



CLINICAL STUDY PROTOCOL

Protocol Number:	CE01-203
Study Drug	Solithromycin (CEM-101)
Title:	A Phase 2/3, Randomized, Open-Label, Multi-center Study to Determine the Safety and Efficacy of Solithromycin in Adolescents (12 to 17 years of age, inclusive) and Children (≥ 2 months to < 12 years of age) with Suspected or Confirmed Community-Acquired Bacterial Pneumonia
Study Phase:	2/3
Sponsor	Cempra Pharmaceuticals, Inc. 6320 Quadrangle Drive, Suite 360 Chapel Hill, NC 27517 Telephone: (919) 313-6601 Fax: (919) 313-6620
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1 SIGNATURE PAGE

The signature of the investigator below constitutes his/her approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol as specified in both the clinical and administrative sections, including all statements regarding confidentiality. This trial will be conducted in compliance with the protocol and all applicable regulatory requirements, in accordance with Good Clinical Practice, including International Conference on Harmonization Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

Principal Investigator

Printed Name: _____

Signature

Date

Representatives of the Duke Clinical Research Institute, who agree to the terms and conditions of this protocol include:

Michael Cohen-Wolkowicz, MD, PhD
Study Medical Monitor

Signature

Date

Representatives of Cempra Pharmaceuticals, Inc. who agree to the terms and conditions of this protocol include:

Robert Hernandez, PhD
Director, Clinical Operations

Signature

Date

2 SYNOPSIS

Title of Study: A Phase 2/3, Randomized, Open-Label, Multi-center Study to Determine the Safety and Efficacy of Solithromycin in Adolescents (12 to 17 years of age, inclusive) and Children (≥ 2 months to <12 years of age) with Suspected or Confirmed Community-Acquired Bacterial Pneumonia

Study No: CE01-203

Planned Number of Investigational Sites: Approximately 90

Clinical Phase: 2/3, to be conducted in the U.S. and approximately 7 additional countries in other regions of the world

Planned Study Period: Approximately 24 months (first subject visit to last subject last visit)

Objectives:

Primary

- Evaluate the safety and tolerability of solithromycin in adolescents and children with community-acquired bacterial pneumonia (CABP)

Secondary

- Evaluate the efficacy of solithromycin in adolescents and children with CABP
- Evaluate the population pharmacokinetics (PK) of solithromycin in adolescents and children with CABP

Rationale

There is a growing body of efficacy and safety data on solithromycin in adults, it was shown to be non-inferior to moxifloxacin in an adult Phase 3 trial in CABP. However, the safety and efficacy of solithromycin have not yet been studied in pediatric subjects with CABP. There is evidence of similarities in children and adults in 1) CABP definitions and pathophysiology, 2) causative organisms, 3) response to intervention, and 4) exposure-response relationship. Therefore, extrapolation of efficacy in pediatric subjects from adult clinical trial efficacy data is reasonable. A safety study in pediatric subjects with CABP, however, is needed to compare the safety and tolerability of solithromycin to comparators. This study will gather necessary safety data and, as a secondary objective, assess the efficacy of solithromycin as a CABP treatment in pediatric subjects.

Methodology

This is a phase 2/3, randomized, open-label, active control, multi-center study to assess the safety and efficacy of solithromycin in children and adolescents with CABP. After informed consent/assent is obtained, subjects will be randomized to receive solithromycin or a comparator drug, administered intravenously (IV) or by mouth (PO) in capsules or suspension formulation. Pharmacokinetic samples will be collected to assess solithromycin disposition in subjects with CABP.

Subject Participation

The duration of participation, from the signing of the informed consent form and assent (if applicable), will be up to 32 days:

- Up to 10 days of therapy (5 to 7 days with solithromycin, 5 to 10 days with comparator antibiotics)
- Up to 32 days of adverse event (AE) and serious AE (SAE) monitoring (28 \pm 4 days will be reported)

Number of Subjects Planned

400 subjects ≥ 2 months to 17 years of age, inclusive, with CABP. Subjects will be randomized (3:1) into 2 groups: solithromycin (N~300) or comparator (N~100). Randomization will be stratified by the following age groups:

Age Group 1: Adolescents from 12 years to 17 years, inclusive

Age Group 2: Children from 6 years to <12 years

Age Group 3: Children from 24 months to <6 years

Age Group 4: Infants from ≥ 2 months to <24 months

A minimum of 40 subjects will be included in each age group. Approximately 20% of subjects will be enrolled in the U.S.

Diagnosis and Main Criteria for Inclusion**Inclusion Criteria:**

1. Written informed consent from parents or other legally acceptable representatives and informed assent from subject (if age appropriate according to local requirements)
2. ≥ 2 months to 17 years of age, inclusive
3. Requiring hospitalization, emergency room, or urgent care visit
4. Presence of CABP based on the following criteria within 72 hours prior to randomization:
 - History of and/or documented fever (rectal, temporal, ear, or oral temperature $\geq 38^{\circ}\text{C}$ or axillary temperature $\geq 37.5^{\circ}\text{C}$) or hypothermia (rectal, temporal, ear, or oral temperature $< 35^{\circ}\text{C}$ or axillary temperature $< 34.5^{\circ}\text{C}$)
 - AND**
 - Chest radiograph infiltrates consistent with bacterial pneumonia (or pneumonia caused by atypical bacterial agents); if a subject is outpatient and starting on oral therapy, a radiograph is not required.
 - AND**
 - Presence of **at least 2** of the following signs or symptoms:
 - a. Cough
 - b. Difficulty breathing
 - c. Production of purulent sputum
 - d. Chest pain
 - e. Grunting
 - f. Hypotension
 - g. Tachycardia, defined as follows:
 - 2 months to < 24 months: ≥ 160 beats/min
 - 24 months to < 10 years: ≥ 140 beats/min
 - ≥ 10 years: ≥ 100 beats/min
 - h. Tachypnea, defined as follows:
 - 2 months to < 12 months: ≥ 50 breaths/min
 - 12 months to < 5 years: ≥ 40 breaths/min
 - ≥ 5 years: ≥ 20 breaths/min
 - i. Physical exam consistent with pulmonary consolidation
 - AND**
 - Presence of **at least 1** of the following:
 - a. Leukocytosis ($\geq 12,000$ white blood cells [WBC]/ mm^3)
 - b. Leukopenia (< 5000 WBC/ mm^3)
 - c. $\geq 10\%$ immature neutrophils (bands) regardless of total peripheral WBC
 - d. Elevated inflammatory markers (C-reactive protein or procalcitonin)
 - e. Oxygen saturation $< 97\%$ on room air
 - f. Organism consistent with a typical respiratory pathogen identified from a blood culture or isolated from an appropriate respiratory culture/polymerase chain reaction (sputum in children old enough to produce an acceptable specimen; sample from the lower respiratory tract airways, if performed [e.g., bronchoalveolar lavage]; or pleural fluid culture)

Exclusion Criteria:

1. Confirmed or suspected respiratory tract infection attributable to sources other than community-acquired bacterial pathogens (e.g., ventilator-associated pneumonia; hospital-acquired pneumonia).
2. Received > 48 hours of potentially effective systemic antibacterial therapy for CABP immediately prior to randomization (exception: clinical or microbiological treatment failure or progression of signs or symptoms of CABP as determined by the investigator).
3. Confirmed or suspected bacterial meningitis.
4. Known active pulmonary tuberculosis.
5. Non-infectious causes of pulmonary infiltrates (e.g., cystic fibrosis, chemical pneumonitis from aspiration, hypersensitivity pneumonia).

6. Evidence or history of clinically significant medical condition that may, in the assessment of the investigator, impair study participation or pose a significant safety risk or diminish the subject's ability to undergo all study procedures and assessments.
7. Hepatic dysfunction evidenced by alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times upper limit of normal (ULN) or direct bilirubin greater than 2 times ULN (If direct bilirubin values are not available in a timeframe consistent with enrollment requirements, total bilirubin must be <2 times ULN).
8. Treatment with the following drugs within 72 hours prior to first dose of study drug or expected to receive these drugs during the treatment phase: drugs that potently inhibit CYP3A4 (nefazodone, fluconazole, ketoconazole, conivaptan, diltiazem, verapamil, aprepitant, imatinib, protease inhibitors, clarithromycin, ciprofloxacin, erythromycin, itraconazole, mibefradil, posaconazole, telithromycin, and voriconazole); CYP3A4 inducers (rifampin, rifabutin, phenytoin, fosphenytoin, carbamazepine, phenobarbital, rufinamide, modafinil, armodafinil, etravirine, efavirenz, nevirapine, rilpivirine, bosentan, troglitazone, pioglitazone, and St. John's wort). In addition, the following drugs may not be co-administered with solithromycin in this trial due to the potential for adverse drug-drug interaction: digoxin, colchicine, midazolam, quinidine, ergotamine, dihydroergotamine, rivaroxaban, apixaban, dabigatran, edoxaban, cisapride, cyclosporine, sildenafil, astemizole, and alfentanil.
9. Breast-feeding females.
10. Positive pregnancy test in females of childbearing potential.
11. History of anaphylaxis to macrolide antibiotics.
12. Previous participation in this study.
13. Subject has received any investigational drug studied under an Investigational New Drug application in the U.S. or under a Clinical Trial Application in the relevant country outside of the U.S. where the subject is being enrolled, taken within 4 weeks before administration of the first dose of study drug.
14. End Stage Renal Disease (dialysis requiring) OR severe renal impairment (defined as serum creatinine > 1.5 fold ULN for age).

Test Product

Dose and Mode of Administration: Solithromycin will be administered IV or PO according to the tables below. If dosing begins with oral therapy, the Day 1 dose will be a loading dose. No loading doses are used with IV solithromycin administration or if switched to oral administration. An IV-to-PO switch can occur after the first IV dose. Subjects starting with oral therapy will receive 5 days of solithromycin treatment and those starting with IV therapy (regardless of if and when they switch to oral therapy) will receive 7 days of solithromycin treatment.

Capsule Dosing Regimens

Age (years)	Weight	Route	Formulation	Day 1 (Max dose: 800 mg)	Days 2 to 5 (Max dose: 400 mg)
6 to 17	>30 kg	PO	Capsules	800 mg	400 mg
	>20 to 30 kg	PO	Capsules	600 mg	400 mg
	≤20 kg	PO	Capsules	400 mg	200 mg

Suspension Dosing Regimens

Age (years)	Route	Formulation	Day 1 (Max dose: 800 mg)	Days 2 to 5 (Max dose: 400 mg)
12 to 17	PO	Suspension	20 mg/kg (800 mg)	10 mg/kg (400 mg)
6 to <12	PO	Suspension	20 mg/kg	10 mg/kg
2 to <6	PO	Suspension	20 mg/kg	10 mg/kg
2 mo to <2	PO	Suspension	20 mg/kg	10 mg/kg

Intravenous Dosing Regimens

Age (years)	Route	Formulation	Days 1 to 7 (Maximum dose: 400 mg)
12 to 17	IV	Solution	8 mg/kg
6 to <12	IV	Solution	8 mg/kg
2 to <6	IV	Solution	8 mg/kg
2 mo to <2	IV	Solution	8 mg/kg

Intravenous to Oral Dosing Regimens

Age (years)	Route	Oral Formulation	Day 1 to Last IV Dosing Day (Max dose: 400 mg)	First Oral Dosing Day to Day 7 (Max dose: 400 mg) ^a
12 to 17	IV/PO	Suspension or Capsules	8 mg/kg	10 mg/kg (400 mg)
6 to <12	IV/PO	Suspension or Capsules	8 mg/kg	10 mg/kg
2 to <6	IV/PO	Suspension	8 mg/kg	10 mg/kg
2 mo to <2	IV/PO	Suspension	8 mg/kg	10 mg/kg

a. The adult dose should be administered unless the subject weighs <40 kg, in which case they receive 10 mg/kg on the first oral dosing day through Day 7. The capsule dose is rounded upwards to the nearest 200 mg.

Comparator Therapy

Dose and Mode of Administration: Comparators will be selected according to subject age and are consistent with current recommendations for treatment of CABP in children. A dosing table is provided below.

Children ≥2 months to <5 years of age:

- Ceftriaxone IV **OR**
- Ampicillin IV **or** amoxicillin IV **OR**
- Amoxicillin-clavulanic acid PO **or** IV **or** amoxicillin PO

Children 5 to 17 years of age (inclusive):

- Ceftriaxone IV **OR**
- Ampicillin IV **or** amoxicillin IV **OR**
- Amoxicillin-clavulanic acid PO **or** IV **or** amoxicillin PO

Azithromycin IV/PO or erythromycin lactobionate IV or erythromycin PO may be added to any of the treatment regimens above. Azithromycin is also acceptable as a first line of treatment.

