiric first-line treatment of CABP in adults.

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11 APPENDICES

11.1 CE Populations (CE-ECR, CE-EOT, and CE-SFU)

Three CE populations were defined, the CE-ECR, CE-EOT, and CE-SFU populations. The CE-ECR population was not prespecified in the protocols and was defined based on FDA recommendations at a meeting on September 9, 2015. The CE populations consist of all patients in the ITT population who also meet criteria listed below. The CE-EOT and CE-SFU population criteria were programmed from the eCRF data and/or reviewed manually by the Sponsor in a blinded manner prior to database lock of each Phase 3 study to confirm each patient's inclusion in or exclusion from the CE populations. The CE populations were determined in the same manner in both Phase 3 studies. CE-ECR is an additional analysis population included in the integrated analyses. Population inclusion criteria that are unique to the CE-ECR population were determined programmatically. Population inclusion criteria that are common for the CE-ECR, as well as the CE-EOT and CE-SFU, populations remain as determined prior to unblinding of each Phase 3 study.

1. Met key inclusion criteria. Patients must have met all the inclusion criteria defining minimal disease criteria to be included in the CE-ECR, CE-EOT, and CE-SFU populations. These include:
    - At least 3 signs and symptoms (new or worsening) of CABP
    - At least 1 systemic sign of infection including fever, hypothermia, or presence of pulmonary rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)
    - Received no more than a single dose of a short-acting systemic antibiotic during the prior 7 days (defined as prior to randomization)
    - PORT Risk Class II, III, or IV (pneumonia severity scores of 51 to 130, inclusive). For Study 300, the upper limit of the pneumonia severity score for enrollment was 105; for Study 301, the upper limit of the pneumonia severity score for enrollment was 130. Patients with pneumonia severity scores greater than the ceilings were included in the CE populations. Patients with pneumonia severity scores <51 were not included in the CE populations.
    - Presence of lobar, multilobar, or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia on a pulmonary imaging study (e.g. CXR [posteroanterior and lateral] or CT of thorax) within 48 hours before the first dose of study drug.
2. Clinical Outcome Assessment
    - For the CE-ECR population:
        - Must not have an ECR of indeterminate. A patient was considered to have an indeterminate response if:
            - Data were missing such that a response cannot be determined
            - There were <2 symptoms of CABP at baseline

- The assessment of ECR occurred outside of the protocol-specified window of 72 (-12/+36 for Study 300, -13/+36 for Study 301) hours following the first dose of study drug (unless determined to be a treatment failure prior to this evaluation)

- For the CE-EOT population:
  - Completed the EOT visit on Day 7 (+2), unless considered a failure prior to Day 7 (+2) based on the investigator assessment of response
  - Did not have a clinical response of indeterminate based on the investigator assessment at EOT
- For the CE-SFU population:
  - Completed the SFU visit 5 to 10 days after the last dose of study drug (Day 12 to 17) unless was considered a failure at either the EOT or SFU visit based on the investigator assessment of clinical response
  - Did not have a clinical response of indeterminate based on the investigator assessment at the SFU visit

3. Received ≥ 2 doses of study drug during the first 48 hours if a clinical failure (based on the investigator assessment of clinical response at the EOT visit [CE-EOT] or SFU visit [CE-SFU]), unless discontinued study drug due to an AE or died
4. Received ≥ 3 doses of study drug during the first 72 hours if a clinical success (based on the investigator assessment of clinical response at the EOT visit [CE-EOT] or SFU visit [CE-SFU])
5. Did not receive another systemic antibacterial from the first dose of study drug through the assessment of ECR (CE-ECR), EOT visit (CE-EOT), or through the SFU visit (CE-SFU) with likely or documented activity against confirmed or potential CABP pathogens, unless considered a non-responder for ECR or clinical failure by the investigator at the EOT visit or the SFU visit. Patients who did not have a pathogen isolated at baseline and received an antibiotic with activity against any potential CABP pathogen were excluded from the CE-ECR, CE-EOT, and CE-SFU populations, unless considered a non-responder for ECR or failure by the investigator at the EOT or SFU visit.
6. Received the correct study drug based on randomization assignment
7. Study personnel involved in the assessment of efficacy or monitoring of the efficacy data were not unblinded to the patient's treatment assignment unless they were unblinded due to the need to manage an AE.
8. Did not meet any key exclusion criteria (such as subsequently diagnosed lung cancer, tuberculosis, or pneumocystis pneumonia) as defined in the study SAPs

11.2 Overview of PK and PD Studies

Table 64 Overview of Clinical Pharmacology / Biopharmaceutic Studies That Characterized the PK and PD of Solithromycin (CABP Studies not Listed)

Study Identification	Design	Subjects (N) Gender Age Range	Solithromycin Administration	Comparator / Other Study Drug Administration
Clinical Pharmacology – Oral				
CE01-101 Single oral dose PK	Randomized, double-blind, placebo-controlled, single-dose, dose-escalating	Healthy adult subjects (N=49) 30 M / 19 F 20-55 years	Solithromycin (n=35) Escalating single oral doses (50, 100, 200, 400, 800, 1200, & 1600 mg)	Placebo (n=14) Single dose
CE01-102 Multiple oral dose PK	Randomized, double-blind, placebo-controlled, multiple-dose, dose-escalating	Healthy adult subjects (N=35) 22 M / 13 F 20-55 years	Solithromycin (n=25) Escalating multiple oral doses (200, 400 & 600 mg QD for 7 days)	Placebo (n=10) Multiple dose QD for 7 days
CE01-106 Drug-drug Interaction with Midazolam	Randomized, open-label, multiple-dose, 2-period, crossover	Healthy adult subjects (N=16) 10 M / 6 F 21-54 years	Solithromycin (n=16) 400 mg oral for 5 days (Days 3-7) or 800 mg oral first day (Day 3) & 400 mg next 4 days (Days 4-7)	Midazolam (n=16) 0.075 mg/kg Single doses × 3 Days 1, 3 & 7
CE01-107 Drug-drug Interaction with Ketoconazole	Open-label, single-dose, single sequence crossover	Healthy adult subjects (N=14) 7 M / 7 F 22-54 years	Solithromycin (n=14) 400 mg oral Day 1 & 11	Ketoconazole (n=14) 400 mg oral Days 7-11

Study Identification	Design	Subjects (N) Gender Age Range	Solithromycin Administration	Comparator / Other Study Drug Administration
CE01-108 Absorption, Metabolism, Excretion	Open-label, single-dose	Healthy adult subjects (N=8) 8 M 22-50 years	[^{14}C]-Solithromycin (n=8) Single oral dose 800 mg (~100 µCi) solution	NA (n=0)
CE01-110 Drug-drug Interaction with Rifampin	Open-label, multiple-dose, single-sequence, crossover	Healthy adult subjects (N=14) 7 M / 7 F 21-43 years	Solithromycin (n=14) 800 mg oral Days 1 & 7 400 mg oral Days 2-5 and 8-11	Rifampin (n=13) 600 mg QD for 13 days
CE01-113 PK in Subjects with Hepatic Impairment	Open-label, multi-dose, healthy-controlled	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 (n=33) Multiple doses 800 mg oral Day 1 & 400 mg oral Days 2-5	NA (n=0)
CE01-114 Concentrations in Epithelial Lining Fluid, Alveolar Macrophages, Saliva and Plasma	Open-label, multiple-dose	Healthy adult subjects (N=31) 25 M / 6 F 20-50 years	Solithromycin (n=31) 400 mg oral QD for 5 days	NA (n=0)
CE01-115 PK in Subjects with Renal Impairment	Open-label, multiple-dose, healthy-controlled	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 (n=25) 800 mg oral Day 1 and 400 mg oral Days 2-5	NA (n=0)

Study Identification	Design	Subjects (N) Gender Age Range	Solithromycin Administration	Comparator / Other Study Drug Administration
CE01-117 Effects on Oropharyngeal and Intestinal Microflora	Open-label, multiple-dose	Healthy adult subjects (N=13) 6 M / 7 F 19-41 years	Solithromycin (n=13) 800 mg oral Day 1 & 400 mg oral Days 2-7	NA (n=0)
CE01-122 Drug-drug Interaction with Digoxin	Open-label, multiple-dose, 2-period, single sequence, crossover	Healthy adult subjects (N=14) 7 M / 7 F 22-45 years	Solithromycin (n=14) 800 mg oral Day 6 & 400 mg oral Days 7-10	Digoxin (n=14) 0.5 mg Q12h Day 1, 0.125 mg QD Days 2-10

Study Identification	Design	Subjects (N) Gender Age Range	Solithromycin Administration	Comparator / Other Study Drug Administration
Clinical Pharmacology – IV and IV to Oral				
CE01-104 Single and Multiple Dose IV PK (Absolute Bioavailability portion of study listed in Biopharmaceutics)	Randomized double-blind, single- and multiple-dose, placebo-controlled, dose-escalation	Healthy adult subjects (N=143) IV only: 84 M / 42 F IV + Oral: 13 M / 4 F 19-55 years	Solithromycin (n=91) Single IV dose 25, 50, 100, 200, 400, 800, & 1000 mg Multiple IV dose 50, 100, 200 mg QD ≤ 7 days Infusion times 0.75 to 3 h	Placebo (n=52) Single dose Multiple dose QD ≤7 days
CE01-109 Thorough QT (ECG Effects of Supratherapeutic Exposure)	Randomized, single-dose, placebo- and active-controlled, 3-way crossover	Healthy adult subjects (N=48) 33 M / 15 F 20-55 years	Solithromycin (n=47) Single IV dose 800 mg (500 mL) IV over 40 minutes	Oral Moxifloxacin (n=44) 400 mg single dose Saline Placebo (n=45) 500 mL over 40 minutes
CE01-116 PK of Single and Multiple IV Doses and of an IV to Oral Regimen	Randomized double-blind, placebo-controlled, dose-escalation, single and multiple doses	Healthy adult subjects (N=92) IV only: 71 M / 14 F IV + Oral: 7 M 19-55 years	Solithromycin (n=62) IV Single dose 400, 600, 800 mg IV to oral multiple dose 200, 400, 800 mg (IV then oral) QD ≤ 7 days Infusion times 0.5 to 1.5 h	Placebo (n=30) Single dose Multiple dose QD ≤7 days

Study Identification	Design	Subjects (N) Gender Age Range	Solithromycin Administration	Comparator / Other Study Drug Administration
CE01-118 PK of Multiple IV Doses, and IV to Oral Regimen, and Combined IV and Oral Dose	Randomized multiple IV dose, IV to oral multiple dose, and combined IV and oral single dose	Healthy adult subjects (N=40) IV only: 10 M / 10 F IV + Oral: 10 M / 10 F 23-66 years	Solithromycin IV only (2 infusion solutions) 400 mg QD ≤ 7 days (n=20) Combined IV + Oral single dose 1200 mg oral, 400 mg IV 5 h later (n=10) IV to oral multiple dose 400 mg IV ≤ 3 days; 800 mg oral Day 4 (or first oral day), then 400 mg oral QD for total of 7 days (n=10) Infusion times 0.5 to 1.0 h	NA (n=0)
CE01-121 PK of Single Supratherapeutic Dose and Central and Peripheral Multiple Doses	Randomized, double-blind, placebo and active controlled. Multiple IV dose, single supratherapeutic dose, central IV administration	Healthy adult subjects (N=40) 30 M / 10 F 18-75 years	Solithromycin (n=30) Multiple dose 400 mg IV QD for 7 days Infusion times 0.5 to 1.0 h Single dose 800 mg over 40 minutes	IV Placebo (n=8) IV Moxifloxacin 400 mg (n=2) Multiple dose QD for 7 days

Study Identification	Design	Subjects (N) Gender Age Range	Solithromycin Administration	Comparator / Other Study Drug Administration
Biopharmaceutics				
CE01-103 Effect of Food on Bioavailability	Randomized, 2-period, fasted/fed, single-dose, crossover	Healthy adult subjects (N=24) 19 M / 5 F 19-50 years	Solithromycin (n=24) 400 mg oral single dose Fasting and fed conditions	NA (n=0)
CE01-104 Absolute Bioavailability of Capsules (PK portion of study listed in Clinical Pharmacology)	Double-blind, single- and multiple-dose, placebo-controlled, dose-escalation; absolute bioavailability capsules	Healthy adult subjects (N=17) IV + Oral: 13 M / 4 F 20-54 years	Solithromycin (n=12) Single dose IV 100, 200, 400 mg then Single dose Oral 400 mg	Placebo (n=5) Single dose IV placebo, then Single dose oral solithromycin 400 mg
CE01-111 Bioequivalence Tablet to Capsules	Randomized, single-dose, crossover	Healthy adult subjects (N=40) 20 M / 20 F 19-55 years	Solithromycin (n=40) 400 mg single dose ×2 Tablet (1×400 mg) or Capsules (2×200 mg)	NA (n=0)
CE01-112 Relative Bioavailability Suspension to Capsules	Randomized, single-dose, crossover	Healthy adult subjects (N=32) 23 M / 9 F 23-55 years	Solithromycin (n=32) 400 mg single dose ×2 Capsules (2×200 mg) or Suspension 400 mg (48.48 mg/mL)	NA (n=0)

ECG=electrocardiogram, IV=intravenous, NA=not applicable; PK=pharmacokinetics; Q12h=once every 12 hours; QD=once daily

11.3 PORT Score Determination

Table 65 PORT Score Determination

Patient Characteristic	Point Assignment
Age	One point for each year of age
Female?	-10 if yes
Neoplastic disease history? [a]	+30, if yes
Liver disease? [1]	+20, if yes
Congestive heart disease? [a]	+10, if yes
Cerebrovascular disease? [a]	+10, if yes
Renal disease? [1]	+10, if yes
Altered mental status? [1]	+20, if yes
Respiratory rate ≥ 30/minute?	+20, if yes
Systolic blood pressure <90 mm Hg?	+20, if yes
Temperature <35°C (95ºF) or ≥ 40ºC (104ºF)	+15, if yes
Pulse ≥ 125	+10, if yes
pH <7.35 (from ABG [b])?	+30, if yes (+0 if ABG not obtained)
Blood urea nitrogen >30 mg/dL (Urea >11 mmol/L)?	+20, if yes
Sodium <130 mmol/L?	+20, if yes
Glucose ≥ 250 mg/dL (≥14 mmol/L)?	+10, if yes
Hematocrit <30%?	+10, if yes
Partial pressure of arterial oxygen <60 mmHg (from ABG if medically indicated) or oxygen saturation <90% (by pulse oximetry)?	+10, if yes
Pleural effusion on radiograph?	+10, if yes
PORT Score	Sum of Applicable Numbers Above

a. Guidelines to Assist Investigators in Determining the Presence of the Following Patient Characteristics: Neoplastic Disease: Defined as any cancer except basal cell or squamous cell cancer of the skin that was active at the time of CABP presentation or diagnosed within one year of presentation. Liver Disease: Defined as clinical or histological diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis. Congestive heart failure: Defined as systolic or diastolic ventricular dysfunction documented by history, physical exam, chest radiograph, echocardiogram, multiple gated acquisition scan or left ventriculogram. Cerebrovascular disease: Defined as a diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or CT scan. Renal Disease: Defined as a history of chronic renal disease or abnormal blood urea nitrogen or creatinine clearance, which is documented in the patient's medical record. Altered Mental Status: Defined as disorientation with respect to person, place or time that is not known to be chronic, stupor or coma.

b. ABG not required, perform only if medically indicated. Abbreviation: ABG=arterial blood gas

Table 66 PORT Risk Class Determination

PORT Risk Class	PORT Score
I (Ineligible for Phase 3 Studies)	0-50
II	51-70
III	71-90
IV (>105 ineligible for Study 300)	91-130
V (Ineligible for Phase 3 Studies)	>130

11.4 Inclusion and Exclusion Criteria

11.4.1 Study 300 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Male and female patients ≥ 18 years of age
2. Acute onset of at least 3 of the following signs and symptoms (new or worsening):
    - Cough
    - Production of purulent sputum
    - Shortness of breath (dyspnea)
    - Chest pain
3. At least 1 of the following:
    - Fever: [defined as body temperature >38°C (100.4°F) measured orally, >38.5°C (101.3°F) measured tympanically, or >39°C (102.2°F) measured rectally]
    - Hypothermia: [defined as body temperature <35°C (95.0°F) measured orally, <35.5°C (95.9°F) measured tympanically, or <36°C (96.8°F) measured rectally]
    - Presence of pulmonary rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)
4. Received no systemic antibiotics other than a single dose of a short-acting antibiotic (penicillins, cephalosporins [not ceftriaxone], tetracyclines, or trimethoprim-sulfamethoxazole) in the 7 days prior to enrollment
5. PORT Risk Class II, III, or IV (pneumonia severity scores of 51 to 105, inclusive)
6. Presence of lobar, multilobar, or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia on a pulmonary imaging study (e.g. CXR posteroanterior and lateral preferred; single view acceptable if conclusive or CT of thorax) within 48 hours before the first dose of study drug; although the Investigator may have interpreted the imaging study to qualify a patient for enrollment, the film was also read by a local radiologist
7. Suitable candidate for oral therapy and able to swallow large capsules intact
8. Females of non-childbearing potential surgically sterile (e.g. tubal ligation) or at least 2 years post-menopausal
9. Females of childbearing potential (including females less than 2 years post-menopausal) had a negative pregnancy test at enrollment and agreed to use highly effective methods of birth control (ie, diaphragm plus spermicide or male condom plus spermicide, oral contraceptive in combination with a second method, contraceptive implant, injectable contraceptive, indwelling intrauterine device, sexual abstinence, or a vasectomized partner) while participating in the study and for 30 days after the last dose of study drug

10. Males agreed to use a double barrier method of contraception (condom plus spermicide or diaphragm plus spermicide) while participating in the study and for 30 days after the last dose of study drug, or the male patient or his female partner were surgically sterile (e.g. vasectomy, tubal ligation) or the female partner was post-menopausal
11. Provided written informed consent
12. Willing and able to attend all study visits and comply with all study procedures

Exclusion Criteria

1. Ventilator-associated pneumonia
2. Known anatomical or pathological bronchial obstruction or a history of bronchiectasis or documented severe COPD defined as forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) <70% and FEV1 <50% predicted; Note: patients with less severe COPD were NOT excluded; patients with COPD without a documented FEV1/FVC or FEV1 may have been enrolled if in the investigator's opinion the COPD was not severe
3. Presence of known:
    - Viral or fungal pneumonia
    - *Pneumocystis jiroveci* pneumonia
    - Aspiration pneumonia
    - Other non-infectious causes of pulmonary infiltrates (e.g. pulmonary embolism, hypersensitivity pneumonia, congestive heart failure)
    - Primary or metastatic lung cancer
    - Cystic fibrosis
    - Active or suspected tuberculosis
    - Empyema (not including sterile parapneumonic effusions)
4. Presence of pneumonia known to be caused by a pathogen resistant to moxifloxacin or solithromycin
5. Hospitalization within 90 days or residence in a long-term-care facility within 30 days prior to the onset of symptoms (ie, healthcare-associated pneumonia)
6. Any condition that could affect drug absorption, e.g. status post gastrectomy
7. History of post-antibiotic colitis within the last 3 months
8. Mean QT interval corrected with the Fridericia formula (QTcF) greater than 450 msec on screening 5-minute summary (or triplicate) ECG
9. Concomitant use of drugs known to prolong the QT interval, including class Ia (quinidine, procainamide) or Class III (amiodarone, sotalol) anti-arrhythmics

10. Concomitant use of drugs, foods, or herbal products known to be moderate to potent inhibitors of CYP3A4 isozymes: oral antifungal agents (e.g. ketoconazole, itraconazole, posaconazole, fluconazole and voriconazole); human immunodeficiency virus (HIV) protease inhibitors (e.g. ritonavir and saquinavir), hepatitis C virus (HCV) protease inhibitors (e.g. boceprevir and telaprevir), nefazodone, fluvoxamine, conivaptan, diltiazem, verapamil, aprepitant, ticlopidine, crizotinib, imatinib; grapefruit or grapefruit juice
11. Any use within the prior 7 days of drugs or herbal products known to be moderate to potent inducers of CYP3A4 isozymes: St. John's Wort, rifampin, rifabutin, anti-convulsants (e.g. phenobarbital, carbamazepine, phenytoin, rufinamide), modafinil, armodafinil, etraverine, efavirenz, bosentan
12. Required current use of drugs with narrow therapeutic indices that are principally metabolized by CYP3A4 or transported by P-gp, for which a drug interaction with solithromycin could result in higher and possibly unsafe exposures to these drugs: e.g. the P-gp substrates digoxin or colchicine and the CYP3A4 substrates, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, midazolam, pimozide, quinidine, sirolimus, tacrolimus, everolimus, and terfenadine
13. Receiving or anticipated to receive a daily dose of $\geq$ 20 mg of systemic prednisone or equivalent within the period starting 14 days prior to enrollment; Note: patients were allowed to receive an acute, short course of methylprednisolone or prednisone (or equivalent) for management of an acute exacerbation of COPD or reactive airway disease in asthmatics
14. Cytotoxic chemotherapy or radiation therapy within the previous 3 months
15. Known history of significant and ongoing renal, hepatic, or hematologic impairment; current treatment for HCV infection
16. Any of the following laboratory parameters:
    - CR_{CL} <30 mL/min calculated by the Cockcroft-Gault formula
    - AST or alanine aminotransferase (ALT) >3× ULN
    - Total bilirubin >2×ULN
    - Neutrophil count $\leq$ 500 neutrophils/mm^3 as measured by differential on complete blood count (CBC) or inferred by total white blood cells (WBCs) >1000/µL
    - Platelet count <50,000 cells/mm^3
17. Known HIV infection
18. Known history of myasthenia gravis
19. Women who were pregnant or nursing
20. Previously randomized in this protocol
21. Any investigational drugs taken or investigational devices used within 4 weeks before administration of the first dose of study drug
22. Concomitant conditions requiring additional antibacterial therapy that was potentially effective for the current CABP

23. History of intolerance or hypersensitivity to fluoroquinolone or macrolide antibiotics
24. History of tendinopathy with fluoroquinolone use
25. Clinical presentation with pneumonia of severity sufficient to result in direct admission to a hospital intensive care unit (regardless of PORT score)
26. Any concomitant condition that, in the opinion of the investigator, would preclude evaluation of a response or make it unlikely that the contemplated course of therapy and follow-up could be completed (e.g. life expectancy <30 days)

11.4.2 Study 301 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Male and female patients ≥ 18 years of age.
2. An acute onset of at least 3 of the following signs and symptoms (new or worsening):
   - Cough
   - Production of purulent sputum
   - Shortness of breath (dyspnea)
   - Chest pain
3. At least 1 of the following:
   - Fever: [defined as body temperature >38°C (100.4°F) measured orally, >38.5°C (101.3°F) measured tympanically or by temporal artery thermometry, >37.5°C [99.5°F] by axillary measurement, or >39°C (102.2°F) measured rectally]
   - Hypothermia: [defined as body temperature <35°C (95.0°F) measured orally, <35.5°C (95.9°F) measured tympanically or by temporal artery thermometry, <34.5°C [94.1°F] by axillary measurement, or <36°C (96.8°F) measured rectally]
   - Presence of pulmonary rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)
4. Received no systemic antibiotics other than a single dose of a short-acting antibiotic (penicillins, cephalosporins [not ceftriaxone], tetracyclines, or trimethoprim-sulfamethoxazole) in the 7 days prior to enrollment.
5. PORT Risk Class II, III or IV (pneumonia severity scores of 51 to 130, inclusive).
6. In the opinion of the investigator, IV therapy was both warranted and feasible.
7. Presence of lobar, multilobar, or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia on a pulmonary imaging study (e.g. CXR, posteroanterior and lateral preferred; single view acceptable if conclusive or computed tomography [CT] of thorax) within 48 hours before the first dose of study drug. The investigator could interpret the imaging study to qualify a patient for enrollment; however, a local radiologist must also read the film.
8. Females of non-childbearing potential surgically sterile (e.g. tubal ligation) or at least 2 years post-menopausal.