	United States	Rest of the World
Amoxicillin	45-90 mg/kg/day <u>orally</u> in 2 or 3 divided doses; not to exceed 3 g/day	45-90 mg/kg/day <u>orally</u> in 2 or 3 divided doses; not to exceed 3 g/day 50-100 mg/kg/day <u>intravenously</u> in equally divided doses every 6 hours
Amoxicillin-clavulanic acid	Children <40 kg: amoxicillin component 90 mg/kg/day orally in divided doses given every 12 hours [4000 mg/day max dose] Children ≥40 kg, 875 mg orally every 12 hours or 500 mg orally every 8 hours [4000 mg/day max dose]	Children <40 kg: 20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given orally every 8 hours Children ≥ 40 kg: One 500 mg/125 mg dose given orally every 8 hours
Amoxicillin-clavulanic acid	-	Children >4kg but< 40kg: amoxicillin component 25 mg/kg intravenously every 8 hours [1000 mg max dose] Children ≥ 40 kg: amoxicillin component 1000 mg intravenously every 8 hours
Ampicillin	150-200 mg/kg/day intravenously in equally divided doses every 6 hours	-
Azithromycin	10 mg/kg intravenously/orally on day 1 [500 mg maximum dose] followed by 5 mg/kg orally every 24 hours [250 mg maximum dose]	10 mg/kg orally on day 1 [500 mg maximum dose] followed by 5 mg/kg orally every 24 hours [250 mg maximum dose]
Ceftriaxone	50-75 mg/kg/day intravenously in equally divided doses every 12 hours; total daily dose should not exceed 2 g	50-80 mg/kg intravenously once daily
Erythromycin	40 mg/kg/day orally every 6 hours	30-50 mg/kg/day orally every 6 hours
Erythromycin lactobionate	15 to 20 mg/kg/day intravenously in equally divided doses every 6 hours	50 mg/kg/day intravenously/orally in equally divided doses every 6 hours

Note: if doses of comparator drugs noted in the dosing table above differ from those prescribed per standard of care, a site can use the locally prescribed dose.

Intravenous-to-oral switch:

Subjects receiving an IV comparator drug in any age group may be switched to oral treatment using amoxicillin-clavulanic acid PO (amoxicillin component 45 mg/kg every 12 hours; subjects weighing ≥ 40 kg, 875 mg every 12 hours or 500 mg every 8 hours) or amoxicillin alone (45 mg/kg every 12 hours, up to a maximum of 4 g/day).

Duration of Treatment: 5 to 10 days. The exact duration of treatment may be determined at the investigator's discretion.

Addition of expanded gram-positive coverage to treatment and comparator groups will be allowed if empiric therapy for methicillin-resistant *Staphylococcus aureus* is desired per local standard of care.

Criteria for Evaluation:

Safety:

Any study team member may perform safety assessments. An independent Data Monitoring Committee will assess the overall study status and safety of subjects at intervals outlined in the committee's charter and will make recommendations to the sponsor on continuing or modifying the study based on these assessments.

Efficacy:

A health care provider designated as a subinvestigator blinded to treatment allocation at the site will document clinical response at specified time points during the study.

Pharmacokinetics:

The table below provides the optimal plasma sampling collection windows for solithromycin according to route of administration. Every effort should be made to collect at least 2 PK samples on Day 1 and at least 2 PK samples on days 3 through 7 during these windows (not to exceed 6 samples total); however, samples obtained outside of the sampling windows are acceptable. Lack of collection of samples or collection outside the optimal windows will not be considered protocol deviations.

IV Time after dose	Oral Time after dose
Prior to dosing (within 1 hour) ^a	Prior to dosing (within 1 hour) ^a
End of infusion (within 10 minutes)	0.5–1.5 hours
2–4 hours	2–4 hours
8–10 hours	8–10 hours
16–18 hours	16–18 hours
20–<24 hours	20–<24 hours

^a Not applicable to Day 1 samples.

Statistical Methods and Data Analysis

Efficacy population: All subjects who are randomized.

Safety population: All subjects who receive at least 1 dose of study drug.

PK population: All subjects who receive at least 1 dose of solithromycin and have at least 1 evaluable PK sample.

MicroITT population: Randomized subjects who have a microbiologically confirmed baseline pathogen.

Safety:

New events that occur or pre-existing conditions that worsen in frequency or intensity will be reported as AEs or SAEs. AEs will be reported for 16 days and SAEs for 28 days post-randomization. The investigator will provide date of onset and resolution, intensity, frequency, actions taken, changes in study drug dosing, relationship to study drug, and outcome. Laboratory determinations performed by local laboratories including hematology values (hemoglobin, hematocrit, WBC count with differential, and platelet count) and serum chemistry values (blood urea nitrogen, calcium, serum creatinine, potassium, sodium, AST, ALT, alkaline phosphatase, total and direct bilirubin, and albumin) obtained within 72 hours prior to the first dose of study drug and while the subject is on therapy will be recorded. Baseline and on-study microbiological cultures of blood, cerebrospinal fluid (CSF), pleural fluid, and respiratory secretions will be recorded if obtained within 72 hours prior to the first dose of study drug and while the subject is on therapy. If an AE or SAE occurs, concomitant medications will be recorded at the time of the event.

Primary safety endpoints will be the proportion of subjects experiencing an AE and the proportion of subjects discontinuing study drug due to a related AE. Additional safety analyses include summaries of AEs, descriptive statistics of laboratory values, frequency distributions and shift tables summarizing abnormal laboratory values, descriptive statistics of vital signs, and frequency distributions of abnormal physical examinations.

Efficacy:

The primary efficacy endpoint is defined as clinical improvement on the last day of treatment (end of treatment response), and the secondary efficacy endpoints are defined as early clinical response at Days 2-4 and clinical success (i.e., cure) at the short-term follow-up visit (16 days [+/- 4 days] post-randomization).

Pharmacokinetics:

Population PK methodologies using nonlinear mixed effects modeling in NONMEM will be used to analyze the concentration data. Data will be reviewed during the study to evaluate PK of solithromycin in pediatric CABP patients. The influence of covariates on PK parameters will be explored. Monte Carlo simulations will be used to evaluate optimal drug exposure. The relationship between drug exposure and safety events will be evaluated by calculating the proportion of subjects with AEs and SAEs at different exposure levels.

Table 1 **Schedule of Assessments and Procedures**

Activity	Screening/Baseline (Day -3 through Day -1) ^a	Treatment Period		Follow-Up	
		Treatment Days up to Last Day of Treatment ^b	Last Day of Treatment (+48 hours)	Day 16 Post Randomization ^{c, d} (±4 days)	Day 28 Post Randomization ^d (±4 days)
Informed consent form	X				
Demographic data	X				
Eligibility criteria	X				
Randomization	X				
Medical history	X				
Physical examination	X	X ^c	X	X	
Vital signs ^e	X	X ^c	X	X	
Chest x-ray ^f	X				
Study-required safety labs ^g	X ^h	X ⁱ	X ^j	X ⁱ	X ⁱ
Review of standard-of-care data: Safety labs ^{g, k} Microbiology assessments ^l Radiological imaging ^m Non-pharmacological treatments ⁿ	X	X	X	X	
Pregnancy test ^o	X	X ^p			
Concomitant medications ^q	X	X	X		
Study drug or comparator administration ^r		X	X		
Pharmacokinetic sampling ^s		X	X		
Adverse event assessment	X	X	X	X	
Serious adverse event assessment	X	X	X	X	X

Activity	Screening/Baseline (Day -3 through Day -1) ^a	Treatment Period		Follow-Up	
		Treatment Days up to Last Day of Treatment ^b	Last Day of Treatment (+48 hours)	Day 16 Post Randomization ^{c, d} (±4 days)	Day 28 Post Randomization ^d (±4 days)
Clinical outcomes and symptom assessments: Early Clinical Response, End of Treatment, and Follow-Up Post Treatment ^t	X	X ^u	X ^v	X ^w	

- a Screening/baseline can occur up to 72 hours prior to randomization. Standard-of-care laboratory data and radiological imaging from up to 72 hours prior to randomization may be used as screening procedures. Screening/baseline and first day of treatment may be the same day.
- b Treatment period is 5 to 7 days for solithromycin and 5 to 10 days for comparators. These assessments and procedures may be done prior to Day 3 if the subject is discharged from the hospital before Day 3.
- c Record vital signs for each day available. Physical examinations should be recorded from baseline and the Day 3 to 4 visit (early clinical outcome assessment) and at the Last Day of Treatment visit.
- d Every effort should be made to bring the subject back. If the subject is unable or unwilling to return, the AEs/SAEs must be collected via telephone/other media.
- e Vital signs taken at the closest time post-drug administration should be noted. If vital signs following drug administration are not available, record the first value of the day.
- f Screening chest x-ray does not need to be repeated if a standard-of-care chest x-ray was performed within 72 hours of randomization. Subjects that are outpatient and starting on oral therapy do not need a screening x-ray.
- g Local laboratory; includes hemoglobin*, hematocrit*, white blood cell count with differential*, platelet count*, blood urea nitrogen*, calcium*, serum creatinine, potassium*, sodium*, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase*, total and direct bilirubin, and albumin*. If laboratories with * designation are not obtained, it will not result in a protocol deviation.
- h A separate study sample is not required if safety labs above are obtained at baseline per standard of care. If multiple laboratory tests are obtained within 72 hours of randomization, record test results closest to randomization.
- i Every effort should be made to obtain safety labs 72 (±24) hours after the first dose to include aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, and white blood cell count with differential. A separate study sample is not required if safety labs above are obtained within the visit window per standard of care.
- j Safety labs must be collected on the last day of dosing or within 48 hours after the last dose. A separate study sample is not required if safety labs above are obtained on the last day of dosing or within 48 hours after the last dose per standard of care.
- k Record the safety labs if performed per standard of care; if multiple laboratory tests are obtained on the same day, record test results closest to administration of study drug.
- l Microbiological assessments will be recorded if performed per routine medical care. These include cultures from sterile body fluids and molecular and serologic tests for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.
- m Radiological imaging of the chest, including chest x-ray or computed tomography (CT) scan, will be recorded if performed per routine medical care.
- n Non-pharmacologic treatments (such as operative procedures) will be recorded if performed per routine medical care.
- o Female subjects of childbearing potential within 24 hours of first dose.
- p If the screening visit for females occurred greater than 24 hours before receiving the study drug.
- q Medications other than antibiotics taken within 72 hours and all antibiotics taken within 7 days prior to first dose of study drug as well as all concomitant medications through the follow-up visit will be recorded.

- r Solithromycin should be administered approximately every 24 hours and at approximately the same time each day (\pm 4 hours) for 5 to 7 days.
- s Only in subjects receiving solithromycin; central laboratory.
- t Symptoms should be recorded at baseline, the Day 3 to 4 visit (early clinical response) visit, the Last Day of Treatment Visit (end-of-treatment response), and at the Day 16 Follow-Up visit). If the subject is discharged on Day 2 (prior to the Day 3 to 4 visit), the early clinical response assessment will be done on the day of discharge.
- u Early clinical response
- v End of Treatment response
- w Day 16 post randomization response (cure)

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AM	alveolar macrophage
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC ₀₋₂₄	area under the concentration versus time curve at 24 hours
AUC _{tau}	area under the concentration-time curve for the dosing interval
BARDA	Biomedical Advanced Research and Development Authority
bpm	beats per minute
CABP	community-acquired bacterial pneumonia
CA-MRSA	community-acquired methicillin-resistant <i>Staphylococcus aureus</i>
CBC	complete blood count
CE	clinically evaluable
CFR	Code of Federal Regulations (U.S.)
CI	confidence interval
C _{max}	maximum measured plasma concentration
CPK	creatine phosphokinase
CRO	clinical research organization
CRU	clinical research unit
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
DCRI	Duke Clinical Research Institute
DLT	dose-limiting toxicities
DMC	data monitoring committee
DMID	Division of Microbiology and Infectious Diseases
ECG	electrocardiogram
ECR	early clinical response
eCRF	electronic case report form
ELF	epithelial lining fluid
EM	electron microscopy
FDA	Food and Drug Administration (U.S.)
FSH	follicle-stimulating hormone
GC	gonorrhea; gonococcal infection
GCP	Good Clinical Practice
GD	gestational day

GI	gastrointestinal
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HED	human-equivalent dose
HEENT	head, eyes, ears, nose, throat
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
IC ₅₀	half-maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intra-uterine device
IV	intravenous
LD	lactation day
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLN	lower limit of normal
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
NIH	National Institutes of Health (U.S.)
NOAEL	no-observed-adverse-effect-level
P	parental
PICC	peripherally inserted central catheter
PK	pharmacokinetic
PO	by mouth
PORT	Pneumonia Patient Outcomes Research Team
QD	daily
<i>S. pneumoniae</i>	<i>Streptococcus pneumoniae</i>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SFU	short-term follow-up
TEAE	treatment-emergent adverse event

TOC	test of cure
TQT	Thorough QT/QTc
ULN	upper limit of normal
WBC	white blood cell
WMA	World Medical Association

5 INTRODUCTION

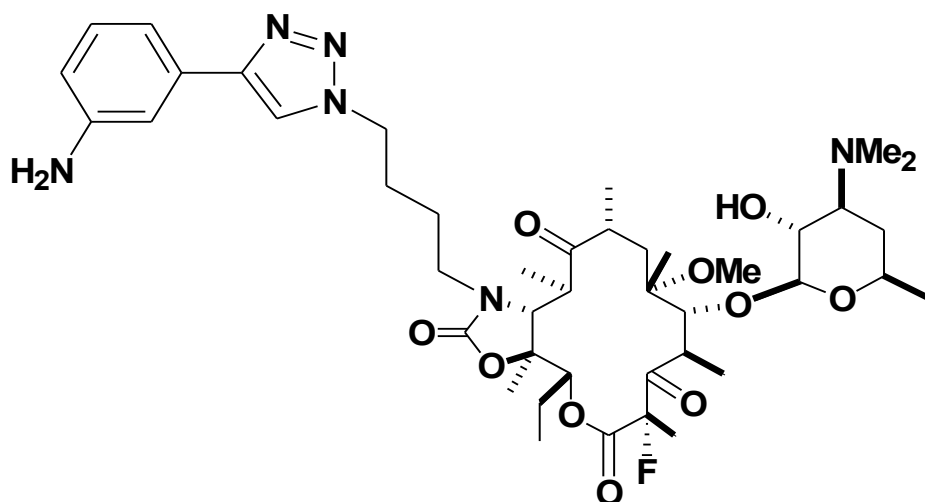
Community-acquired bacterial pneumonia (CABP) is common worldwide and associated with significant mortality ([World Health Organization 2012](#)). In children, the microorganisms responsible for CABP differ by age and include *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Hemophilus influenzae*, group A *Streptococcus*, *Legionella*, and *Staphylococcus aureus* ([Michelow 2004](#), [Heiskanen-Kosma 1998](#), [Principi 2001](#), [Ranganathan 2009](#)). Among these organisms, *S. pneumoniae* is the most common cause of pneumonia in children older than 1 week of age ([Gereige 2013](#)), yet 30% of pneumococcal isolates worldwide are resistant to macrolides ([Farrell 2008](#)). Additionally, *Mycoplasma pneumoniae*, another common cause of pneumonia in children, has been found to have significant macrolide resistance in the pediatric population (up to 27% in the U.S. and 80% in Asia ([Wolff 2008](#), [Liu 2009](#))).