9. Females of childbearing potential (including females <2 years post-menopausal) must have had a negative pregnancy test at enrollment and agreed to use highly effective methods of birth control (ie, diaphragm plus spermicide or male condom plus spermicide, oral contraceptive in combination with a second method, contraceptive implant, injectable contraceptive, indwelling intrauterine device, sexual abstinence, or a vasectomized partner) while participating in the study and for 30 days after the last dose of study drug.
10. Males agreed to use a double barrier method of contraception (condom plus spermicide or diaphragm plus spermicide) while participating in the study and for 30 days after the last dose of study drug, or the male patient or his female partner must have been surgically sterile (e.g. vasectomy, tubal ligation) or the female partner must be postmenopausal.
11. The patient voluntarily signed and dated the IRB/IEC approved ICF prior to any study-specific screening procedures.
12. The patient was able to attend all study visits and comply with all study procedures.

Exclusion Criteria

1. Ventilator-associated pneumonia
2. Known anatomical or pathological bronchial obstruction or a history of bronchiectasis or documented severe COPD defined as forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) <70% and FEV1 <50% predicted. Note: Patients with less severe COPD were NOT excluded. Patients with COPD without a documented FEV1/FVC or FEV1 could be enrolled if in the investigator's opinion the COPD was not severe.
3. Current diagnosis of:
    - Fungal pneumonia
    - *Pneumocystis jiroveci* pneumonia
    - Aspiration pneumonia
    - Other non-infectious causes of pulmonary infiltrates (e.g. pulmonary embolism, hypersensitivity pneumonia, congestive heart failure)
    - Primary or metastatic lung cancer
    - Cystic fibrosis
    - Active or suspected tuberculosis
    - Empyema (not including sterile parapneumonic effusions).
4. Presence of pneumonia known to be caused by a pathogen resistant to moxifloxacin or solithromycin.
5. Hospitalization within 90 days or residence in a long-term-care (skilled nursing) facility within 30 days prior to the onset of symptoms (i.e. healthcare-associated pneumonia).
6. Any condition that could affect drug absorption, e.g. status post gastrectomy.
7. History of post-antibiotic colitis within the last 3 months.
8. Mean QTcF (QT interval corrected with the Fridericia formula) >460 msec on screening 5-minute summary (or triplicate) ECG.

9. Concomitant use of drugs known to prolong the QT interval, including Class Ia (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmics.
10. Concomitant use of drugs, foods, or herbal products known to be moderate to potent inhibitors of CYP3A4 isozymes: oral antifungal agents (e.g. ketoconazole, itraconazole, posaconazole, fluconazole, and voriconazole); human immunodeficiency virus (HIV) protease inhibitors (e.g. ritonavir and saquinavir), hepatitis C virus (HCV) protease inhibitors (e.g. boceprevir and telaprevir), nefazodone, fluvoxamine, conivaptan, diltiazem, verapamil, aprepitant, ticlopidine, crizotinib, imatinib; grapefruit or grapefruit juice.
11. Any use within the prior 7 days of drugs or herbal products known to be moderate to potent inducers of CYP3A4 isozymes: St. John's Wort, rifampin, rifabutin, anti-convulsants (e.g. phenobarbital, carbamazepine, phenytoin, rufinamide), modafinil, armodafinil, etraverine, efavirenz, bosentan.
12. Required current use of drugs with narrow therapeutic indices that are principally metabolized by CYP3A4 or transported by P-gp, for which a drug interaction with solithromycin could result in higher and possibly unsafe exposures to these drugs: e.g. the P-gp substrates digoxin or colchicine and the CYP3A4 substrates, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, midazolam, pimozide, quinidine, sirolimus, tacrolimus, everolimus, and terfenadine.
13. Received or anticipated to receive a daily dose of $\geq$ 20 mg of systemic prednisone or equivalent within the period starting 14 days prior to enrollment. Note: Patients were allowed to receive an acute, short course of methylprednisolone or prednisone (or equivalent) for management of an acute exacerbation of COPD or reactive airway disease in asthmatics.
14. Cytotoxic chemotherapy or radiation therapy within the previous 3 months.
15. Known history of significant and ongoing renal, hepatic, or hematologic impairment; current treatment for HCV infection.
16. Any of the following laboratory parameters:
    - CR_{CL} <30 mL/min calculated by the Cockcroft-Gault formula
    - AST or ALT >3× ULN
    - Total bilirubin >2×ULN
    - Platelet count <50,000 cells/mm^3
17. Known HIV infection.
18. Known history of myasthenia gravis.
19. Women who were pregnant or nursing.
20. Previously randomized in this protocol.
21. Any investigational drugs taken within 4 weeks before administration of the first dose of study drug.
22. Concomitant conditions requiring additional antibacterial therapy that would be potentially effective for the current CABP.
23. History of intolerance or hypersensitivity to fluoroquinolone or macrolide antibiotics.
24. History of tendinopathy with fluoroquinolone use.
25. Clinical presentation with pneumonia that required mechanical ventilation.

26. Any concomitant condition that, in the opinion of the investigator, would preclude evaluation of a response or make it unlikely that the contemplated course of therapy and follow-up could be completed (e.g. life expectancy <30 days).

11.5 Pathogen Identification

Table 67 Testing Methods for Detection of Causative CABP Pathogens in the mITT and mITT-2 Populations

mITT Population	mITT-2 Population
Isolation from culture of baseline pleural fluid, BAL or blood specimen.	Isolation from culture of baseline pleural fluid, BAL or blood specimen.
Isolation from culture of baseline sputum specimen in the presence of Gram stain with ≥ 10 PMNs/LPF and <10 SECs/LPF (except for *Legionella* spp.).	Isolation from culture of baseline sputum specimen in the presence of a Gram stain with ≥ 10 PMNs/LPF and <10 SECs/LPF (except for *Legionella* spp.).
Detection of *L. pneumophila* or *S. pneumoniae* antigen in urine.	Detection of *L. pneumophila* antigen in urine.
Detection of *M. pneumoniae* from an OP swab by culture with an isolate, or by culture without an available isolate but species confirmed by qPCR.	Detection of *M. pneumoniae* from an OP swab by culture with an isolate or by culture without an available isolate but species confirmed by qPCR.
Quantitative *M. pneumoniae* qPCR assay of OP swabs.	Not included
Identification meeting diagnostic criteria (≥ 1000 *lytA* gene copies/mL) in quantitative pneumococcal PCR assays of NP swabs.	Not included
Semi-quantitative multiplex PCR positivity from sputum (for a panel of pathogens that includes *H. influenzae*, *M. catarrhalis*, *S. aureus*, and *S. pneumoniae*) for Study 300 only.	Not included
Diagnostic 4-fold rise between acute and convalescent sera in pathogen-specific antibody titers (combined IgG/IgA/IgM single assay response to *L. pneumophila* and IgG assay for *M. pneumoniae*).	Not included

BAL=bronchoalveolar lavage, LPF=low power field, NP=nasopharyngeal, OP=oropharyngeal, PCR=polymerase chain reaction, PMN=polymorphonuclear leukocyte; SEC=squamous epithelial cells; qPCR=quantitative PCR

The SAP outlined algorithms for programmatic determination of the pathogen status of target species (*S. pneumoniae, S. aureus, H. influenzae, M. catarrhalis, L. pneumophila,* and *M. pneumoniae*) using the methods described above. Other species identified from blood and respiratory specimens, were reviewed in a blinded manner by the Sponsor on a case-by-case basis for determination of whether the organism was a pathogen for CABP.

11.6 Outcomes by Pathogen

Early clinical response rate by baseline pathogen in the MITT-2 population is shown in Table 68. Clinical success rates at SFU by baseline pathogen in the ME-SFU-2 population are shown in Table 69.

Table 68 Early Clinical Response Rate by Baseline Pathogen in the mITT-2 Populations (Individual and Pooled Studies)

	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral (N=119) n/N (%)	Moxi Oral (N=106) n/N (%)	Soli IV to Oral (N=103) n/N (%)	Moxi IV to Oral (N=90) n/N (%)	Soli Pooled (N=222) n/N (%)	Moxi Pooled (N=196) n/N (%)
Gram-Positive Bacteria						
Streptococcus pneumoniae	21/28 (75.0)	30/37 (81.1)	21/25 (84.0)	21/26 (80.8)	42/53 (79.2)	51/63 (81.0)
MDRSP	5/8 (62.5)	4/5 (80.0)	8/8 (100.0)	8/11 (72.7)	13/16 (81.3)	12/16 (75.0)
PSSP	13/15 (86.7)	22/28 (78.6)	15/19 (78.9)	11/13 (84.6)	28/34 (82.4)	33/41 (80.5)
PISP	6/8 (75.0)	6/6 (100.0)	3/3 (100.0)	9/11 (81.8)	9/11 (81.8)	15/17 (88.2)
PRSP	2/4 (50.0)	1/2 (50.0)	3/3 (100.0)	1/2 (50.0)	5/7 (71.4)	2/4 (50.0)
Macrolide-Resistant	5/7 (71.4)	5/5 (100.0)	7/7 (100.0)	7/10 (70.0)	12/14 (85.7)	12/15 (80.0)
Quinolone-Resistant	0/0	0/0	0/0	0/0	0/0	0/0
Beta-haemolytic streptococcui	1/3 (33.3)	2/3 (66.7)	2/2 (100.0)	1/1 (100.0)	3/5 (60.0)	3/4 (75.0)
Streptococcus pyogenes	1/1 (100.0)	2/2 (100.0)	2/2 (100.0)	0/0	3/3 (100.0)	2/2 (100.0)
Streptococcus agalactiae	0/1 (0.0)	0/0	0/0	0/0	0/1 (0.0)	0/0
Streptococcus dysgalactiae	0/1 (0.0)	0/1 (0.0)	0/0	1/1 (100.0)	0/1 (0.0)	1/2 (50.0)
Staphylococcus aureus	9/14 (64.3)	5/7 (71.4)	15/21 (71.4)	13/16 (81.3)	24/35 (68.6)	18/23 (78.3)
MRSA	0/0	0/0	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)	2/2 (100.0)
MSSA	9/14 (64.3)	5/7 (71.4)	14/20 (70.0)	11/14 (78.6)	23/34 (67.6)	16/21 (76.2)
Macrolide-Resistant	2/2 (100.0)	1/1 (100.0)	1/5 (20.0)	2/2 (100.0)	3/7 (42.9)	3/3 (100.0)
Quinolone-Resistant	0/0	0/0	1/1 (100.0)	2/3 (66.7)	1/1 (100.0)	2/3 (66.7)
Nocardia cyriacigeorgica	0/0	0/0	0/0	1/1 (100.0)	0/0	1/1 (100.0)

	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral (N=119) n/N (%)	Moxi Oral (N=106) n/N (%)	Soli IV to Oral (N=103) n/N (%)	Moxi IV to Oral (N=90) n/N (%)	Soli Pooled (N=222) n/N (%)	Moxi Pooled (N=196) n/N (%)
Gram-Negative Bacteria						
Haemophilus influenzae	33/37 (89.2)	21/26 (80.8)	14/18 (77.8)	17/20 (85.0)	47/55 (85.5)	38/46 (82.6)
Haemophilus parainfluenzae	4/6 (66.7)	3/5 (60.0)	1/2 (50.0)	1/2 (50.0)	5/8 (62.5)	4/7 (57.1)
Moraxella catarrhalis	10/11 (90.9)	4/4 (100.0)	4/4 (100.0)	3/3 (100.0)	14/15 (93.3)	7/7 (100.0)
Enterobacter cloacae	1/1 (100.0)	0/0	0/0	0/0	1/1 (100.0)	0/0
Escherichia coli	0/0	3/3 (100.0)	1/2 (50.0)	0/1 (0.0)	1/2 (50.0)	3/4 (75.0)
Klebsiella oxytoca	0/0	1/1 (100.0)	0/0	0/0	0/0	1/1 (100.0)
Klebsiella pneumoniae	4/5 (80.0)	1/3 (33.3)	7/9 (77.8)	2/3 (66.7)	11/14 (78.6)	3/6 (50.0)
Morganella morganii	0/0	0/1 (0.0)	0/0	0/0	0/0	0/1 (0.0)
Salmonella species	0/0	0/1 (0.0)	0/0	0/0	0/0	0/1 (0.0)
Serratia liquefaciens	1/1 (100.0)	0/0	0/0	0/0	1/1 (100.0)	0/0
Serratia marcescens	0/1 (0.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/2 (50.0)	2/2 (100.0)
Acinetobacter calcoaceticus	0/0	0/0	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Alcaligenes xylosoxidans	0/0	0/0	0/0	1/1 (100.0)	0/0	1/1 (100.0)
Pasteurella multocida	0/0	0/0	1/1 (100.0)	0/0	1/1 (100.0)	0/0
Pseudomonas aeruginosa	1/3 (33.3)	0/1 (0.0)	3/3 (100.0)	5/6 (83.3)	4/6 (66.7)	5/7 (71.4)

	Study 300		Study 301		Pooled Phase 3 Studies	
	Soli Oral (N=119) n/N (%)	Moxi Oral (N=106) n/N (%)	Soli IV to Oral (N=103) n/N (%)	Moxi IV to Oral (N=90) n/N (%)	Soli Pooled (N=222) n/N (%)	Moxi Pooled (N=196) n/N (%)
Atypical Pathogens						
Mycoplasma pneumoniae	17/18 (94.4)	18/22 (81.8)	17/21 (81.0)	14/18 (77.8)	34/39 (87.2)	32/40 (80.0)
Macrolide-Resistant	0/0	2/2 (100.0)	1/1 (100.0)	0/0	1/1 (100.0)	2/2 (100.0)
Legionella species	4/7 (57.1)	2/3 (66.7)	1/2 (50.0)	0/0	5/9 (55.6)	2/3 (66.7)
Legionella pneumophila	4/7 (57.1)	2/2 (100.0)	1/1 (100.0)	0/0	5/8 (62.5)	2/2 (100.0)
Legionella dumoffii	0/0	0/1 (0.0)	0/0	0/0	0/0	0/1 (0.0)
Legionella longbeachae	0/0	0/0	0/1 (0.0)	0/0	0/1 (0.0)	0/0

MDRSP=multiple drug resistant *S. pneumoniae*; ME= microbiologically evaluable; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-susceptible *S. aureus*; PISP=*S. pneumoniae* with intermediate penicillin susceptibility; PRSP=penicillin-resistant *S. pneumoniae;* PSSP=penicillin-susceptible *S. pneumoniae*; SFU=Short-term Follow-up.

Table 69 Investigator Assessment of Clinical Success at SFU by Baseline Pathogen in the ME-SFU-2 Populations (Individual and Pooled Studies)

Baseline Pathogen	Study CE01-300		Study CE01-301		Pooled Phase 3 Studies	
	Solithromycin Oral (N=113) n/N1 (%)	Moxifloxacin Oral (N=97) n/N1 (%)	Solithromycin IV to Oral (N=94) n/N1 (%)	Moxifloxacin IV to Oral (N=86) n/N1 (%)	Solithromycin Pooled (N=207) n/N1 (%)	Moxifloxacin Pooled (N=183) n/N1 (%)
Gram-Positive Bacteria						
Streptococcus pneumoniae	23/26 (88.5)	30/35 (85.7)	18/23 (78.3)	23/25 (92.0)	41/49 (83.7)	53/60 (88.3)
MDRSP	8/8 (100.0)	5/5 (100.0)	6/6 (100.0)	10/11 (90.0)	14/14 (100.0)	15/16 (93.8)
PSSP	11/13 (84.6)	22/27 (81.5)	14/19 (73.7)	11/12 (91.7)	25/32 (78.1)	33/39 (84.6)
PISP	7/8 (87.5)	5/5 (100.0)	3/3 (100.0)	11/11 (100.0)	10/11 (90.9)	16/16 (100.0)
PRSP	4/4 (100.0)	2/2 (100.0)	1/1 (100.0)	1/2 (50.0)	5/5 (100.0)	3/4 (75.0)
Macrolide-Resistant	7/7 (100.0)	4/4 (100.0)	6/6 (100.0)	9/10 (90.0)	13/13 (100.0)	13/14 (92.9)
Beta-haemolytic streptococci	3/3 (100.0)	3/3 (100.0)	2/2 (100.0)	1/1 (100.0)	5/5 (100.0)	4/4 (100.0)
Streptococcus pyogenes	1/1 (100.0)	2/2 (100.0)	2/2 (100.0)	0/0	3/3 (100.0)	2/2 (100.0)
Streptococcus agalactiae	1/1 (100.0)	0/0	0/0	0/0	1/1 (100.0)	0/0
Streptococcus dysgalactiae	1/1 (100.0)	1/1 (100.0)	0/0	1/1 (100.0)	1/1 (100.0)	2/2 (100.0)
Staphylococcus aureus	10/14 (71.4)	4/7 (57.1)	17/20 (85.0)	16/16 (100.0)	27/34 (79.4)	20/23 (87.0)
MRSA	0/0	0/0	0/1 (0.0)	2/2 (100.0)	0/1 (0.0)	2/2 (100.0)
MSSA	10/14 (71.4)	4/7 (57.1)	17/19 (89.5)	14/14 (100.0)	27/33 (81.8)	18/21 (85.7)
Macrolide-Resistant	2/2 (100.0)	1/1 (100.0)	3/5 (60.0)	2/2 (100.0)	5/7 (71.4)	3/3 (100.0)
Quinolone-Resistant	0/0	0/0	0/1 (0.0)	3/3 (100.0)	0/1 (0.0)	3/3 (100.0)

Baseline Pathogen	Study CE01-300		Study CE01-301		Pooled Phase 3 Studies	
	Solithromycin Oral (N=113) n/N1 (%)	Moxifloxacin Oral (N=97) n/N1 (%)	Solithromycin IV to Oral (N=94) n/N1 (%)	Moxifloxacin IV to Oral (N=86) n/N1 (%)	Solithromycin Pooled (N=207) n/N1 (%)	Moxifloxacin Pooled (N=183) n/N1 (%)
Gram-Negative Bacteria						
Haemophilus influenzae	27/34 (79.4)	21/25 (84.0)	15/16 (93.8)	19/20 (95.0)	42/50 (84.0)	40/45 (88.9)
Haemophilus parainfluenzae	6/6 (100.0)	1/4 (25.0)	1/2 (50.0)	2/2 (100.0)	7/8 (87.5)	3/6 (50.0)
Moraxella catarrhalis	9/10 (90.0)	3/4 (75.0)	4/4 (100.0)	3/3 (100.0)	13/14 (92.9)	6/7 (85.7)
Enterobacter cloacae	0/1 (0.0)	0/0	0/0	0/0	0/1 (0.0)	0/0
Escherichia coli	0/0	3/3 (100.0)	2/2 (100.0)	0/1 (0.0)	2/2 (100.0)	3/4 (75.0)
Klebsiella oxytoca	0/0	1/1 (100.0)	0/0	0/0	0/0	1/1 (100.0)
Klebsiella pneumoniae	4/5 (80.0)	2/3 (66.7)	5/7 (71.4)	2/3 (66.7)	9/12 (75.0)	4/6 (66.7)
Morganella morganii	0/0	0/1 (0.0)	0/0	0/0	0/0	0/1 (0.0)
Serratia marcescens	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	2/2 (100.0)	2/2 (100.0)
Acinetobacter calcoaceticus	0/0	0/0	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Acaligenes xylosoxidans	0/0	0/0	0/0	0/1 (0.0)	0/0	0/1 (0.0)
Pasteurella multocida	0/0	0/0	1/1 (100.0)	0/0	1/1(100.0)	0/0
Pseudomonas aeruginosa	3/3 (100.0)	0/0	3/3 (100.0)	5/6 (83.3)	6/6 (100.0)	5/6 (83.3)
Atypical Pathogens						
Mycoplasma pneumoniae	16/18 (88.9)	18/20 (90.9)	17/19 (89.5)	16/16 (100.0)	33/37 (89.2)	34/36 (94.4)
Macrolide-Resistant	0/0	2/2 (100.0)	1/1 (100.0)	0/0	1/1 (100.0)	2/2 (100.0)
Legionella species	6/7 (85.7)	2/2 (100.0)	1/2 (50.0)	0/0	7/9 (77.8)	2/2 (100.0)
Legionella pneumophila	6/7 (85.7)	2/2 (100.0)	1/1 (100.0)	0/0	7/8 (87.5)	2/2 (100.0)
Legionella longbeachae	0/0	0/0	0/1 (0.0)	0/0	0/1 (0.0)	0/0

MDRSP=multiple drug resistant *S. pneumoniae*; ME= microbiologically evaluable; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-susceptible *S. aureus*; PISP=*S. pneumoniae* with intermediate penicillin susceptibility; PRSP=penicillin-resistant *S. pneumoniae;* PSSP=penicillin-susceptible *S. pneumoniae*; SFU=Short-term Follow-up.