Solithromycin, a 4th-generation macrolide fluoroketolide, has excellent in vitro activity against all of these organisms, including community-acquired methicillin-resistant *S. aureus* (community-acquired methicillin-resistant *Staphylococcus aureus* [CA-MRSA]) ([Farrell 2010](#)). The pharmacokinetics (PK) of oral solithromycin in adolescents has been previously characterized in a phase 1 study. The PK of both intravenous (IV) and oral solithromycin in adolescents and children has been investigated. In the completed PK studies of solithromycin in adolescents and children, the drug exhibits a favorable safety profile and exposure comparable to adult exposure following study dosing. In a global phase 3 trial comparing 5 days of oral solithromycin alone versus 7 days of oral moxifloxacin alone for treatment of CABP in adults, solithromycin was shown to be non-inferior to moxifloxacin in early clinical response and short-term follow-up ([Oldach 2015](#)). All of these results suggest that solithromycin could be used as monotherapy against pediatric CABP and other infections. However, a larger safety and efficacy study of solithromycin in children and adolescents has not yet been conducted.

5.1 Nonclinical

5.1.1 Solithromycin (CEM-101) Nonclinical Pharmacology

Solithromycin is the first fluoroketolide in the macrolide class of antibiotics. It is being developed in IV and oral formulations for the treatment of patients with CABP. Its extended spectrum of activity and pharmacological properties provide potential for clinical use in other therapeutic areas such as gonococcal infections, malaria, and biodefense. Solithromycin is chemically described as: (3aS, 4R, 7S, 9R, 10R, 11R, 13R, 15R, 15aR)-1-[4-[4-(3-aminophenyl)-1H-1, 2, 3-triazol-1-yl]butyl]-4-ethyl-7-fluorooctahydro-11-methoxy-3a, 7, 9, 11, 13, 15-hexamethyl-10-[[3, 4, 6-trideoxy-3-(dimethylamino)- β -D-xylo-hexopyranosyl]oxy]-2H-Oxacyclotetradecino[4, 3-d]oxazole-2, 6, 8, 14(1H, 7H, 9H)-tetrone. The chemical structure is shown in Figure 1. The molecular weight is 845 daltons.

Figure 1 Chemical Structure of Solithromycin

Nonclinical and clinical data on solithromycin are briefly summarized below. Please refer to the current Investigator's Brochure for additional details.

5.1.2 Mechanism of Action

Solithromycin inhibits bacterial protein synthesis via a unique pattern of ribosomal binding to domains II and V, as well as to the peptide tunnel, of the 23S component of the 50S ribosomal subunit. This binding pattern provides for multiple and tight ribosomal interaction sites. Solithromycin was also found to have a higher affinity to *erm*-modified (methylated) ribosomes than telithromycin, azithromycin, or erythromycin, which likely accounts for its improved activity relative to these agents against macrolide-resistant bacteria.

5.1.3 In Vitro Microbiological Activity

Solithromycin has potent in vitro activity against common respiratory pathogens. It has greater activity against gram-positive aerobes, including *S. pneumoniae* and *Streptococcus pyogenes*, compared with the macrolides clarithromycin and azithromycin and the ketolide telithromycin. Solithromycin retains potent activity against pneumococcal strains with both *ermB* (ribosomal methylation)- and *mefA* (macrolide efflux)-acquired resistance genotypes. Solithromycin is highly active against the atypical pathogens associated with CAP, including *Legionella pneumophila*, *C. pneumoniae*, and *M. pneumoniae*. Its potency against gram-negative respiratory tract pathogens, including *M. catarrhalis* and *H. influenzae* is comparable to that of azithromycin. Solithromycin exhibits good activity against the USA-300 strain of CA-MRSA and methicillin-susceptible *S. aureus*. Solithromycin is active against *S. pyogenes* and other beta-hemolytic streptococcal species and has marked in vitro potency against enterococcal species (*Enterococcus faecium*, *Enterococcus fecalis*), including vancomycin-resistant strains. Solithromycin is also active in vitro against *Bordetella pertussis*.

Solithromycin is active against the sexually transmitted disease pathogens *Neisseria gonorrhoeae*, *Mycoplasma hominis*, *C. trachomatis*, and *Ureaplasma urealyticum*. Solithromycin is also active against some enteric pathogens, including *Shigella* spp., *Campylobacter jejuni*, and *Salmonella*

spp; however, it is not active against *E coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Serratia marcescens*. The effect of solithromycin on human fecal flora is being studied in a healthy-volunteer trial. The in-life portion has been completed and no *Clostridium difficile* toxin gene or toxin were identified in stool samples.

Against intracellular (intraphagocytic) *S. aureus*, solithromycin was more potent than azithromycin and clarithromycin and was able to reduce the intracellular bacterial counts to a greater extent than the older macrolides. Unlike azithromycin and clarithromycin, solithromycin is bactericidal against most pneumococci. Studies of interactions with other antibiotics have found solithromycin to be synergistic or additive with vancomycin, levofloxacin, gentamicin, ceftriaxone, and trimethoprim/ sulfamethoxazole.

5.1.4 Nonclinical Safety Assessment

5.1.4.1 Safety Pharmacology

In an in vitro human ether-à-go-go related gene (hERG) study that assessed the tendency of solithromycin to inhibit the repolarizing current in the cardiac action potential, solithromycin inhibited the hERG channel at a half-maximal inhibitory concentration (IC₅₀) of 25.2 μM. Solithromycin did not induce deleterious cardiovascular effects or QT prolongation in a cardiovascular safety study in dogs. Solithromycin and older macrolides could be differentiated from telithromycin by the activity of telithromycin and/or its metabolites against a number of nicotinic acetylcholine receptor subtypes in vitro. The profile of blockade of several receptor subtypes could help explain the unusual adverse events (AEs) of reversible blurred vision and rapid progression of exacerbations of myasthenia gravis that have been observed with telithromycin. The lack of motilin receptor activation predicts that solithromycin, unlike other macrolides, will not induce gastrointestinal contractions through this mechanism.

5.1.4.2 Rat Toxicology

Repeat-dose oral toxicity and toxicokinetics of solithromycin in male and female Sprague-Dawley derived CD® rats were evaluated over a dosing period of 13 weeks in a Good Laboratory Practice (GLP) compliant study. Solithromycin was administered at doses of 20, 50, and 125 mg/kg/d. No solithromycin-related mortality or clinical signs were observed nor were there adverse effects of solithromycin administration on hematology, organ weights, ophthalmology, gross pathology, or microscopic pathology. Slightly lower body weights (8%) were observed for males at 125 mg/kg/d at the end of the study relative to controls. On Day 45, increased serum liver enzyme values (alkaline phosphatase [ALP], aspartate aminotransferase [AST], and/or alanine aminotransferase [ALT]) were observed in all solithromycin-treated groups; however, they were mild in severity, within the laboratory's historical control range (except for ALP), generally absent or diminished by Day 92, without any histopathological correlate, and therefore not considered toxicologically significant. Kupffer cell hyperplasia was observed in males at 125 mg/kg and was not considered toxicologically significant. Tissue concentrations were highest in liver, lymph node, and spleen with mean concentrations (combined male and female) at 125 mg/kg/d on Day 91 that were 28-, 23-, and 18-fold higher than maximum measured plasma concentration (C_{max}), respectively. Tissues with the next highest concentrations were the salivary gland, lung, thymus, and heart. Concentrations in these tissues ranged from 2- to 10-fold higher than plasma C_{max}. A no-observed-

adverse-effect-level (NOAEL) of 125 mg/kg/d, the highest dose administered, was established in this study.

Dosing for the 13-week study was determined from repeat-dose oral toxicity and toxicokinetics of solithromycin in male and female Sprague-Dawley derived CD® rats over a dosing period of 28 days. Solithromycin was administered at doses of 40, 100, 250, and 500/250 mg/kg/d. Solithromycin treatment at doses of 250 mg/kg/d or higher resulted in significant toxicity, including changes in clinical chemistry and hematology parameters that were associated with microscopic changes in the liver and hematopoietic system. The NOAEL for solithromycin for the majority of toxicity findings in this study was 100 mg/kg/d. However, based on findings of histiocytosis in lymph nodes and in the lungs and vacuolar degeneration in the cecum, the overall NOAEL for the study was considered to be 40 mg/kg/d.

5.1.4.3 Monkey Toxicology

A 13-week, GLP-compliant study evaluated doses of 20, 50, and 125 mg/kg/d in cynomolgus monkeys. All toxicologically significant findings were confined to the 125 mg/kg/d dose level and are consistent with the liver being a target organ. ALT and AST changes correlated with Kupffer cell hyperplasia and centrilobular hepatocyte vacuolation (phospholipidosis by EM). In addition, histiocytosis consistent with phospholipidosis was noted in several other tissues. These solithromycin-related effects appear to be reversible, as all of the clinical pathology alterations and many of the findings in the liver, lung, and spleen were normalized or reduced after the 12-week recovery period. Based on these findings, the NOAEL was determined to be 50 mg/kg/d. Administration of solithromycin had no effects on mortality, urinalysis, ophthalmology, or electrocardiograms (ECGs).

Dose-related increases in solithromycin exposures (C_{\max} and area under the concentration versus time curve at 24 hours [AUC_{0-24}]) were observed on Days 1, 29, and 91. Solithromycin exposures were higher on Days 29 and 91 than on Day 1. Most of the accumulation due to repeated dosing was observed by Day 29 with less additional accumulation by Day 91.

Doses for the 13-week study were determined from a 14-day study that utilized doses of 40, 100 or 200 mg/kg/d. Based on the findings in this study, the NOAEL was considered to be 40 mg/kg/d. Changes in clinical chemistry parameters included increased ALT and AST at 100 and 200 mg/kg/d that correlated with centrilobular hepatocyte vacuolation (phospholipidosis by electron microscopy [EM]) at 200 mg/kg/d. Solithromycin treatment was also associated with histiocytosis/ phospholipidosis in other tissues, such as the gastrointestinal (GI), splenic, and lymphatic systems. Tissue concentrations of solithromycin were measured in lung, liver, and heart from these animals. Concentrations were highest in the liver and lung and reached a multiple of 711 and 503 times, respectively, the maximum concentration in plasma at 200 mg/kg/d.

The findings of histiocytosis and phospholipidosis are commonly observed for lipophilic molecules and have been reported for other macrolides, such as clarithromycin, azithromycin, and telithromycin ([Reasor 2006](#)).

The mechanism by which CEM-101 induces phospholipidosis appears to be related, at least in part, to its ability to inhibit lysosomal phospholipase A1. As seen with azithromycin, CEM-101

accumulated in lysosomes and caused lysosomal phospholipidosis in relation to its capacity to inhibit lysosomal phospholipases. CEM-101 and azithromycin showed no association of phospholipidosis with apoptosis either in incubated cells (up to at least 100 µg/mL) or in electroporated cells, even with substantial accumulation. Therefore it was concluded that CEM-101, like azithromycin, inhibits lysosomal phospholipase A1 and induces lysosomal phospholipidosis in vitro but does not induce apoptosis.

5.1.4.4 Carcinogenicity

Carcinogenicity studies have not been conducted with solithromycin.

5.1.4.5 Reproductive Toxicity

Segment 1, 2, and 3 reproductive toxicity studies with oral solithromycin have been completed. Effects on male and female fertility and early embryonic development to implantation were evaluated in rats. Effects on embryo-fetal development were evaluated in rats and rabbits. Effects on perinatal and postnatal development were studied in rats.

The Segment 1 study in rats evaluated the potential toxic effect of solithromycin on the estrous cycle, tubal transport, implantation, and development of preimplantation stages of the embryo, and on functional effects of male fertility. Three treatment groups of 25 male and 25 female Sprague Dawley rats/group were administered solithromycin at respective doses of 50, 100 or 220 mg/kg/d. No apparent solithromycin-related changes were noted in estrous cyclicity, sperm parameters, or uterine and reproductive parameters in male and female animals treated with solithromycin. Microscopic examination of the testes did not reveal any treatment-related changes. Administration of solithromycin at 50, 100 and 220 mg/kg/d by oral gavage to male and female rats during the premating, postmating, and gestation periods resulted in general toxicity at 100 and 220 mg/kg/d, as evidenced by clinical findings and body weight and food consumption effects in these groups; there was also one solithromycin-related mortality at 220 mg/kg/d. The reproductive parameters in the both male and female rats were considered to be unaffected by treatment with solithromycin. The NOAEL for reproductive toxicity was determined to be 220 mg/kg/d, the highest dose tested.

The Segment 2 study in rats evaluated the developmental toxicity, including the teratogenic potential, of solithromycin in pregnant rats. Three treatment groups of 25 time-mated female CD® rats/group were administered solithromycin at respective doses of 50, 100, or 220 mg/kg/d. Administration of solithromycin to pregnant rats from gestational day (GD) 6 to 17 produced significant maternal toxicity, particularly at 220 mg/kg/d, based on clinical signs, body weight and food consumption effects. A significant increase in food consumption at 220 mg/kg/d following cessation of dosing indicated a compensatory effect based on the significant body weight effects noted. The maternal necropsy, including uterine and external, visceral, and skeletal fetal evaluations did not reveal any adverse effects that could be attributed to treatment. The NOAEL for developmental toxicity was determined to be 220 mg/kg/d, the highest dose tested. In addition, no signs of teratogenic potential in the fetuses were identified at the doses evaluated.

The Segment 2 study in rabbits evaluated the developmental toxicity, including the teratogenic potential, of solithromycin in pregnant rabbits. Three treatment groups of 23 time-mated female New Zealand White rabbits/group were administered solithromycin at respective doses of 20, 110, or 200 mg/kg/d. Administration of solithromycin to pregnant rabbits from GD 6 to 18 resulted in maternal toxicity at 110 and 200 mg/kg/d, as evidenced by body weight and food consumption effects, including abortions at 200 mg/kg/d. Slight decreases in viable fetuses and litter size, and increases in postimplantation loss and resorptions, were also noted at 200 mg/kg/d. No solithromycin-related changes were seen in fetal body weight or identified following the fetal external, visceral, and skeletal examinations in the treated animals, as compared to controls. The NOAEL for developmental toxicity was determined to be 110 mg/kg/d. No evidence of a teratogenic effect was evident in any of the treatment groups at doses up to 200 mg/kg/d.

A Segment 3 study in rats evaluated the possible adverse effects of solithromycin (50, 100 and 200 mg/kg/d) on the pregnant/lactating female and on the development of the conceptus and the offspring following exposure of the female from implantation through weaning.

No mortalities related to solithromycin were observed for the parental (P) females or the selected offspring (F₁). Oral administration of solithromycin at 200 mg/kg/d to P females from GD 6 to lactation day (LD) 20 produced maternal toxicity, based on decreased body weight (9%) and food consumption effect, and developmental toxicity in the pups at this dose level, based on decreases in mean body weight during the preweaning period.

No other toxicologically meaningful or adverse changes related to solithromycin were observed in the F₁ pups in any dose group during the lactation, postweaning, growth, or reproductive phases.

Solithromycin and the active side chain metabolites *N*-acetyl-CEM-101 and CEM-214 were detected in milk of the lactating dam 6 hours post-dose on LD 12. The concentrations in milk were significantly higher than seen in rat plasma with similar doses in previous studies.

The NOAEL for general maternal toxicity in P females was 100 mg/kg/d, based on the body weight and food consumption effects at 200 mg/kg/d. The NOAEL for F₁ developmental toxicity was also 100 mg/kg/d, based on the decreases in pup weight during the preweaning period. No other drug-related effects were observed in the F₁ pups based on evaluation of behavior, physical development, or reproductive indices.

5.2 Clinical

5.2.1 Clinical Pharmacology and Biopharmaceutics

5.2.1.1 In Vitro

Solithromycin was determined to be 78 to 84% bound to human plasma proteins, similar to other macrolides. Binding to human serum albumin was 43 to 50%, and binding to α -1-acid glycoprotein was 7 to 10%.

Solithromycin is metabolized primarily in the liver. In vitro analysis of metabolism by reaction phenotyping using both a chemical inhibitor and recombinant CYP450 indicates that CYP3A4 is likely the major CYP450 enzyme governing the metabolism of solithromycin.

Studies to assess the interaction of solithromycin with the cytochrome P450 enzyme system have shown that solithromycin is an inhibitor (including an auto-inhibitor) and substrate of CYP3A isozymes and undergoes minimal metabolism by other CYP450 enzymes. Solithromycin did not induce CYP3A isozymes. The rate of CYP3A4 inactivation by solithromycin was comparable to that of clarithromycin, which was slightly slower than erythromycin.

Solithromycin, like other macrolide antibiotics, is both a substrate and inhibitor of p-glycoprotein (P-gp, also known as MDR1) in vitro. Solithromycin also has the potential to inhibit the uptake transporter OATP1B3, but at exposures unlikely to be achieved in clinical dosing, and if so, only transiently. Therefore, clinically significant drug-drug interactions as a result are not expected. Solithromycin did not inhibit any of a panel of important efflux transporters, including breast cancer resistance protein and bile salt export pump, or uptake transporters, including OATP1B2, OAT1, OAT3, OCT1, and OCT2, to a clinically significant extent.

5.2.1.2 Solithromycin Capsules

The PK of oral solithromycin has been studied in healthy adults enrolled in phase 1 PK trials and in drug-drug interaction studies. Single-dose solithromycin, ranging from 50 to 1600 mg, was administered to 35 subjects (7 cohorts of 5 subjects each; mean age 34 years, mean weight 73.5 kg); C_{max} following 400 (~5.5 mg/kg) and 800 (~11 mg/kg) mg doses were 0.78 and 1.32 $\mu\text{g/mL}$ at 4.0 and 3.5 hours to peak concentration, respectively. Area under the concentration-time curve for the dosing interval (AUC_{tau}) in these 2 study doses was 6.94 $\mu\text{g}\cdot\text{h/mL}$ and 13.67 $\mu\text{g}\cdot\text{h/mL}$, respectively. With repeated single daily doses of 200, 400 and 600 mg over 7 days, AUC_{tau} and C_{max} were 1.7 to 2.2 times greater on Day 7 than on Day 1, indicating accumulation over the dosing period, with steady state probably achieved by approximately Day 4. Food had no effect on the bioavailability of solithromycin following a single dose of 400 mg.

5.2.1.3 Solithromycin for Injection

Study CE01-121 evaluated a single-vial formulation that contains 400 mg solithromycin with 3 amino acids as buffering agents. Peripheral and central (via a peripherally inserted central catheter [PICC]) venous administration of 400 mg daily (QD) solithromycin (or placebo) infused in 250 mL for 7 days was assessed. The peripheral infusion cohorts received 400 mg solithromycin infused over either 30 or 60 minutes; the PICC cohort received 400 mg infused over 60 minutes.

This study also evaluated the PK of a single 800-mg IV dose infused over 40 minutes to achieve supratherapeutic plasma concentrations for a planned thorough QT/QTc (TQT) study, as described in Section 5.2.2.2.

Twenty subjects received solithromycin 400 mg QD for 7 days via a peripheral IV line (10 subjects received 30-minute infusions, 10 subjects received 60-minute infusions), and 5 received 400 mg doses for 7 days via a PICC line.

Infusion of multiple 400-mg doses solithromycin over 30 minutes compared to 60 minutes resulted in a 1.5-fold higher mean C_{max} on both Days 1 (3.2 vs 2.2 $\mu\text{g/mL}$) and 7 (4.2 vs 2.9 $\mu\text{g/mL}$).

Central infusion of 400 mg via a PICC line resulted in a C_{\max} of 2.4 and 3.3 $\mu\text{g/mL}$, after 1 and 7 days, respectively. These C_{\max} values were slightly (~1.1-fold) higher than after peripheral venous administration at the same dose and duration on both Day 1 (2.17 $\mu\text{g/mL}$) and Day 7 (2.85 $\mu\text{g/mL}$).

AUC_{0-24} values were similar after peripheral infusion of 400 mg solithromycin over either 30 or 60 minutes. They were slightly (1.1-fold) higher when solithromycin was administered via a PICC line, on both Day 1 (6.5 $\mu\text{g}\cdot\text{h/mL}$, 60 min PICC; 5.3 $\mu\text{g}\cdot\text{h/mL}$, 60 min peripheral; and 5.9 $\mu\text{g}\cdot\text{h/mL}$, 30 min peripheral) and Day 7 (14.6 $\mu\text{g}\cdot\text{h/mL}$, 60 min PICC; 12.6 $\mu\text{g}\cdot\text{h/mL}$, 60 min peripheral; and 13.6 $\mu\text{g}\cdot\text{h/mL}$, 30 min peripheral). However, given the large standard deviations observed in all 3 cohorts, the differences are not considered meaningful.

Solithromycin accumulated approximately 2-fold over 7 days of 400 mg dosing in all 3 multiple dose cohorts (Table 2).

Table 2 Mean Pharmacokinetic Parameters for Solithromycin in Plasma on Day 1 and Day 7 (CE01-121)

Parameter	Multiple Dose		
	400 mg	400 mg	400 mg
	250 mL over 60 minutes, Peripheral Administration	250 mL over 30 minutes, Peripheral Administration	250 mL over 60 minutes Central/PICC Administration
Day 1			
N	10	10	5
Mean C_{\max} , $\mu\text{g/mL}$	2.170	3.200	2.400
Mean T_{\max} , h	0.9	0.475	1
Median $t_{1/2}$, h	ND	ND	ND
Mean AUC_{0-24} , $\mu\text{g}\cdot\text{h/mL}$	5.340	5.930	6.540
Day 7			
N	6	7	5
Mean C_{\max} , $\mu\text{g/mL}$	2.850	4.200	3.310
Mean T_{\max} , h	1	0.429	0.8
Median $t_{1/2}$, h	8.64	8.04	8.23
Mean AUC_{0-24} , $\mu\text{g}\cdot\text{h/mL}$	12.600	13.600	14.600
Mean CL_{ss} , L/h	36.2	32.0	16.5
Mean V_{ss} , L	346	303	275
Mean accumulation ratio	2.26	2.08	2.14

AUC_{0-24} , area under the concentration versus time curve at 24 hours; CL_{ss} , clearance at steady state; C_{\max} , maximum measured plasma concentration; N, number; ND, not done; PICC, peripherally inserted central catheter; $t_{1/2}$, half-life; T_{\max} , time of maximum drug concentration; V_{ss} , volume of distribution at steady state

Study CE01-116 evaluated single and multiple ascending IV doses as well as an IV-to-oral step-down regimen. Seven subjects received an IV to oral step-down regimen consisting of 7 daily doses of 400 mg solithromycin. With IV-to-oral dosing, the C_{\max} was higher during the IV infusion on Days 1 and 3 as compared to oral dosing on Days 4 and 7. However, the systemic exposure, as measured by solithromycin AUC_{0-24} , was similar on Day 3 (IV; 13.00 $\mu\text{g}\cdot\text{h}/\text{mL}$) and on Day 4 or Day 7 (oral; 11.4 and 10.9 $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively).

Study CE01-118 evaluated multiple IV doses, a combined oral and IV single dose, as well as an IV-to-oral step-down regimen in 40 healthy adults, all of which received solithromycin infused in tri-buffer in either 4.3% mannitol in sterile water or 0.9% sodium chloride. Of 20 subjects enrolled in the randomized 400-mg multiple-dose cohort, 9 completed the 7-day IV dosing regimen, and 11 switched to oral dosing before Day 7 due to infusion-related AEs. Ten subjects received a single 1200-mg oral dose followed 5 hours later by a single 400-mg IV dose, and 10 subjects received the 7-day IV-to-oral step-down regimen of 400 mg IV followed by 800 mg oral on Day 4 (3 subjects began oral dosing prior to Day 4 due to infusion-related AEs) and 400 mg orally on subsequent days.

Mean Day 1 C_{\max} , in the IV-to-oral step-down cohort, for 5 subjects who received 400 mg over 60 minutes, was 1.4 $\mu\text{g}/\text{mL}$ and for 4 subjects who received 400 mg over 30 minutes was 1.6 $\mu\text{g}/\text{mL}$. In this cohort, in the 7 subjects who received 400 mg IV for 3 days followed by 800 mg orally on Day 4 and 400 mg orally on Days 5 to 7, Day 3 mean C_{\max} was 2.65 $\mu\text{g}/\text{mL}$, and the mean AUC_{τ} was 10.76 $\mu\text{g}\cdot\text{h}/\text{mL}$; on Day 4 (first oral dosing day of 800 mg) the mean C_{\max} was 1.7 $\mu\text{g}/\text{mL}$ with a mean AUC_{τ} of 19.97 $\mu\text{g}\cdot\text{h}/\text{mL}$.

5.2.1.4 Solithromycin for Oral Suspension

Study CE01-112 evaluated a pediatric suspension that was developed and tested for PK and safety in a phase 1, open-label, randomized, crossover study in healthy adult subjects. The primary objective of the study was to determine the relative bioavailability of solithromycin suspension compared to solithromycin capsules administered as a single 400-mg dose under fasting conditions. The suspension area under the concentration curve (AUC) was 100.5 % of the capsule AUC and the suspension C_{\max} was 95.03% that of the capsules. These highly comparable measurements did not demonstrate bioequivalence, given the variability of CEM-101 PK (as with other macrolides) and the sample size. Based on the protocol-specified lower and upper limits of 90% confidence interval (CI) of the ratio of geometric least squares means for the 2 PK parameters used to evaluate bioequivalence, 400 mg solithromycin suspension was not demonstrated to be bioequivalent to 400 mg solithromycin capsules following oral administration under fasted conditions.