11.6.1 Narratives for Pneumococcal Bacteremia Patients with Treatment Failure at SFU

Solithromycin Treatment Failures

Study 300, solithromycin group: A 42 year old female with PORT II pneumonia presented with fever (38.9 C), tachycardia (104 bpm), BP 110/65 and 88% oxygen saturation by pulse oximetry. Baseline WBC was 17,000/μL, C-reactive protein was 359 mg/L and procalcitonin was 9.27 ng/mL. The solithromycin MICs for the baseline blood and sputum pneumococcus isolates were 0.015 μg/mL. By Day-4, symptom improvement defined an ECR response, the patient was afebrile, BP was 135/75, pulse was 88, pulse oximetry had improved to 94%, and WBC had dropped to 11,000/μL. At EOT on Day 7, vital signs remained stable (afebrile, with BP 115/70, HR 68, respirations 16, and O2 saturation 95%) and WBC had dropped further to 10,000/μL. The investigator initiated therapy with erythromycin on Day 8, after review of a chest radiograph that had not shown resolution of the pneumonia. Radiographic signs of pneumonia do not resolve in 7 days, a topic reviewed with the investigator after this event. From the sponsor perspective, this patient was effectively treated by Day 7.

Study 300, solithromycin group: A 47 year old male with PORT III pneumonia presented with fever (38 C), tachycardia (120 bpm), BP 100/70, and 95% pulse oximetry saturation. Baseline WBC was 21,000/μL, C-reactive protein was 477 mg/L and procalcitonin was 11.74 ng/mL. The solithromycin MICs for the baseline blood and sputum isolates ranged from 0.004 to 0.03 μg/mL. At Day 4, therapy was declared ineffective, although the patient was at that point afebrile, BP was 120/70, pulse was 100, pulse oximetry 94%, and WBC had dropped to 15,000/μL The Day 4 symptom grading met criteria for an ECR, with dyspnea and chest pain dropping from moderate to mild severity, while cough and difficulty with sputum production were unchanged (and considered to be of moderate severity). Alternate therapy with ciprofloxacin plus rifampin was initiated. From the sponsor perspective, there is clear evidence of at least a partial beneficial response from therapy in this case.

Study 301, solithromycin group: A 46 year old male with PORT III pneumonia presented with fever (38.8 C), tachypnea (33 bpm), BP 100/60, and 93% pulse oximetry saturation. Baseline WBC was 31,600/μL, C-reactive protein was 294 mg/L and procalcitonin was 19.17 ng/mL. The solithromycin MICs for the baseline blood and sputum isolates were 0.004 μg/mL. Therapy for this patient was considered successful at ECR and EOT. By Day 7, WBC had dropped to 13,500/μL and vital signs had normalized. At the SFU visit on Day 15, the patient was afebrile, with WBC of 3,600/μL, but symptoms of coughing had worsened. New therapy with levofloxacin was initiated. This scenario is consistent with a relapse following effective therapy.

Study 301, solithromycin group: A 29 year old male with PORT II pneumonia who presented without fever (36.5 C), but was hypotensive (BP 89/50), tachycardic (HR 130), and tachypneic (30 bpm), with 96% pulse oximetry saturation. Baseline WBC was 10,600/μL, C-reactive protein was 272 mg/L and procalcitonin was 30.85 ng/mL. The solithromycin MICs for the baseline blood and sputum isolates were 0.008 μg/mL. By Day 4, WBC had dropped to 6,100/μL, BP was 130/80, HR was 71, respiratory rate was 20, and oxygen saturation was 100% on pulse oximetry. Symptoms of cough, chest pain, and sputum production had all improved (defining an ECR). On

Day 4, phlebitis at an infusion site was noted and IV study drug was discontinued. Therapy with oral amoxicillin/clavulanic acid was initiated. From the sponsor perspective, a switch to oral therapy with blinded study drug would have been appropriate in this circumstance, particularly given the investigator's decision to initiate an orally administered antibiotic as an alternative. There was clear evidence of antimicrobial efficacy in this case.

Moxifloxacin treatment failures

Study 300, moxifloxacin group: This 35 year old male with a PORT III pneumonia presented with fever and tachycardia, with a WBC count of 19,300/μL. At Day 4, vital signs were normal, symptoms had improved (defining an ECR) and WBC had dropped to 5,700/μL. The patient completed oral outpatient therapy with study drug, but did not return for Day 7 or subsequent follow-up visits, and is therefore defined as a treatment failure for ITT analyses. This appears, otherwise, to have been a successful treatment episode.

Study 300, moxifloxacin group: This 63 year old male with PORT IV pneumonia presented without fever, with tachycardia (HR 128), and with WBC of 22,000/μL. By Day 7, WBC had risen to 38,000/μL, and a diagnosis of empyema was established. Chest tube drainage and additional antibiotic therapy was required.

Study 300, moxifloxacin group: This 25 year old male with PORT II pneumonia presented with fever (38.3 C), hypotension (88/50), tachypnea (32 bpm), and 97% oxygen saturation on pulse oximetry. Baseline WBC was 5,100/μL, C-reactive protein was 364 mg/L and procalcitonin was 22.24 ng/mL. The moxifloxacin MICs for the baseline blood and sputum pneumococcal isolates were 0.12 and 0.25 μg/mL. Also cultured from sputum at baseline was *Hemophilus parainfluenzae*, with a moxifloxacin MIC of 0.12 μg/mL. At Day 4, symptoms had improved (defining an ECR) and vital signs normalized. At Day 7, therapy was considered unsuccessful by the investigator, and treatment with amoxicillin was initiated (with hemoptysis noted on Day 8). Interestingly, pneumococcus was not isolated from sputum cultures obtained on Day 7, but *H. parainfluenzae* was, with a moxifloxacin MIC of 4.0 μg/mL. It is possible that pneumococcus was effectively treated, with treatment failure attributable to development of moxifloxacin-resistance in this second organism.

Study 300, moxifloxacin group: This 59 year old male with PORT II pneumonia presented without fever, with normal blood pressure and respirations, although with tachycardia (HR 110) and 95% oxygen saturation on pulse oximetry. Baseline WBC was 12,600/μL, C-reactive protein was 508 mg/L and procalcitonin was 31.96 ng/mL. The moxifloxacin MICs for the baseline blood and sputum pneumococcal isolates were 0.25 μg/mL. Also cultured from sputum at baseline was *Staphylococcus aureus*, with a moxifloxacin MIC of 0.06 μg/mL. At Day 4, symptoms had improved (defining an ECR), vital signs were stable and WBC had dropped to 7,800/μL. At Day 7, vital signs remained normal, one symptom (chest pain) had worsened from mild to moderate, and WBC had risen to 10,600/μL. Therapy was considered unsuccessful by the investigator, and new treatment with ceftriaxone plus erythromycin was initiated. Follow-up blood and sputum cultures were negative for any pathogen. In this case, it is possible that mixed infection with staphylococcus contributed to the outcome.

11.7 Serious Adverse Event Listings

Table 70 Non-fatal SAEs in Study 200

Patient #/ Sex / Age (years)	Preferred Term	Day of Onset	Duration # Days	Intensity	Relationship
Solithromycin					
125-003 / Male / 82	Pneumonia	10	12	Severe	Unrelated
	COPD	10	12	Severe	Unrelated
	Humerus fracture	10	Ongoing	Severe	Unrelated
	Metabolic encephalopathy	11	11	Severe	Unrelated
	Acute respiratory failure	12	5	Severe	Unrelated
	Sepsis	13	9	Severe	Unrelated
	Cardiac failure congestive	16	6	Severe	Unrelated
	Pneumonia aspiration	19	3	Severe	Unrelated
137-003 / Female / 39	Pleuritic pain	6	2	Severe	Unrelated
Levofloxacin					
107-001 / Male / 31	Pneumonia	20	12	Moderate	Unrelated
107-006 / Male / 57	Enterococcal infection	25	26	Severe	Unrelated
112-002 / Female / 55	Gastroenteritis	3	3	Severe	Unrelated
128-001 / Female / 62	Convulsion	3	1	Severe	Related
	Hyponatremia	3	7	Severe	Related
128-009 / Male / 71	ARDS	2	13	Severe	Unrelated
128-014 / Female / 49	Hypovolemic shock	2	3	Severe	Unrelated

ARDS = acute respiratory distress syndrome

Table 71 Non-fatal SAEs in Study 300

Patient / Sex / Age (years)	Preferred Term	Day of Onset	Duration # Days	Intensity	Relationship
Solithromycin[a]					
128-0005 / Female / 58	Hypoxia	10	3	Severe	Unrelated
	Pneumonia	10	4	Severe	Unrelated
	Septic shock	10	4	Severe	Unrelated
	Respiratory failure	13	1	Severe	Unrelated
132-0390 / Female / 54	Asthma	4	1	Severe	Unrelated
144-0686 / Male / 50	Renal failure	4	25	Severe	Unrelated
151-0264 / Male / 64	Pneumonia	2	9	Severe	Unrelated
183-0311 / Male / 63	Pneumonia influenzal	6	38	Severe	Unrelated
191-0015 / Male / 81	Empyema	6	23	Severe	Unrelated
203-0760 / Female / 74	COPD	15	15	Moderate	Unrelated
210-0163 / Male / 65	Cardiac failure	2	6	Moderate	Unrelated
271-0576 / Male / 69	Pneumonia pseudomonal	13	2	Mild	Unrelated
283-0617 / Female / 81	Oesophageal obstruction	21	2	Mild	Unrelated
302-0338 / Male / 76	Atrial fibrillation	4	1	Severe	Unrelated
309-0233 / Male / 86	Pneumonia	16	7	Moderate	Unrelated
352-0621 / Male / 39	Pneumonia	8	8	Moderate	Unrelated

Patient / Sex / Age (years)	Preferred Term	Day of Onset	Duration # Days	Intensity	Relationship
502-0238 / Male / 68	Deep vein thrombosis	25	9	Severe	Unrelated
601-0167 / Male / 78	Pulmonary embolism	3	10	Mild	Unrelated
704-0220 / Male / 51	Respiratory failure	21	27	Severe	Unrelated
	Lung cancer metastatic	37	Ongoing	Severe	Unrelated
708-0351 / Male / 73	Infectious pleural effusion	22	13	Moderate	Unrelated
716-0281 / Female / 50	Pneumonia	4	19	Severe	Unrelated
718-0480 / Female / 62	Bronchitis chronic	18	7	Moderate	Unrelated
801-0566 / Female / 36	Pregnancy	3	3	Moderate	Unrelated
806-0553 / Female / 31	Pulmonary tuberculosis	14	36	Moderate	Unrelated
904-0120 / Female / 57	Pleural effusion	8	5	Moderate	Unrelated
905-0114 / Female / 54	Pneumonia	6	16	Severe	Unrelated
Moxifloxacin					
126-0557 / Male / 62	Pneumonia	21	5	Mild	Unrelated
151-0370 / Female / 75	Atrial fibrillation	14	6	Severe	Unrelated
208-0229 / Female / 82	Cardiac failure congestive	7	5	Moderate	Unrelated
271-0165 / Male / 32	Pleural effusion	11	11	Severe	Unrelated
271-0184 / Male / 71	Acute respiratory failure	15	14	Moderate	Unrelated
272-0852 / Male / 44	Respiratory failure	1	50	Severe	Unrelated
287-0779 / Female / 61	Pneumonia	22	22	Severe	Unrelated
302-0461 / Male / 63	Empyema	7	15	Severe	Unrelated
305-0665 / Male / 78	Lung neoplasm malignant	15	Ongoing	Moderate	Unrelated
351-0655 / Male / 71	Pneumonia	14	9	Moderate	Unrelated
456-0385 / Male / 45	Thyroiditis subacute	8	5	Moderate	Unrelated
456-0474 / Female / 63	Ventricular failure	4	8	Moderate	Unrelated
601-0605 / Female / 76	Gastritis erosive	23	10	Moderate	Unrelated
701-0804 / Male / 59	Leukemia	20	Ongoing	Severe	Unrelated
714-0689 / Male / 62	Lung carcinoma cell type unspecified stage IV	16	Ongoing	Severe	Unrelated
715-0109 / Male / 25	Infectious pleural effusion	16	16	Moderate	Unrelated
717-0324 / Male / 48	Lung abscess	5	32	Moderate	Unrelated
805-0342 / Female / 80	Femur fracture	7	7	Severe	Unrelated
806-0104 / Male / 53	Deep vein thrombosis	7	8	Moderate	Unrelated
806-0830 / Male / 60	Lung neoplasm malignant	18	Unknown	Severe	Unrelated
907-0398 / Male / 70	Pulmonary tuberculosis	4	35	Moderate	Unrelated

QD=once daily; SAE=serious adverse event.

a. An additional SAE occurred in CE01-300 not included in the dataset or this table (CE01-300-710-0382).

Table 72 Non-fatal SAEs in Study 301

Patient / Sex /Age (yrs)	Preferred Term	Day of Onset	Duration # Days	Intensity	Relationship
Solithromycin					
1007-002/ Male/ 59	Pneumonia	2	6	Mild	Unrelated
1016-004/ Male/ 80	Chest pain	17	3	Moderate	Unrelated
1026-003/ Male/ 33	Respiratory failure	3	4	Moderate	Unrelated
	Pneumonia worsening	3	10	Moderate	Unrelated
1051-003/ Female/ 90	Chronic obstructive pulmonary	18	4	Moderate	Unrelated
	Pneumonia	32	8	Moderate	Unrelated
1074-021/ Male/ 63	Pancreatitis	13	4	Severe	Unrelated
1410-001/ Female/ 82	Asthmatic crisis	8	3	Severe	Unrelated
2005-001/ Female/ 74	Respiratory tract infection	9	5	Moderate	Unrelated
2112-003/ Female/ 33	Urticaria	1	1	Moderate	Related
2502-002/ Male/ 42	Pneumothorax	14	70	Severe	Unrelated
2504-006/ Male/ 61	Lobar pneumonia	7	8	Severe	Unrelated
2603-004/ Female/ 81	Large intestine perforation	8	17	Severe	Unrelated
2607-012/ Male/ 75	Pulmonary oedema	2	1	Severe	Unrelated
	Hypertensive crisis	2	1	Severe	Unrelated
2614-009/ Male/ 61	Endocarditis bacterial	7	unknown	Severe	Unrelated
3101-008/ Male/ 46	Lung abscess	8	8	Severe	Unrelated
3101-010/ Male/ 44	Pulmonary tuberculosis	21	ongoing	Moderate	Unrelated
3107-008/ Male/ 67	Anaphylactic reaction	1	1	Moderate	Related
3306-017/ Male/ 32	Haemoptysis	16	10	Severe	Unrelated
3306-019/ Male/ 69	Acute myocardial infarction	30	14	Severe	Unrelated
	Acute respiratory failure	30	14	Severe	Unrelated
	Pneumonia	30	18	Severe	Unrelated
3308-001/ Male/ 40	Pneumonia	3	20	Moderate	Unrelated
3309-001/ Female/ 63	Hydronephrosis	14	12	Severe	Unrelated
	Pneumonia	25	11	Severe	Unrelated
3601-010/ Male/ 48	Pleural effusion	7	11	Moderate	Unrelated
3602-022/ Female/ 80	Hypertension	16	15	Mild	Unrelated
3606-011/ Male/ 54	Empyema	5	15	Moderate	Unrelated
3609-001/ Female/ 66	Pleural effusion	12	17	Mild	Unrelated
3801-002/ Male/ 29	Pneumonia	14	37	Severe	Unrelated
Moxifloxacin					
1059-003/ Male/ 60	Hypertension	7	4	Mild	Unrelated
	Lung adenocarcinoma	9	ongoing	Severe	Unrelated
1079-001/ Male/ 81	Bronchitis	34	14	Moderate	Unrelated
	Chronic obstructive pulmonary disease	34	14	Moderate	Unrelated
2112-007/ Female/ 45	Thrombophlebitis	14	ongoing	Moderate	Unrelated
2112-008/ Male/ 69	Cardiac failure	15	9	Severe	Unrelated
2113-001/ Male/ 45	Empyema	3	15	Moderate	Unrelated

Patient / Sex /Age (yrs)	Preferred Term	Day of Onset	Duration # Days	Intensity	Relationship
2211-036/ Female/ 72	Cardiovascular insufficiency	2	13	Severe	Unrelated
	Atrial fibrillation	2	13	Severe	Unrelated
2411-004/ Male/ 62	Pneumonia	16	10	Moderate	Unrelated
2412-001/ Female/ 37	Respiratory tract infection viral	7	5	Mild	Unrelated
2415-003/ Male/ 70	Small cell lung cancer	21	ongoing	Severe	Unrelated
2617-009/ Female/ 68	Acute leukaemia	9	ongoing	Severe	Unrelated
3107-005/ Male/ 53	Anaphylactic reaction	2	1	Moderate	Related
3205-011/ Male/ 79	Lung adenocarcinoma	4	ongoing	Severe	Unrelated
	Pulmonary embolism	4	ongoing	Severe	Unrelated
	Deep vein thrombosis	4	ongoing	Severe	Unrelated
3306-005/ Female/ 57	Acute respiratory failure	3	5	Severe	Unrelated
	Acute respiratory failure	8	6	Severe	Unrelated
	Acute respiratory failure	21	15	Severe	Unrelated
3306-016/ Male/ 74	Pneumonia	3	9	Severe	Unrelated
	Acute respiratory failure	3	9	Severe	Unrelated
3306-020/ Male/ 72	Pneumonia	6	19	Severe	Unrelated
3308-007/ Female/ 77	Acute coronary syndrome	4	10	Moderate	Unrelated
	Acute respiratory failure	7	7	Moderate	Unrelated

QD=once daily; SAE=serious adverse event.

Table 73 Non-fatal SAEs in Non-integrated Studies

Sex /Age (yrs)	Preferred Term	Day of Onset	Duration # Days	Relationship
Toyama Phase 2 CAP Study (T4288-201)				
Solithromycin				
Female/ 64	Delirium	3	14	Related
Male/ 79	Hypercapnia	4	4	Unrelated
Male/ 84	Cardiac failure congestive	2	8	Unrelated
Female/ 63	Constipation aggravated	5	5	Unrelated
Levofloxacin				
Male/ 83	Status asthmaticus	9	10	Unrelated
Pediatric PK Study CE01-119				
Male/ 15	Abscess limb	5	80	Unrelated
Pediatric PK Study CE01-120				
Female/ 4	Drug fever	6	5	Unrelated
	PICC line occlusion	6	5	Unrelated
COPD Study CE01-204				
Male/ 69[a]	Cholestatic hepatitis	22	29	Related

a. Narrative for this patient can be found in Section 11.8.1.

11.8 Patient Narratives

11.8.1 Narratives of Patients Meeting Hy's Law Laboratory Criteria

Study 301/Solithromycin: This 34-year-old white female with an unremarkable past medical history was enrolled with PORT II pneumonia. No bacterial pathogen was identified. She completed solithromycin dosing (3 IV and 4 oral doses), with therapy considered successful at EOT and SFU. Baseline and Day 7 labs were normal. At the SFU visit on Day 12, asymptomatic elevation of ALT (130 U/L, 3.8×ULN) with normal bilirubin was observed. She returned for follow-up evaluation on Day 26, which revealed normal aminotransferase levels but elevated total bilirubin (2.9 mg/dL). She remained asymptomatic, without evidence of jaundice, and refused to return for additional evaluation. As the patient had an elevated serum ALP but not an elevated serum ALT at the time of peak bilirubin, the bilirubin elevations cannot be attributed to hepatocellular injury. In addition, less than 20% of the total serum bilirubin was conjugated (direct reacting), which is not expected for a Hy's Law case. For these reasons, the sponsor does not consider this patient to be a Hy's Law case. Reviewers in the expert panel of hepatic safety consultants concurred with the Sponsor's assessment.

Study 300/Solithromycin: This 58-year-old white female with a history of cirrhosis, non-obstructive biliary calculi, morbid obesity, hypertension, COPD, and poly-substance abuse, enrolled with a multi-lobar PORT III pneumonia. The patient was on no medications chronically and received no concomitant medications while receiving study drug. Baseline labs were remarkable for elevated ALT, AST and bilirubin, impaired coagulation, and low albumin. Although not recognized at enrollment, it was clear in retrospect that she had decompensated end stage liver disease. At baseline (prior to study drug dosing), laboratory parameters met Hy's Law criteria with an AST 3.1×ULN and total bilirubin >2×ULN, and an INR of 2.0. She received oral solithromycin as an outpatient for 5 days. Clinical improvement was noted at Days 4 and 7. During study drug treatment, liver function tests remained stable. On Day 10, she was hospitalized with dyspnea, hypoxia, and hypotension. A toxicology panel was positive for benzodiazepines, cocaine, and opiates; an ultrasound indicated underlying cirrhosis. Respiratory failure occurred shortly after admission, and mechanical ventilation was initiated. She remained hypoxic, hypotensive and acidotic and developed renal and hepatic impairment consistent with shock liver and progressive pre-renal azotemia. On Day 11 liver function deteriorated, coincident with multi-organ failure. She died on Day 13. No autopsy was performed. SAEs of multi-organ system failure, hypoxia, pneumonia, septic shock, and respiratory failure were not considered by the investigator to be drug related. As her end-of-life, markedly abnormal aminotransferase and bilirubin values were secondary to sepsis and multi-organ failure, this was not considered solithromycin related. Because an alternative, clinically rational explanation for this patient's hepatic decompensation was present, this was not considered a Hy's Law case by the study sponsor. The hepatic safety panel members concurred with the Sponsor's assessment.

Study 301/Moxifloxacin: This 54-year-old white male with a medical history of coronary artery disease, alcohol abuse, HCV infection and cirrhosis was enrolled with a PORT IV pneumonia. At baseline, ALT was 37 U/L, AST 101 U/L, albumin 2.2 g/dL, total bilirubin 2.7 mg/dL (direct bilirubin, 1.2 mg/dL), and platelets 66,000/µL. He received 2 doses of IV moxifloxacin but developed respiratory failure requiring intubation and mechanical ventilation with suspected sepsis

on Day 2. Study drug was discontinued and multiple alternative antibiotics were started. Influenza infection was diagnosed on Day 5. On Day 7, his aminotransferase and bilirubin values met laboratory criteria for Hy's Law (ALT 45, AST 148 and total bilirubin 3.7 mg/dL). Life support was discontinued upon instruction from family members and he died on Day 14. No autopsy was performed. As this patient's abnormal aminotransferase and bilirubin values were secondary to his preexisting underlying liver disease and the cardiovascular instability of his current illness, this was not considered a Hy's law case.