The secondary objective of the study was to compare the PK, safety, and tolerability of a single 400 mg oral dose of solithromycin suspension to that of solithromycin capsules. The PK parameter data showed considerable inter-subject variability, but good comparability between the capsule formulation and the suspension formulation when evaluated descriptively. No difference in the safety or tolerability was observed between the solithromycin suspension and capsule formulations.

Study CE01-124 evaluated and optimized the taste of compounded solithromycin suspension preparations in healthy adult subjects. The suspension had an acceptable taste and viscosity.

5.2.2 Additional Clinical Pharmacology Studies

5.2.2.1 Drug-drug Interactions

Four drug-drug interaction studies have been conducted with solithromycin capsules. Solithromycin significantly decreased the clearance of midazolam, a CYP3A substrate, resulting in increased midazolam plasma concentrations (AUC increases of up to 9.0-fold were observed in a steady-state dosing interaction trial). Caution should be observed in the co-administration of solithromycin with CYP3A4 substrates with a narrow therapeutic window. Inhibition of CYP3A4 by ketoconazole resulted in a 1.5-fold increase in solithromycin C_{max} and a 2.6-fold increase in the area under the concentration-time curve from time zero to infinity of a single dose of solithromycin. Co-administration of solithromycin with potent CYP3A4 inhibitors should be avoided. When solithromycin was co-administered with rifampin, a potent CYP3A4 inducer, solithromycin C_{max} and AUC were decreased by greater than 90%. Induction of CYP3A4 significantly increases the first-pass metabolism of solithromycin, and its administration immediately following or concomitantly with CYP3A4 inducers may result in therapeutic failure due to accelerated metabolism. Solithromycin when co-administered with digoxin, a CYP3A4 substrate, increased digoxin AUC_{0-tau} and C_{max} by ~38% and ~46%, respectively. Co-administration of solithromycin and digoxin appeared to be safe and well tolerated with no safety concerns regarding clinical laboratories, vital signs, physical examinations, or ECG assessments. Monitoring of serum digoxin concentrations should be considered when solithromycin is first introduced to subjects and following any changes in solithromycin dose.

5.2.2.2 Special Populations and Special Studies

5.2.2.2.1 Solithromycin in Hepatic-Impaired Subjects (CE01-113)

The safety, PK, and protein binding of solithromycin were compared in 24 subjects with mild, moderate, and severe hepatic impairment to 8 healthy subjects with normal hepatic function. The PK of plasma solithromycin in subjects with mild and moderate hepatic impairment were similar to those in subjects with normal liver function following a single oral 800-mg dose on the first day and 400 mg QD on 4 subsequent days. Total exposure to solithromycin at steady state decreased by approximately 41% for subjects with severe hepatic impairment compared to subjects with normal hepatic function. No evidence of accumulation was observed following 5 days of QD doses in mild, moderate, or severe cohorts. The mean plasma protein binding percentage was not significantly affected by mild or moderate hepatic impairment, but was slightly lower in the severe cohort. The results indicated that no dosage adjustment is needed when administering solithromycin to subjects with mild, moderate, or severe hepatic impairment.

5.2.2.2.2 Thorough QT Study (CE01-109)

This randomized, placebo- and active-controlled, 3-way crossover study evaluated the ECG effects of a supratherapeutic exposure to solithromycin in 48 healthy adult subjects. Subjects were randomized to 1 of 6 different treatment sequences, each comprising 3 treatment periods in which subjects received IV solithromycin (800 mg infused over 40 minutes), IV saline placebo, and

positive control oral moxifloxacin (400 mg) with a 7-day washout between administrations. Continuous 12-lead ECGs were obtained for 25 hours using Holter recorders.

The geometric mean solithromycin C_{\max} was 5.7 $\mu\text{g/mL}$ (mean AUC_{0-24} 23,360 $\text{ng}\cdot\text{hr/mL}$). Change from baseline QTcF was similar after dosing with solithromycin and placebo, and the resulting placebo-adjusted QTcF change from baseline was small at all time points for solithromycin (largest change was 2.8 ms with an upper bound of the 90% CI of 4.9 ms). QTc prolongation after moxifloxacin dosing confirmed the study's assay sensitivity with mean placebo-adjusted increase of 9.7 to 10.9 ms at the 3 pre-defined time points. In a concentration-effect analysis, a statistically significant, negative slope of solithromycin concentration versus QTcF change was observed consistent with the conclusion of the primary by-time point analysis. Thus unlike older macrolides, ketolides, and respiratory quinolone antibiotics, solithromycin does not cause QT prolongation. However, solithromycin did show an effect of exposure-related increased heart rate in this study; immediately after the end of the infusion, the placebo-adjusted, mean change-from-baseline heart rate peaked at 15 beats per minute (bpm). In adult subjects with CABP who received a lower dose of orally administered solithromycin, there was a mean decline in heart rate following initiation of therapy (see Section 5.2.4).

5.2.2.2.3 Pulmonary Pharmacokinetics (CE01-114)

Study CE01-114 evaluated the PK of solithromycin after 5 consecutive daily doses of 400 mg in lung epithelial lining fluid (ELF) and alveolar macrophages (AM). The mean solithromycin ELF to plasma ratio based on solithromycin AUC_{0-24} values ranged from 8.8 to 14.0. The corresponding mean ratio for solithromycin AM to plasma ranged from 132 to 345. Both analyses indicate a high degree of solithromycin penetration into human ELF and AM.

5.2.2.2.4 Absorption, Metabolism, Excretion, and Mass Balance (CE01-108)

In CE01-108, after a single dose of 800 mg radiolabeled solithromycin (^{14}C -CEM-101, 100 μCi) in solution, mean plasma concentrations and total radioactivity concentration equivalents peaked 4 hours post-dose and remained quantifiable in most subjects for up to 48 hours (solithromycin) and 24 hours (total radioactivity). The $t_{1/2}$ of solithromycin and its active side chain metabolites (CEM-214 [Hydroxyl destriazolyl-phenylamino CEM-101] and *N*-Acetyl-CEM-101 [CEM-122]) was approximately 7.5 hours.

5.2.2.2.5 Pediatric Subjects

Solithromycin PK in adolescents following oral administration of capsules was investigated in a phase 1, open-label, multi-center study of 13 adolescents (12 to ≤ 17 years of age) with a suspected or confirmed bacterial infection (protocol CE01-119). Add-on treatment to all subjects using a loading dose of 12 mg/kg (maximum 800 mg) on Day 1 and 6 mg/kg (maximum 400 mg) on Days 2 to 5. On Day 1, the average (SD) C_{\max} and AUC_{0-24} were 0.97 $\mu\text{g/mL}$ (0.73) and 11.62 $\mu\text{g}\cdot\text{h/mL}$ (8.55), respectively. On Days 3 to 5, C_{\max} and AUC_{0-24} for solithromycin were 0.74 $\mu\text{g/mL}$ (0.61) and 9.28 $\mu\text{g}\cdot\text{h/mL}$ (6.30), respectively. PK parameters estimated in 13 adolescents on Day 1 (median dose [range] 800 mg [400 to 800]) and Days 2 to 5 (median dose 400 mg [200 to 400]) were comparable to observed values in healthy adults (Table 3).

For *Streptococcus pneumoniae* (*S. pneumoniae*) minimum inhibitory concentration (MIC) values of 0.015-0.03 µg/mL (>80% of isolates), and assuming protein binding of 78%, therapeutic exposures (1-log₁₀ colony-forming unit reduction target) were observed in ≥90% of subjects with available Day 3–5 AUC₀₋₂₄ (N=10). For higher *S. pneumoniae* MICs (up to 0.125 µg/mL), therapeutic exposures were observed in ≥80% of subjects with available Day 3–5 AUC₀₋₂₄. Assuming a 10-fold higher exposure in ELF, therapeutic exposures in the lung would be expected in ≥90% of these adolescents (up to an MIC of 0.125 µg/mL). Drug exposure was therapeutic against *S. pneumoniae* MICs (up to 0.125 µg/mL) for the vast majority of adolescents in this study.

Table 3 Comparison of Adolescent and Adult PK Parameter Estimates in the CE01-119 Study

Day	Parameter Mean (SD)	Adolescents (n=13) ^a	Adult Value ^b (n=14)
	Solithromycin		
1	C _{max} (µg/mL)	0.97 (0.73)	1.53 (0.55)
	AUC ₀₋₂₄ (µg*h/mL)	11.62 (8.55)	17.9 (7.52)
3/4/5	C _{max} (µg/mL)	0.74 (0.61)	1.17 (0.36)
	AUC ₀₋₂₄ (µg*h/mL)	9.28 (6.30)	16.7 (7.16)
	t _{1/2} (h)	5.65 (1.29)	8.02 (1.34)

AUC₀₋₂₄, area under the concentration versus time curve at 24 hours; C_{max}, maximum measured plasma concentration; n, number; SD, standard deviation; t_{1/2}, half-life

a. Not all parameters have a total of 13 adolescents contributing data, and subjects were treated for 3-5 days.

b. Adults received an 800-mg single dose on Day 1 and 400 mg daily on Days 2-5. Data were taken from study CE01-110.

Solithromycin PK in adolescents (12 to <17 years) and children (<12 years) following oral (capsules, suspension) and intravenous administration was further investigated in a phase 1, open-label, multi-center study (protocol CE01-120). Across both Phase 1 studies, 23 adolescents aged 12 to 17 years (10 IV, 13 oral), 34 children 6 to <12 years (8 IV, 10 oral capsules and 17 oral suspension), 17 children 2 to <6 years (8 IV and 9 oral suspension) and 23 children <2 years (8 IV and 16 oral suspension) have been enrolled. Population pharmacokinetic modeling was used to determine the dosing regimens for oral and intravenous dosing from the data collected.

5.2.3 Summary of Efficacy

Three randomized, double-blind efficacy studies in CABP with oral solithromycin have been completed. One open-label efficacy study in uncomplicated urogenital gonorrhea (GC) with single dose oral solithromycin has been completed.

The Phase 2 oral CABP study (CE01-200) compared 5-day regimens of solithromycin (800 mg×1 on Day 1 followed by 400 mg QD on Days 2-5) and levofloxacin (750 mg QD Days 1-5). One

hundred thirty-two patients were enrolled and randomized (1:1) to solithromycin or levofloxacin. A total of 132 patients were randomized; 65 were randomized to receive solithromycin and 67 were randomized to receive levofloxacin.

In the ITT population at TOC, clinical success was observed in 55 (84.6%) patients randomized to receive solithromycin and 58 (86.6%) patients randomized to receive levofloxacin. In the CE population, clinical success was observed in 46 (83.6%) patients who received solithromycin and 54 (93.1%) patients who received levofloxacin. Early clinical success at Day 3 (according to the proposed Biomarkers Consortium criteria) was observed for 47 (72.3%) and 48 (71.6%) patients in the solithromycin and levofloxacin groups, respectively.

The Phase 3 CABP Studies CE01-300 and CE01-301, were randomized, double-blind, active-controlled, multi-center, non-inferiority studies with moxifloxacin as the active comparator.

In the oral Study CE01-300, the dosing regimen of solithromycin evaluated was 800 mg as a single 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 in CE01-300 was 400 mg QD on Days 1 through 7.

In the IV to oral Study CE01-301, all patients in both treatment groups received IV treatment on Day 1. Patients continued on IV treatment during the 7-day treatment course until predefined oral switch criteria related to clinical improvement were met and the Investigator felt it was appropriate to transition the patient to oral drug. Patients remained on IV treatment for the full 7 days if they did not meet the oral switch criteria or at the Investigator's discretion. The dosing regimen, whether IV to oral or IV only was 7 days. Patients randomized to solithromycin received 400 mg IV as a single dose on Day 1 and on all subsequent IV dosing days. For patients who transitioned to oral treatment in the solithromycin group, the first oral dose of solithromycin following IV therapy was 800 mg administered as a single dose, followed by 400 mg oral QD for the remainder of the study drug administration period. Moxifloxacin was administered as a 400 mg QD dose whether it was an IV or oral dosing day.

Solithromycin demonstrated non-inferiority to moxifloxacin in the treatment of CABP in each Phase 3 study.

5.2.3.1 Primary Efficacy Outcome: Early Clinical Response (ECR)

Table 4 provides a summary of the primary efficacy outcome, ECR in the ITT population, in the individual and pooled Phase 3 CABP studies. ECR was defined as improvement at 72 hours (Day 4) after the first dose of study drug in at least 2 of the following 4 cardinal symptoms of CABP: cough, dyspnea/shortness of breath, chest pain due to pneumonia and difficulty with sputum production.

Solithromycin and moxifloxacin ECR responder rates in the ITT population were similar in each Phase 3 study and in the pooled studies, approximately 78 to 79% of patients. Solithromycin was non-inferior to moxifloxacin for the ECR outcome in each study and in the pooled studies. The lower limit of the 95% confidence interval (CI) around the treatment difference in responder rates (solithromycin minus moxifloxacin) was greater than the prespecified NI boundary of -10%.

Table 4 Primary Efficacy Outcome: Early Clinical Response in Individual Phase 3 Studies and Pooled Studies

Early Clinical Response	Study CE01-300		Study CE01-301		Pooled Phase 3 Studies	
	Solithromycin Oral (N=425) n (%)	Moxifloxacin Oral (N=431) n (%)	Solithromycin IV to Oral (N=434) n (%)	Moxifloxacin IV to Oral (N=429) n (%)	Solithromycin Pooled (N=859) n (%)	Moxifloxacin Pooled (N=860) n (%)
Responder	332 (78.1)	336 (78.0)	344 (79.3)	342 (79.7)	676 (78.7)	678 (78.8)
Difference (95% CI)	0.16 (-5.6,5.9)		-0.46 (-6.1,5.2)		-0.16 (-4.0,3.7)	
Nonresponder	93 (21.9)	95 (22.0)	90 (20.7)	87 (20.3)	183 (21.3)	182 (21.2)
Nonresponder	81 (19.1)	83 (19.3)	76 (17.5)	78 (18.2)	157 (18.3)	161 (18.7)
Indeterminate	12 (2.8)	12 (2.8)	14 (3.2)	9 (2.1)	26 (3.0)	21 (2.4)

Source Data: pooled CE01-300 and CE01-301 data

CI=confidence interval; N=number of patients in the ITT population; n=number of patients within a specific category.

Notes: The time window for determining early clinical response was 72h -12/+36h for CE01-300 and 72h -13/+36h for CE01-301). Difference=For studies CE01-300 and CE01-301, difference in responder rates (solithromycin minus moxifloxacin). For the pooled Phase 3 studies, the weighted (by study) difference in responder rates is presented. Percentages were calculated as 100 x (n/N). For studies CE01-300 and CE01-301, the CI was calculated using an unadjusted continuity corrected Z-test. For the pooled Phase 3 studies, the CI was stratified (for study) and calculated using the method of Miettinen and Nurminen with the inverse variance of the difference used as stratum weights. Per the ISE SAP, patients from Site 710 in Study 300 were excluded from all pooled results, unless otherwise noted.

ECR in the clinically evaluable (CE-ECR) population in each study was consistent with the results observed for the primary efficacy analysis in the ITT population. In the pooled studies, the ECR responder rates in the CE-ECR population were 81.5% in the solithromycin group compared with 82.0% in the moxifloxacin group. Consistent results were observed in each study.

In subgroup analyses in the ITT population, a consistent effect was observed for ECR responder rates by geographic region and in demographic subpopulations, e.g., age, weight, gender and ethnicity.

Subpopulation analyses were also conducted for characteristics related to baseline disease severity. Responder rates and treatment differences were consistent in analyses of patients classified as PORT II (treatment difference: 1.14; 95% CI: -5.1, 7.3) or PORT III/V (treatment difference: -0.93; 95% CI: -5.9, 4.0). No differences in responder rates were noted based upon prior history of asthma/COPD or receipt a single dose of a short-acting antibiotic within 7 days prior to randomization.

5.2.4 Summary of Safety

As of 30 April 2016, more than 2000 subjects and patients received systemic exposure to solithromycin. The major source of safety data are the two Phase 3 pivotal studies in patients with CABP (n=856).

5.2.4.1 Overview of Adverse Events

Macrolides, as a class, are well-tolerated and widely utilized. The most common AEs reported with the use of existing macrolides are GI, such as diarrhea, nausea and vomiting; others include headache and dizziness.

Oral solithromycin has been well tolerated, the most common AEs being mild GI events in Phase 1 and 2 trials. The most common AEs in the Phase 1 IV trials were related to infusion site tolerability; there were no other unique AEs relative to events reported in oral trials.

Infrequent reports of local and systemic allergic reactions have occurred with oral and IV solithromycin, including anaphylaxis, urticaria, erythema and maculopapular rashes.

The AE profile of the 5-day CABP regimen compared favorably with that of levofloxacin in the Phase 2 CABP trial. In the Phase 3 oral CABP study, solithromycin demonstrated a similar AE profile to that of moxifloxacin. In the Phase 2 GC study, the most common AEs were mild GI disorders, primarily diarrhea and nausea. Although both doses were acceptably tolerated, treatment-related GI AEs occurred less frequently with the 1000 mg dose than with 1200 mg.

In the Phase 3 oral CABP study, 6 (1.4%) patients in the solithromycin group and 6 (1.4%) patients in the moxifloxacin group died during the study. None of the SAEs resulting in death was considered related to study drug. A total of 28 (6.6%) patients in the solithromycin group and 27 (6.3%) patients in the moxifloxacin group reported at least 1 non-fatal SAE. No patient in either treatment group had an SAE that was considered related to study drug. The most common AEs observed in patients receiving solithromycin were headache (4.5%) and diarrhea (4.2%).

In the Phase 3 IV to oral CABP study, 5 (1.2%) patients in the solithromycin group and 7 (1.6%) patients in the moxifloxacin group died during the study. None of the SAEs resulting in death was considered related to study drug. A total of 30 (6.9%) patients in the solithromycin group and 23 (5.4%) patients in the moxifloxacin group reported at least 1 non-fatal SAE. Only 3 SAEs were considered related to study drug by the investigators (urticaria and anaphylactic reaction in 1 patient each in solithromycin and anaphylactic reaction in 1 moxifloxacin patient). The most frequently reported infusion site related TEAEs were infusion site pain (10.4%), infusion site phlebitis (10.0%) and infusion related reaction (6.5%). Infusion site related TEAEs were mostly mild or moderate in intensity and infrequently led to discontinuation of study drug or withdrawal from the study (in 1 moxifloxacin and 10 solithromycin patients). Apart from infusion site related events, the most common AEs observed in patients receiving solithromycin were diarrhea (5.9%) and headache (4.2%).

In the adolescent oral phase 1 study (CE01-119), 12 AEs were reported, of which 9, including 1 SAE (limb abscess), were unrelated to solithromycin. Three subjects had AEs related to study drug: 2 separate episodes of mild headache and 1 episode of increased transaminases ($<3\times$ ULN).

The most common AEs reported after multiple IV doses were general disorders and administrative site conditions (infusion-related pain) followed by nervous system disorders and vascular disorders (phlebitis), with the majority mild in severity.

Solithromycin, like most antibiotics and like all macrolide antibiotics, has been associated with hepatic aminotransferase elevations. In the pooled Phase 3 CABP trials, ALT elevations to $>3\times\text{ULN}$, $>5\times\text{ULN}$ and $>10\times\text{ULN}$ were seen in 7.2%, 2.4% and 0.1% of solithromycin recipients compared to 3.6%, 1.0% and 0.2% of moxifloxacin recipients. Elevations of ALT to $>3\times\text{ULN}$ were 5.4% in the oral study and 9.1% in the IV to oral study. These elevations were typically asymptomatic, not associated with bilirubin elevation and readily reversible, with improvement in many cases seen during continued dosing. There have been no Hy's Law cases.

Multiple lines of evidence point to an exposure-response relationship for ALT elevation with solithromycin.

In the pooled Phase 3 CABP studies, rates of bilirubin elevation to levels $>\text{ULN}$ were comparable between solithromycin and moxifloxacin (4.3% vs 4.0%, respectively), and elevations $>2\times\text{ULN}$ were uncommon ($<0.5\%$) in both treatment groups. Solithromycin was more frequently associated with alkaline phosphatase elevation to $>1.5\times\text{ULN}$ than moxifloxacin (5.2% versus 2.9%, respectively), consistent with the potential to induce mild degrees of cholestasis, as has been observed with older macrolides and other antibiotics.

Solithromycin was generally well tolerated in subjects with cirrhosis of Child Pugh Class A, B and C severity in a controlled Phase 1 trial. In the Phase 3 CABP studies, the overall incidence of AEs was similar among subjects with and without hepatic impairment. ALT elevation to $>5\times\text{ULN}$ occurred with identical frequency among patients with and without hepatic impairment (2.4%), and AST elevation $>5\times\text{ULN}$ occurred in 1 patient with baseline hepatic impairment.

Analysis of ALT elevation by patient characteristics including age, sex, race, history of chronic liver disease and concomitant exposure to statins have not revealed a population at particular risk for these events.

While solithromycin can cause asymptomatic, reversible ALT elevation and mild degrees of cholestasis, the overall liver safety profile of clinically important events was comparable to moxifloxacin and may be comparable to the older macrolides.

When solithromycin is taken for longer than 7 days, rare cases of jaundice and itching have occurred. These events were reversible after solithromycin treatment was stopped.

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. A thorough QT study of solithromycin was negative, demonstrating that solithromycin does not have a propensity to prolong the QT interval in a clinically significant manner in healthy subjects.

In the pooled Phase 3 CABP studies, cardiac AEs were observed more frequently in moxifloxacin recipients (4.7%) than solithromycin recipients (3.0%). Most of these events reflected the underlying chronic diseases of enrolled patients in the context of the severe physiologic stress of CABP and were not considered study drug related.

The thorough QT study revealed that healthy subjects with supratherapeutic exposure to solithromycin experience an increase in heart rate. The exact mechanism for this effect is unknown, although a variety of receptors and cardiac channels have been evaluated in vitro. However, in the Phase 3 studies, the central tendency for observed heart rate was a decline from baseline over time comparable to that observed with moxifloxacin, as the physiologic stressors of CABP diminished with response to therapy. Fewer patients receiving solithromycin than moxifloxacin experienced a potentially clinically significant tachycardia (>120 bpm) that was associated with an increase over baseline of ≥ 15 bpm (1.3% and 1.8%, respectively).

In the Phase 3 studies, categorical changes from baseline in the QTcF interval of >30 msec occurred less frequently with solithromycin (16.7%) than with moxifloxacin (28.0%). Post-baseline changes resulting in a QTcF >500 msec occurred in $<1\%$ of patients in both treatment groups. Based on these data and the results of the thorough QT study, it is clear that solithromycin does not present intrinsic QT prolongation risks. However, as a CYP3A4 inhibitor, solithromycin may pose secondary risk of QT prolongation through inhibition of metabolism of other QT-prolonging drugs.

5.3 Rationale for the Present Study

Although there is evidence of efficacy and safety of solithromycin in adults, the safety and efficacy of solithromycin have not been established in children. There is evidence of similarities in children and adults in 1) CABP definitions and pathophysiology, 2) causative organisms, 3) response to intervention and 4) exposure-response relationship. Therefore, extrapolation of efficacy in pediatric subjects from adult clinical trial efficacy data is reasonable. A safety study in pediatric subjects with CABP, however, is needed to compare the safety and tolerability of solithromycin to comparators. The proposed study will gather necessary safety data and, as a secondary objective, provide an assessment of solithromycin efficacy as CABP treatment in pediatric subjects.

5.4 Rationale for the Dosage Regimen

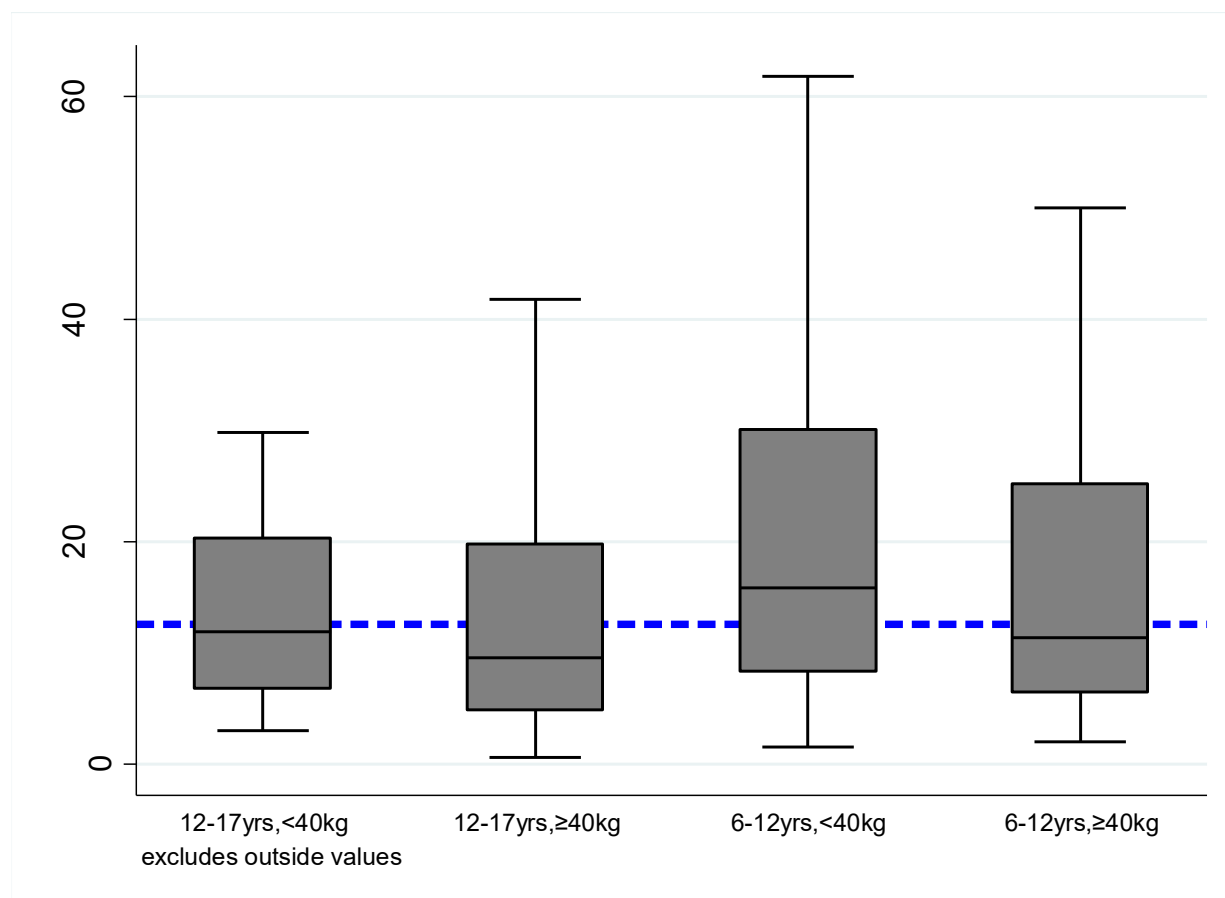
The dosing regimens to be studied are intended to provide therapeutic solithromycin exposures against CABP, as efficacy in pediatric subjects with CABP will be extrapolated from the results in the phase 3 adult CABP trials. The dosing regimens for each age group and each of the 3 formulations (capsule, IV infusion, and suspension) were determined in phase 1 studies in children.