Study CE01-204/Solithromycin (COPD Pilot Study): 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 included fluticasone/salmeterol and salbutamol metered-dose inhalers and oral finasteride 5 mg QD. At baseline and Day 8, all hepatic safety tests were in the normal range. At Day 23, ALT of 476 U/L (11.9×ULN), AST of 368 U/L (9.0×ULN) and ALP of 1316 U/L (10.1×ULN) were noted, as well as elevation of total bilirubin to 4.0 mg/dL (3.4×ULN) with direct bilirubin 2.2 mg/dL (3.6×ULN). Administration of solithromycin and finasteride was discontinued (last dose Day 23). The patient was mildly icteric, with pruritus. An ultrasound of the liver and biliary tract was normal, and viral hepatitis screens were negative. One day later on Day 24, improvement was evident. The patient was monitored for an additional 4 weeks and the results continued to improve with only ALP remaining 1.3×ULN at the final follow-up visit. The patient did not require hospitalization for this event and liver function as measured by prothrombin time (INR) remained normal throughout (either 0.9 or 1 at all timepoints evaluated – Day 15, 23, 24, and 34). Solithromycin plasma concentrations on Day 7, 14 and 23 were within the expected range. The concomitant elevation of ALP, ALT and bilirubin characterize this event as an episode of cholestatic hepatitis, a recognized complication of all macrolides. The R-value (ALT fold elevation/ALP fold elevation) in this case is 1.2. An R-value <2 is consistent with cholestatic liver injury while a R-value ≥ 5 is consistent with hepatocellular injury. Upon discontinuation of both solithromycin and finasteride the laboratory abnormalities resolved, and no clinically significant events related to the LFT elevation were reported.

11.8.2 Death Narratives

Solithromycin Group:

Multi-organ failure: This narrative is presented above, in the Hy's Law discussion (Section 11.8.1).

Acute respiratory failure: This 48-year-old female died of respiratory failure 22 days following a single dose of solithromycin. Enrollment chest radiograph showed diffuse pulmonary infiltrates. She received 1 dose of study medication and was admitted to the hospital. Within hours, her clinical condition deteriorated, with dehydration, hyperosmolar hyperglycemic crisis, and worsened dyspnea. She was transferred to the ICU and withdrawn from the study. Standard of care IV antibiotics (moxifloxacin, meropenem, linezolid, and clarithromycin) and fluid resuscitation were immediately initiated. She was intubated for mechanical ventilation and developed ARDS. After a prolonged ICU stay (21 days), she died. No autopsy was performed. SAEs of acute respiratory failure (fatal) and acute renal failure were not considered by the investigator to be drug related.

Bronchospasm: This 59-year-old female died on Study Day 3 with an SAE of bronchospasm. She was admitted to the hospital at study entry with markedly elevated CRP (196 mg/L), WBC (18.87 K) and procalcitonin (0.44 mg/L) and a left upper lobe infiltrate on CXR. She received solithromycin on Study Days 1 and 2. By the morning of Study Day 2, the symptoms had worsened with increased dyspnea and onset of diffuse wheezing. Solucortef and aminophylline were administered, and the patient improved. On Day 3, she was found to be markedly distressed with acute bronchospasm (4:30 AM). IV steroids, atarax, and aminophylline therapy were ordered, but the patient died shortly thereafter (4:38 AM). The SAE of bronchospasm was not considered by the investigator to be study drug related.

Cerebrovascular accident: This 68-year-old female with a history of hypertension, congestive heart failure, and Type 2 diabetes died on Study Day 5 with a presumptive diagnosis of cerebrovascular accident (CVA). The patient was noted to have been very lethargic prior to study entry. On presentation, she was in respiratory distress with severe dyspnea and chest pain. Baseline blood pressure was 133/92 mmHg and heart rate 110 bpm; ECGs (×3) revealed a mean QTcF of 448 msec, and possible anteroseptal infarct of unknown age. She received solithromycin on Days 1 to 4. On Days 2 and 3, the patient was somnolent with depressed sensorium, and did not appear to be improving. On Day 4, given a possible diagnosis of meningitis, study drug was discontinued and IV ceftriaxone was initiated. Day 4 ECG was unchanged from baseline, without QT prolongation. On Day 5, the patient was confused and disoriented, with hyperkalemia. That evening the patient was found deceased. The cause of death remains unclear. The investigator suspects that subdural hematoma or chronic meningitis may have been present; however, the patient succumbed before diagnostic evaluations could be completed and no autopsy was performed. The investigator considered a possible CVA the most likely possible diagnosis, but this was not confirmed. The event was not considered by the investigator to be study drug related.

Acute myocardial infarction: This 72-year-old male with a history of hypertension (untreated) and chronic pancreatitis died on Study Day 3 with a MI. Baseline heart rate was 96 bpm and blood pressure was 155/90 mmHg. Baseline ECG showed sinus rhythm heart rate of 84 bpm with non-specific T wave changes, left ventricular hypertrophy, and frequent premature atrial contractions, some of which were not conducted. On Day 3, the patient had sudden deterioration, with heart rate 82 bpm (on metoprolol), blood pressure of 80/60 mmHg, and cyanosis, with subsequent clinical deterioration and death. There was no evidence for arrhythmia as a primary event in this SAE. An autopsy revealed an acute subendocardial MI of the lateral wall of the left ventricle. The investigator considered this event unrelated to study drug.

Cerebral Vascular Accident: This 64-year-old male had a history of hypertension, diabetes and a prior CVA that resulted in persistent hemiparesis. Prior evaluation for the CVA revealed complete left internal carotid occlusion and severe right internal carotid stenosis. He was enrolled with pneumonia with *S. pneumoniae* and *Klebsiella pneumoniae* isolated from sputum. A profound systemic inflammatory response was present at baseline (CRP was 295 mg/L and procalcitonin was 43.8 ng/mL). On Day 7, at EOT, the investigator felt there was an incomplete response to therapy, and IV ceftriaxone and ciprofloxacin were administered. The patient was subsequently discharged but was readmitted to hospital on Day 13 with a diagnosis of acute stroke. Cerebral MRI on Day 15 revealed residual left sided CVA findings and acute ischemic right sided stroke of the pons and mesencephalon. The patient died on Day 19. The death certificate attributed death to

"tentorial and subtentorial acute ischemic stroke". The CVA was not considered study drug related by the investigator.

Cardiac arrest: This 81-year-old female with a past medical history of hypertension and atrial fibrillation died on Study Day 8 with cardiac arrest. She received 2 doses of IV and 5 doses of oral solithromycin. Baseline ECG showed atrial fibrillation, with a heart rate of 116 bpm. The investigator assessment of clinical response was success at the EOT visit, and the patient was doing well clinically the day prior to her death. ECG on Day 7 showed atrial fibrillation, with a heart rate of 92 bpm and QTcF <400 msec. At approximately 02:00 on Study Day 8, she experienced a cardiac arrest at home for which attempted cardiopulmonary resuscitation performed by paramedics was unsuccessful. She was not transported to a hospital and an autopsy was not performed. The cardiac arrest was not considered study drug related by the investigator.

Cardiac arrest: This 67-year-old white male with a past medical history of hypertension with left ventricular hypertrophy, alcoholic hepatitis, insulin dependent type 2 diabetes and atrial fibrillation died on Study Day 3 with cardiac arrest. Baseline vital signs included a respiratory rate of 32 breaths per minute and blood pressure 151/60 mmHg. In the study he received 2 doses of IV study drug and was noted to be improving. He was last checked on at 01:00 on Study Day 3 and appeared to be well and without complaints. At 07:00 he was found deceased. An autopsy was performed that revealed extensive lipomatosis of right ventricle, cardiomegaly, left ventricular hypertrophy, aorta with extensive complex atherosclerosis. Baseline ECG revealed a conduction defect (bifascicular block). No post-baseline ECGs were obtained prior to this sudden event. The cardiac arrest was not considered study drug related by the investigator.

Myocardial infarction: This 71-year-old male with a history of hypertension died on Study Day 24 with a myocardial infarction. Baseline ECG was abnormal (sinus tachycardia, first-degree AV block, ST-T abnormality) and indicated an old myocardial infarction. In the study he received 3 IV and 4 oral doses of solithromycin and was considered a success at EOT. Repeat ECGs on Day 4 and Day 7 were not appreciably different than baseline. At SFU, the investigator considered treatment unsuccessful, and he was treated with ceftriaxone/tazobactam 4 g daily, for 7 days intramuscularly (through Study Day 18). On Study Day 24, the patient died in his bed at home. Details regarding the circumstances of his death were not available and no autopsy was performed; the investigator reported the fatal event as possible myocardial infarction given the information available. The event was not considered study drug related.

Upper airway obstruction, myocardial infarction, and Septic shock: This 80-year-old female presented with a history of diabetes mellitus, hypertension, bronchial asthma and thyroid enlargement, which recently had grown rapidly and significantly in size. Vital signs at baseline included a blood pressure of 92/61 mmHg. Laboratory results at baseline revealed a WBC count of $14x10^9$/L with neutrophils 81%, elevated CRP of 63 mg/L (reference range ≤2.87 mg/L) and procalcitonin of 0.12 ug/L (reference range <0.06 ug/L). Sputum culture obtained grew *Pseudomonas putida*. On Study Day 3 she had a marked progression of dyspnea and development of stridor and was intubated for mechanical ventilation and moved to the ICU due to upper airway obstruction. The last dose of solithromycin was given on Study Day 4 when a CXR indicated progression of the pneumonic infiltrates and she was started on meropenem. On Study Day 5, her ECG showed sinus tachycardia, heart rate 120 bpm, short QT (223 msec), with non-specific T-wave abnormalities. An elevated troponin I value of 1.405 ng/mL (reference range

0.02-0.06 ng/mL) was recorded. She was started on digoxin, metoprolol, and atorvastatin. On Study Day 8 she was diagnosed with septic shock and died. An autopsy was not performed.

Cardiac failure: This 89-year-old male with a history of cardiomyopathy, pacemaker implant, and COPD died on Study Day 7 with cardiac failure. The baseline ECG showed sinus rhythm with atrioventricular (AV) dissociation, ventricular escape rhythm and complete heart block with a QTcF of 459 msec. No local ECGs were done after this baseline central ECG, including on Day 4 (a major protocol deviation), during the 6 days of treatment with IV solithromycin. On Study Day 4 vital signs were unremarkable and clinical signs and symptoms of pneumonia were improved. WBC count remained elevated, but decreased inflammatory markers were noted. On Study Day 6 he became increasingly agitated; oxygen saturation was 94%, and heart rate 65 bpm. Local laboratory tests revealed an electrolyte imbalance with hyponatremia (sodium 128 mmol/L) and hypochloremia (chloride 92 mmol/L). Hartmann's solution and furosemide were administered. He did not complain of heart/chest pain during admission, and it was also confirmed that no evaluations of cardiac biomarkers (troponins, CK-MB, BNP) were performed during the hospitalization. On Study Day 7, he experienced heart failure and died in his sleep at 03:44. An autopsy was not performed. Cardiac failure was not considered study drug related by the investigator.

Moxifloxacin Group:

ARDS: This 38-year-old male with history of hypertension and morbid obesity (BMI 62) died with an SAE of ARDS on Study Day 10. At enrollment, he presented with high fever (39.4°C), severe cough, and moderate dyspnea. A chest x-ray showed diffuse bilateral infiltrates. He received moxifloxacin on Days 1 and 2, but his clinical condition deteriorated rapidly. Study drug was discontinued and IV ceftriaxone plus azithromycin was initiated. On Day 3, he was transferred to ICU and intubated. Anti-infective therapy was broadened to include vancomycin, imipenem, and oseltamivir. Respiratory virus nucleic acid assays detected adenovirus, with no other pathogen identified. The patient progressively worsened, with ARDS attributed to viral pneumonitis. He died on Day 10. No autopsy was performed. The SAE of ARDS was not considered study drug related by the investigator.