Data from two phase 1 studies in children ($N=92$) were merged and used to develop a population PK model that informs dosing for this study for all formulations. A two compartment model with linear elimination characterized the solithromycin data following both oral (capsule and suspension) and intravenous administration. To account for the growth effects, actual body weight was included in the model using allometric scaling. Using the final model, Monte Carlo simulations were performed to identify pediatric dosing that matches adult exposure (area under the concentration versus time curve from 0 to 24 hours and maximal drug concentrations after multiple doses) observed in the phase 3 program.

The selected dosing regimen for adolescents (12-17 years) receiving solithromycin via oral administration (capsules or suspension) was 800 mg on Day 1 and 400 mg on Days 2-5 if they weigh ≥ 40 kg. For subjects 12 to 17 years and <40 kg, a capsule dosing regimen of 20 mg/kg on

Day 1 (800 mg maximum) and 10 mg/kg on Days 2-5 (400 mg maximum) was selected based on simulated exposure (Figure 2). Suspension dosing for adolescents was selected based on data obtained from a bioequivalence study in adults between capsules and suspension and the similar bioavailability estimates obtained for both formulations in the population PK model.

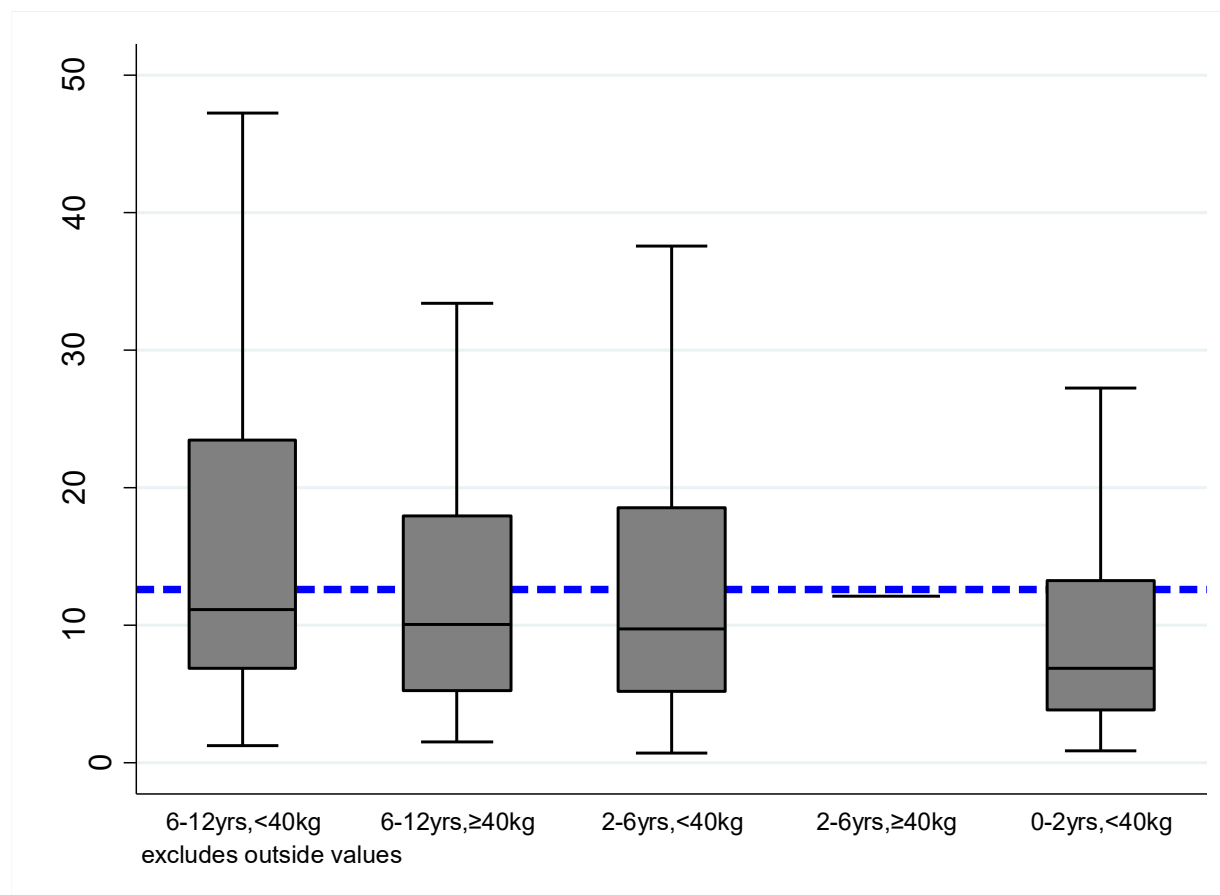
Figure 2 Simulated Day 5 Exposure following a Capsule Dose of 20 mg/kg on Day 1 and 10 mg/kg on Days 2-5.



Note: Doses rounded upward to the nearest 200 mg. The dashed line represents an adult Day 4 AUC₀₋₂₄ of 12.6 mcg*h/mL.

For the suspension dosing for children <12 years of age, a dose of 20 mg/kg on Day 1 (800 mg maximum) and 10 mg/kg on Days 2-5 (400 mg maximum) resulted in a comparable simulated Day 5 AUC₀₋₂₄ across pediatric age groups (Figure 3). Although the median simulated exposure appears to be lower in the 0-2 years age group, the simulated exposure was within the range observed in adults and it's possible that the observed values may be higher due to immature CYP3A4 metabolism in this age group.

Figure 3 Simulated Day 5 Exposure following a Suspension Dose of 20 mg/kg on Day 1 and 10 mg/kg on Days 2-5



Note: The dashed line represents an adult Day 4 AUC_{0-24} of 12.6 mcg*h/mL. There is only one subject in the 2-6 years ≥ 40 kg category

Intravenous daily dosing of 8 mg/kg resulted in comparable simulated Day 5 AUC_{0-24} across all pediatric age groups: median (standard deviation) 14.4 mcg*h/mL (23.4) for 12-17 years; 14.1 mcg*h/mL (25.4) for 6-<12 years; 11.0 mcg*h/mL (26.0) for 2-<6 years; and 9.4 mcg*h/mL (19.1) for 0-<2 years. The adult exposure used for matching purposes was 12.6 mcg*h/mL.

Because of the complete efficacy extrapolation approach to determination of efficacy in the pediatric population, the duration of study drug regimens are the same as those in adults. Oral-only dosing is for 5 days intravenous-only and IV-to-oral dosing are for 7 days duration.

5.5 Rationale for the Comparator

Comparators were selected following review of the Pediatric Infectious Diseases Society/Infectious Diseases Society of America guidelines for empiric therapy of CABP (Bradley 2011), recent publications on CABP therapy in children (Aurangzeb 2003; Kogan 2003; Bradley 2007; Awashti 2008; Ribeiro 2011; Lodha 2013), and the most recently conducted trials of CABP in children listed on ClinicalTrials.gov (www.clinicaltrials.gov). The group of acceptable

comparator drugs was selected to include drugs commonly used per standard of care in both the U. S. and at international sites participating in this trial.

6 STUDY OBJECTIVES

Primary

- Evaluate the safety and tolerability of solithromycin in adolescents and children with CABP

Secondary

- Evaluate the efficacy of solithromycin in adolescents and children with CABP
- Evaluate the population PK of solithromycin in adolescents and children with CABP

7 STUDY DESIGN

This is a phase 2/3, randomized, open-label, active-control, multi-center study to assess the safety and efficacy of solithromycin in children and adolescents with CABP. Approximately 400 subjects (~300 in the solithromycin group and ~100 in the comparator group) will be enrolled. Randomization will be stratified by age group (12 through 17 yo, 6 to <12 yo, 2 to <6 yo, and 2 months to <2 yo). At least 40 subjects will be randomized into each age group.

Subjects who meet all inclusion/exclusion criteria and sign the informed consent/assent will be enrolled. Subjects will be randomized to receive solithromycin or a comparator antibiotic, administered IV and/or by mouth (PO) based on weight and age. Subjects will be treated daily for 5 to 7 days with oral solithromycin and 5 to 7 days with IV or IV-to-oral solithromycin. Subjects will be treated for 5 to 10 days with comparator antibiotics. Subjects will have safety and efficacy assessments during and after treatment.

7.1 Duration of Subject Participation

The duration of subject participation from signing the informed consent form (ICF) will be approximately 32 days (includes up to 10 days of study drug/comparator drug administration, a follow-up visit at 16 days [\pm 4 days] after randomization, AE monitoring for 16 (\pm 4) days, and SAE monitoring for 28 (\pm 4) days post-randomization). Adverse event monitoring 28 days after randomization can be conducted by telephone/other media visit. The study duration from first subject first visit until last subject last visit will be approximately 24 months.

7.2 Number of Subjects

Approximately 400 subjects \geq 2 months to 17 years of age, inclusive, will be enrolled as follows:

- Age Group 1: Adolescents from 12 years to 17 years, inclusive
- Age Group 2: Children from 6 years to <12 years
- Age Group 3: Children from 24 months to <6 years
- Age Group 4: Infants from \geq 2 months to <24 months

A minimum of 40 subjects will be enrolled in each age group. Approximately 20% of subjects will be enrolled at U.S. centers.

7.3 Study Drug Dosage and Administration

Solithromycin will be administered IV or PO according to Table 5 through Table 8 below. If dosing begins with oral therapy, the Day 1 dose will be a loading dose. No loading doses are used with IV solithromycin administration or if switched to oral administration. An IV-to-PO switch can occur after the first IV dose. Subjects starting with oral therapy will receive 5 days of solithromycin treatment, and those starting with IV therapy (regardless of if and when they switch to oral therapy), will receive 7 days of solithromycin treatment.

For subjects receiving the capsule formulation, 200 mg solithromycin capsules will be used to provide the absolute dose of either 200 mg, 400 mg, or 800 mg. The capsule dose will be rounded upwards to the nearest 200 mg, not to exceed an 800 mg loading dose and 400 mg maintenance dose. Study drug should be swallowed with water approximately every 24 hours and at approximately the same time each day (± 4 hours). Study drug can be taken without regard to food.

Table 5 Capsule Dosing Regimens

Age (years)	Weight	Route	Formulation	Day 1 (Max dose: 800 mg)	Days 2 to 5 (Max dose: 400 mg)
6 to 17	>30 kg	PO	Capsules	800 mg	400 mg
	>20 to 30 kg	PO	Capsules	600 mg	400 mg
	≤ 20 kg	PO	Capsules	400 mg	200 mg

Subjects requiring an oral dosage form other than capsules will receive suspension formulation, provided at 275 mg/5 mL strengths, to achieve the age-appropriate mg/mL and solithromycin dose. Any dosing variations within 10% of the calculated suspension dose is not considered a deviation.

Table 6 Suspension Dosing Regimens

Age (years)	Route	Formulation	Day 1 (Max dose: 800 mg)	Days 2 to 5 (Max dose: 400 mg)
12 to 17	PO	Suspension	20 mg/kg (800 mg)	10 mg/kg (400 mg)
6 to <12	PO	Suspension	20 mg/kg	10 mg/kg
2 to <6	PO	Suspension	20 mg/kg	10 mg/kg
2 mo to <2	PO	Suspension	20 mg/kg	10 mg/kg

No loading doses are used with IV solithromycin administration. Intravenous solithromycin should be infused over approximately 60 minutes (± 20 minutes) approximately every 24 hours (± 4 hours). Changes to the infusion duration should be discussed with the study medical monitor prior to study drug administration. Any dosing variations within 10% of the calculated IV dose is not considered a deviation.

Table 7 Intravenous Dosing Regimens

Age (years)	Route	Formulation	Days 1 to 7 (Maximum dose: 400 mg)
12 to 17	IV	Solution	8 mg/kg
6 to <12	IV	Solution	8 mg/kg
2 to <6	IV	Solution	8 mg/kg
2 mo to <2	IV	Solution	8 mg/kg

A subject can be converted from the IV to an oral formulation following 1 or more IV doses. The first oral dose will be 10 mg/kg with a maximum of 400 mg.

Table 8 Intravenous to Oral Dosing Regimens

Age (years)	Route	Oral Formulation	Day 1 to Last IV Dosing Day (Max dose: 400 mg)	First Oral Dosing Day to Day 7 (Max dose: 400 mg) ^a
12 to 17	IV/PO	Suspension or Capsules	8 mg/kg	10 mg/kg (400 mg)
6 to <12	IV/PO	Suspension or Capsules	8 mg/kg	10 mg/kg
2 to <6	IV/PO	Suspension	8 mg/kg	10 mg/kg
2 mo to <2	IV/PO	Suspension	8 mg/kg	10 mg/kg

- a. The adult dose should be administered unless the subject weighs <40 kg, in which case they receive 10 mg/kg on the first oral dosing day through Day 7. The capsule dose is rounded upwards to the nearest 200 mg.