Cardiac failure congestive: This 72-year-old female with a history of congestive heart failure and hypertension died on Study Day 10. She was enrolled with a radiologic diagnosis of congestive heart failure and possible pneumonia. Her baseline ECG demonstrated sinus tachycardia, a possible anterior infarct (age unknown), inferior/lateral ST-T wave changes (possible due to hypertrophy or ischemia), with heart rate of 118 bpm and QTc of 360ms. The patient received moxifloxacin from Days 1 to 7 and was also treated with diuresis. ECGs collected on Days 4 and 7 revealed no evolving ischemic changes. The patient did not return for her SFU visit and the investigator later learned that she was admitted to a remote hospital on Day 8 and died on Day 10. The investigator was informed by family members that the cause of death was considered to be congestive heart failure. The investigator was unable to obtain medical records or a death certificate. The SAE of congestive heart failure was not considered study drug related by the investigator.

Respiratory failure and Cardiac failure: This 68-year-old obese male was enrolled with a history of hypertension, and heart failure). At baseline, the patient was moderately cyanotic.

Multiple CABP pathogens were identified: *S. aureus*, *H. influenzae*, *Moraxella catarrhalis*, and *S. pneumoniae*. The patient received moxifloxacin on Days 1 to 7. On Day 4, the patient was intubated. On Study Day 8, a CT scan revealed bilateral CABP, insignificant fluid in both pleural spaces, and dilated cardiac chambers. Pulmonary embolism was ruled out. From Days 9 to 15, he was treated with ceftriaxone plus clarithromycin. Repeated efforts to wean the patient from the ventilator were unsuccessful, and progressive heart failure ensued. On Day 22, the patient died from respiratory and cardiac failure. Autopsy findings included diffuse cardiosclerosis, chronic obstructive lung disease, pleural adhesions and bilateral hydrothorax, and reactive interstitial myocarditis. The SAEs of respiratory and cardiac failure were not considered study drug related by the investigator.

Pulmonary embolism: This 53-year-old male with a history of chronic heart failure, hypertension, ischemic heart disease, and probable cirrhosis died on Study Day 5 with an SAE of pulmonary embolism. Pneumococcal pneumonia was diagnosed at baseline. On Day 2, the patient's condition worsened. Ceftriaxone and metronidazole were added to his blinded study drug. An episode of atrial fibrillation was observed (<1 minute duration) on heart monitor. On Day 4, heart rate was 92 bpm, with QTcF of 445 msec (less than the baseline value of 450 msec). Later that day (D4), the patient had an episode of ventricular fibrillation, requiring resuscitation. He was intubated survived until death on Day 5. An autopsy revealed bilateral pneumonia and a pulmonary embolism in right lung. The pulmonary embolism was concluded to be the immediate cause of ventricular fibrillation and death. The event was not considered study drug related by the investigator.

Acute respiratory failure: This 63-year-old female with a history of coronary artery disease, congestive heart failure, hypertension, aortic stenosis, recurrent atrial fibrillation, and prior stroke died on Study Day 10 with an SAE of acute respiratory failure. The patient received moxifloxacin on Days 1 to 3. On Day 4, the patient experienced acute respiratory failure and was moved to the ICU with a diagnosis of pulmonary edema and acute respiratory failure. Blinded study drug dosing was discontinued, and standard of care IV antibiotics were initiated (moxifloxacin and imipenem/cilastatin). An echocardiogram revealed left ventricular hypertrophy, mild aortic stenosis, and diastolic dysfunction with normal ejection fraction. On Day 7, elevated troponin-I and CK-MB was noted, and a diagnosis of MI without ST-segment change was established. The patient was intubated for mechanical ventilation on this day. Her condition continued to worsen and she died on Day 10. An autopsy was not permitted by the family. The investigator did not consider the events study drug related.

Hepatorenal syndrome: This 73-year-old male with a medical history of chronic ischemic heart disease, atrial fibrillation, and congestive heart failure died on Study Day 7 with an SAE of hepatorenal syndrome. The patient received moxifloxacin on Days 1 to 6. By Day 4, the patient had improved, with resolution of his fever and improved laboratory results. On Day 7, the patient experienced increased dyspnea, altered mental status, and diffuse pain in the abdomen. Laboratory assessments revealed ALT of 3586 U/L, AST of 3400 U/L, and total bilirubin of 32 µmol/L (with direct bilirubin 17 µmol/L). D dimer was >10,000 ng/mL (normal range, <500 ng/mL), and creatinine climbed from normal values on Day 4 (1.1 mg/dL) to 2.7 mg/dL, with acute renal failure. An abdominal ultrasound revealed an abdominal aortic aneurysm, without evidence of rupture. The patient rapidly worsened and suffered cardiopulmonary arrest from which he could not be resuscitated. An autopsy determined the cause of death to be acute hepatorenal failure as a

consequence of an abdominal aortic aneurysm thrombosis. The investigator did not consider the events to be study drug related.

Respiratory failure, Sepsis, and Influenza: This patient is discussed above in the Hy's Law narrative section (Section 11.8.1).

Cardiac arrest: This 50-year-old female died on Study Day 6 with cardiac arrest. She improved over 5 days receiving IV moxifloxacin and was switched to oral moxifloxacin on Study Day 6. On Study Day 6 she was found in clinical distress with hyperventilation. An ECG revealed extreme tachycardia, suspected anteroseptal myocardial infarction, slight ST-T abnormality and right axis deviation. Shortly thereafter she went into cardiac arrest, CPR was unsuccessful, and the patient died. An autopsy was not performed due to family decision. The investigator felt the event was possibly related to pulmonary embolism or acute myocardial infarction.

Gastric haemorrhage, Septic shock, and Renal failure acute: This 74-year-old male with a history of hypertension, and cardiomegaly presented with vital signs at baseline of blood pressure 150/70 mmHg, and oxygen saturation of 72% on room air. His CABP symptoms improved over the first 4 days in the study. The evening of Study Day 5 he became nauseous and started vomiting. On Study Day 6 a nasogastric tube was inserted and coffee ground emesis was noted. Moxifloxacin was discontinued, and pantoprazole and metoclopramide were started. Acute renal failure was noted. He was treated with furosemide and methylprednisolone. He was intubated on Study Day 6 and placed on mechanical ventilation. On Study Day 7 he went into cardiac and respiratory arrest due to septic shock. Resuscitation was unsuccessful and he died. No autopsy was performed.

Aspiration: This 77-year-old female with a past history of hypertension, diabetes mellitus, myocardial infarction, cerebral arteriosclerosis and mild dementia inhaled a piece of food on Study Day 2. Removal of the obstruction and resuscitation efforts were unsuccessful.

Myocardial infarction, Acute respiratory failure, and COPD: This 60-year-old male with a medical history of hypertension, and tuberculosis was enrolled with a baseline WBC count of 20.79×10^9/L, elevated CRP of 187 mg/L and procalcitonin of 5.80 ng/mL. On Study Day 2, severe dyspnea occurred for which he required intubation and mechanical ventilator support. After a few hours, he self-extubated and went into asystole. CPR was initiated and he was re-intubated and resuscitated. On Study Day 3 moxifloxacin was discontinued, meropenem was started, and he was referred to surgery for chest tube insertion. An ECG done on this day was read as heart rate approximately 160/min, diffuse ST elevation, and sinus tachycardia. Central laboratory results from this date showed elevated ALT 59 U/L, AST 162 U/L, and ALP 272 U/L, low albumin 21 g/L, normal total bilirubin 21 µmol/L, and elevated direct bilirubin of 9 µmol/L. The patient continued to deteriorate over the next 24 hours and he died on Study Day 4. The investigator determined myocardial infarction to be the cause of death. Per the death certificate, acute respiratory failure was the immediate cause of death. The investigator considered myocardial infarction as the alternative cause of the events.

Cardiac failure congestive: This was an 81-year-old white male with a medical history of chronic cardiomyopathy decompensation, arterial hypertension, rectotomy due to rectal cancer and enterostomy, and prostate surgery who died on Study Day 27 with cardiac failure congestive. He received 7 days of IV moxifloxacin, and was considered a clinical success at EOT and SFU by the investigator. ECGs done at screening and during the study drug administration showed sinus

rhythm, with heart rates ranging from 62 to 80, QTcF intervals <450 msec, and, on Day 7 only, several premature atrial contractions. On Study Day 17 he was re-hospitalized due to fatigue, marked exhaustion, and poor appetite. He developed a worsening of dementia and urinary tract infection. On Study Day 22 he experienced hypertension with chest pain and he was administered nitroglycerin and labetalol. After that, became hypotensive and dopamine IV was administered. His condition continued to deteriorate and he required intubation and mechanical ventilation. On Study Day 24 heart rate was increased to 120 bpm and amiodarone and diltiazem IV were administered for the indication of 'paroxysmal supraventricular tachycardia and congestive heart failure.' He continued to deteriorate and died on Study Day 27 due to cardiac insufficiency.

Adrenal gland cancer: This was a 65-year-old white male with a past medical history of COPD, emphysema, and status post tuberculosis, who died on Study Day 12 with adrenal gland cancer. At baseline she presented to the emergency room complaining of abdominal pain, moderate chest pain, dyspnea, difficulty with sputum production and severe cough. An abdominal ultrasound showed enlarged lymph nodes in the right para-aortal/aortocaval region up to 11 mm and soft tissue changes in both adrenal lodges (adrenal gland cancer was suspected). Seven days of IV moxifloxacin were administered and the patient was considered a clinical success at EOT; she remained in the hospital for supportive therapy. On Study Day 10, a neurologist was consulted to evaluate patient confusion, and a diagnosis of suspected brain metastases was made. A panel of cancer biomarkers revealed a carcinoembryonic antigen of 146 ng/mL (reference range 0.52 to 8.9 ng/mL). On Study Day 12 she was incapable of following commands. She was treated with dexamethasone and albuterol. Subsequently she was transferred to the intensive care unit, given 2 g of ceftriaxone, and died despite resuscitation measures. An autopsy was not performed, but advanced adrenal cancer was the suspected cause of death.

11.8.3 Other Patient Narratives of Interest

NASH Study CE01-205: 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 planned 13-week study drug administration. Baseline liver biopsy revealed NAS with a NAFLD activity score of 6 based on findings of steatosis, ballooning hepatocyte degeneration and lobular inflammation, with Ishak scale fibrosis score of 2. In addition, portal inflammation was noted.

At screening, ALT was 64 U/L AST 51 U/L (1.4×ULN), ALP 83 U/L, gamma-GGT 27 U/L, and total bilirubin 0.6 mg/dL. The patient initiated study drug dosing with 200 mg of oral solithromycin daily. An episode of ALT (to 4.5×ULN) and AST (to 6.5×ULN) elevation, without bilirubin or ALP rise (but associated with an elevated GGT value) was recognized on Day 29. Study drug dosing was held from Day 30 to Day 44, and resumed (on Day 45 at 200 mg three times weekly) after recovery of ALT and AST to the baseline range. The patient tolerated rechallenge and remained asymptomatic, and completed the planned 13 week treatment period.

Liver function as measured by prothrombin time (INR) remained normal throughout and was 1.0 at all timepoints, on Day 1, Day 29, Day 54, and Day 89.

Solithromycin concentrations were determined (at estimated T_{max}, approximately 4 hours post-dose) on Day 1, Week 1, and Week 4. There was no evidence of excessive drug exposure or

accumulation. The respective concentrations were 249, 186 and 168 ng/mL, respectively on these three occasions.

The patient tolerated rechallenge dosing without AE and at Day 89, the final day of study drug dosing, ALT, AST and gamma-GGT levels were at or below baseline values. A follow up liver biopsy was obtained at EOT. Histological examination revealed NASH (NAS of 4) with decreases in ballooning degeneration and lobular inflammation. Portal inflammation was again observed with bile ductile changes consistent with resolution of cholestasis.