Comparator drug:

Comparators will be selected according to age and are consistent with current recommendations for treatment of CABP in children. A dosing table is provided below.

Children ≥2 months to <5 years of age:

- Ceftriaxone IV **OR**
- Ampicillin IV **or** amoxicillin IV **OR**
- Amoxicillin-clavulanic acid PO **or** IV **or** amoxicillin PO

Children 5 to 17 years of age (inclusive):

- Ceftriaxone IV **OR**
- Ampicillin IV **or** amoxicillin IV **OR**
- Amoxicillin-clavulanic acid PO **or** IV **or** amoxicillin PO

Azithromycin IV/PO or erythromycin lactobionate IV or erythromycin PO may be added to any of three treatment regimens above. Azithromycin is also acceptable as a first line of treatment.

Table 9 Recommended Comparator Regimens

	United States	Rest of the World
Amoxicillin	45-90 mg/kg/day orally in 2 or 3 divided doses; not to exceed 3 g/day	45-90 mg/kg/day orally in 2 or 3 divided doses; not to exceed 3 g/day 50-100 mg/kg/day intravenously in equally divided doses every 6 hours
Amoxicillin-clavulanic acid (oral)	Children <40 kg: amoxicillin component 90 mg/kg/day orally in divided doses given every 12 hours [4000 mg/day max dose] Children ≥40 kg, 875 mg orally every 12 hours or 500 mg orally every 8 hours [4000 mg/day max dose]	Children <40 kg: 20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given orally every 8 hours Children ≥ 40 kg: One 500 mg/125 mg dose given orally every 8 hours
Amoxicillin-clavulanic acid (IV)	-	Children >4kg but < 40kg: amoxicillin component 25 mg/kg intravenously every 8 hours [1000 mg max dose] Children ≥ 40 kg: amoxicillin component 1000 mg intravenously every 8 hours
Ampicillin	150-200 mg/kg/day intravenously in equally divided doses every 6 hours	-
Azithromycin	10 mg/kg intravenously/orally on day 1 [500 mg maximum dose] followed by 5 mg/kg orally every 24 hours [250 mg maximum dose]	10 mg/kg orally on day 1 [500 mg maximum dose] followed by 5 mg/kg orally every 24 hours [250 mg maximum dose]
Ceftriaxone	50-75 mg/kg/day intravenously in equally divided doses every 12 hours; total daily dose should not exceed 2 g	50-80 mg/kg intravenously once daily
Erythromycin	40 mg/kg/day orally every 6 hours	30-50 mg/kg/day orally every 6 hours
Erythromycin lactobionate	15 to 20 mg/kg/day intravenously in equally divided doses every 6 hours	50 mg/kg/day intravenously/orally in equally divided doses every 6 hours

Note: if doses of comparator drugs noted in the dosing table above differ those prescribed per standard of care, a site can use the locally prescribed dose.

IV-to-PO switch:

Subjects receiving an IV comparator drug (i.e., ceftriaxone, ampicillin) in any age group may be switched to oral treatment using amoxicillin-clavulanic acid PO (amoxicillin component, 45 mg/kg every 12 hours; subjects weighing ≥40 kg, 875 mg every 12 hours or 500 mg every 8 hours) or amoxicillin alone (45 mg/kg every 12 hours, up to a maximum of 4 g/day).

Subjects must receive 5 to 10 days of treatment with comparator. The exact duration of treatment may be determined at the investigator's discretion.

7.4 Data Monitoring Committee

An independent data monitoring committee (DMC) will be created and a DMC charter developed that defines the scope and schedule of its activities. The DMC charter will pre-specify rules

governing safety reporting, analyses, and study activities (i.e., stopping rules). The DMC will be charged with assessing the overall study status and safety of subjects at intervals outlined in their charter and also in response to emergent data that might require unscheduled evaluation. The DMC will make recommendations to the sponsor with regard to continuing or modifying the study conduct based on these assessments.

7.5 Age Group Initiation

Enrollment will occur simultaneously for all age groups.

7.6 Stopping Rules

The DMC will establish through its charter rules to govern study activities. The DMC will assess overall study status and subjects. In general, it is anticipated that new enrollment and dosing will be halted for a DMC-guided safety review if serious unexpected adverse reactions occur in ≥ 2 subjects in any single age group. The DMC will make recommendations to the sponsor regarding resumption of the study.

8 SELECTION OF STUDY POPULATION

The following criteria for enrollment must be followed. The subject will not be enrolled unless the inclusion/exclusion criteria are met. The investigator or other study site personnel must document in the source documents that the ICF and assent form (as applicable) were signed and dated prior to study screening. The date the ICF was obtained will be recorded in the source documents and electronic case report form (eCRF). The presence of inclusion criteria and absence of exclusion criteria will be verified in the eCRF.

8.1 Inclusion Criteria

1. Written informed consent from parent or other legally acceptable representative and informed assent from subject (if age appropriate according to local requirements)
2. ≥ 2 months to 17 years of age, inclusive
3. Requiring hospitalization, emergency room, or urgent care visit
4. Presence of CABP based on the following criteria within 72 hours of randomization:
 - History of and/or documented fever (rectal, temporal, ear, or oral temperature $\geq 38^{\circ}\text{C}$ or axillary temperature $\geq 37.5^{\circ}\text{C}$) or hypothermia (rectal, temporal, ear, or oral temperature $< 35^{\circ}\text{C}$ or axillary temperature $< 34.5^{\circ}\text{C}$)

AND

- Chest radiograph infiltrates consistent with bacterial pneumonia (or pneumonia caused by atypical bacterial agents); if a subject is outpatient and starting on oral therapy, a radiograph is not required.

AND

- Presence of **at least 2** of the following signs or symptoms:
 - a. Cough
 - b. Difficulty breathing
 - c. Production of purulent sputum
 - d. Chest pain
 - e. Grunting
 - f. Hypotension
 - g. Tachycardia defined as follows:
 - 2 months to < 24 months: ≥ 160 bpm
 - 24 months to < 10 years: ≥ 140 bpm
 - ≥ 10 years: ≥ 100 bpm
 - h. Tachypnea, defined as:
 - 2 months to < 12 months: ≥ 50 breaths/minute
 - 12 months to < 5 years: ≥ 40 breaths/minute

- ≥ 5 years: ≥ 20 breaths/minute
 - i. Physical exam consistent with pulmonary consolidation
- AND**
- Presence of **at least 1** of the following:
 - a. Leukocytosis ($\geq 12,000$ white blood cells [WBC]/mm³)
 - b. Leukopenia ($< 5,000$ WBC/mm³)
 - c. $\geq 10\%$ immature neutrophils (bands) regardless of total peripheral WBC
 - d. Elevated inflammatory markers (C-reactive protein or procalcitonin)
 - e. Oxygen saturation $< 97\%$ on room air
 - f. Organism consistent with a typical respiratory pathogen identified from a blood culture or isolated from an appropriate respiratory culture/polymerase chain reaction (sputum in children old enough to produce an acceptable specimen; sample from the lower respiratory tract airways, if performed [e.g., bronchoalveolar lavage]; or pleural fluid culture)

8.2 Exclusion Criteria

1. Confirmed or suspected respiratory-tract infection attributable to sources other than community-acquired bacterial pathogens (e.g., ventilator-associated pneumonia; hospital-acquired pneumonia).
2. Received > 48 hours of potentially effective systemic antibacterial therapy for CABP immediately prior to randomization (exception: clinical or microbiological treatment failure or progression of signs or symptoms of CABP as determined by the investigator).
3. Confirmed or suspected bacterial meningitis.
4. Known active tuberculosis.
5. Non-infectious causes of pulmonary infiltrates (e.g., cystic fibrosis, chemical pneumonitis from aspiration, hypersensitivity pneumonia).
6. Evidence or history of clinically significant medical condition that may, in the assessment of the investigator, impair study participation or pose a significant safety risk or diminish the subject's ability to undergo all study procedures and assessments.
7. Hepatic dysfunction evidenced by ALT or AST > 3 times ULN or direct bilirubin greater than 2 times ULN (if direct bilirubin values are not available in a time frame consistent with enrollment requirements, total bilirubin must be < 2 times ULN).
8. Treatment with the following drugs within 72 hours prior to first dose of study drug or expected to receive these drugs during the treatment phase: drugs that potently inhibit CYP3A4 (nefazodone, fluconazole, ketoconazole, conivaptan, diltiazem, verapamil, aprepitant, imatinib, protease inhibitors, clarithromycin, ciprofloxacin, erythromycin, itraconazole, mibefradil, posaconazole, telithromycin, and voriconazole); CYP3A4 inducers (rifampin, rifabutin, phenytoin, fosphenytoin, carbamazepine, phenobarbital, rufinamide, modafinil, armodafinil, etravirine, efavirenz, nevirapine, rilpivirine, bosentan, troglitazone, pioglitazone,

and St. John's wort). In addition, the following drugs may not be co-administered with solithromycin in this trial due to the potential for adverse drug-drug interaction: digoxin, colchicine, midazolam, quinidine, ergotamine, dihydroergotamine, rivaroxaban, apixaban, dabigatran, edoxaban, cisapride, cyclosporine, sildenafil, astemizole, and alfentanil.

9. Breast-feeding females.
10. Positive pregnancy test in females of childbearing potential.
11. History of anaphylaxis to macrolide antibiotics.
12. Previous participation in this study.
13. Has received any investigational drugs studied under an Investigational New Drug (IND) application in the U.S. or under a Clinical Trial Application in the relevant country outside of the U.S. where the subject is being enrolled, taken within 4 weeks before administration of the first dose of study drug.
14. End Stage Renal Disease (dialysis requiring) OR severe renal impairment (defined as serum creatinine > 1.5 fold ULN for age).

8.3 Prior and Concomitant Treatment

Reasonable efforts will be made to determine all relevant treatment (concomitant medications, including all prescription/non-prescription medications, herbal medications, and vitamin supplements; supportive therapies; and concomitant non-pharmacological treatments) received by the subject within 72 hours prior to randomization through the follow-up visit. All antibiotics taken within 7 days prior to first dose of study drug also need to be provided. The medication name, daily dose, and duration of the treatment/procedure (start and stop dates) will be recorded in the eCRF. Concomitant treatments (non-pharmacological treatments) include specific surgical or diagnostic procedures performed per routine medical care.

8.3.1 Permitted Treatment

Medications to treat any other medical conditions or AEs the subject experiences during the study are permitted. Addition of expanded gram-positive coverage (clindamycin, vancomycin, linezolid, daptomycin) to treatment and comparator groups will be allowed if empiric therapy for MRSA is desired. Oral step-down therapy for subjects on comparator should be informed by antimicrobial susceptibility testing.

8.3.2 Prohibited Medications and Therapies

For a list of prohibited medications taken prior to or during the study, see exclusion criteria (Section 8.2). If for any reason a subject requires any of the prohibited medications during the study, the investigator should discuss with the medical monitor prior to initiation of therapy. If a subject is unable to comply with these restrictions, the subject's continued participation in the study will be re-evaluated by the investigator, in consultation with the medical monitor.

9 STUDY DRUGS

9.1 Solithromycin (CEM-101)

Solithromycin will be provided as hard gelatin capsules that contain 200 mg solithromycin, as a powder for oral suspension (POS), or as a lyophilized powder for infusion after reconstitution and dilution. The IV formulation of solithromycin (Solithromycin for Injection) is provided as a lyophilized formulation in 50 mL clear glass vials containing 400 mg of solithromycin for single use only. The lyophilized cake is reconstituted with sterile water for injection and then added to sterile 0.9% sodium chloride injection. Detailed instructions for reconstitution and dilution will be provided in the pharmacy manual. The inactive ingredients for all formulations will be listed in the pharmacy manual. Detailed instructions for the reconstitution of the powder for oral suspension to 275 mg/5 mL will be listed in the pharmacy manual.

Solithromycin suspension contains aspartame and patients with phenylketonuria should be aware that the suspension contains 78 µg of phenylalanine (as a component of aspartame) per mL.

9.2 Comparator

Comparator antibiotics may be administered “off the shelf” at the doses described above based on age range, local availability, and local treatment preferences. Comparator antibiotic preparation will be performed per local standard of care.

9.3 Study Drug Label and Packaging

Cempra Pharmaceuticals or its designee will package study drug solithromycin. It will be labeled and supplied according to applicable regulatory requirements.

Comparators will be procured by the site and the commercial labeling will be retained.

9.4 Study Drug Storage Conditions

The investigator or an approved representative (e.g., pharmacist) will ensure that study drug (solithromycin) is stored in a locked secured area (with access limited to appropriate study personnel) only under recommended storage conditions and in accordance with applicable regulatory requirements.

The oral capsules will be stored at controlled room temperature 59°F to 77°F (15°C to 25°C) and protected from light. Vials of lyophilized solithromycin should be stored at room temperature (15°C to 25°C; 59°F to 77°F) and protected from light. Daily temperature logs must be kept at the clinical site and all temperature excursions during storage must be reported to Cempra GCP QA to obtain approval for continued use.

Once prepared, the reconstituted vials should be used within 2 hours when stored at room temperature; they should not be refrigerated or frozen. Room light exposure is allowed. Once the reconstituted solithromycin solution has been added to the saline bag, the infusion solution in the saline bag can be kept at room

temperature (15°C to 25°C; 59°F to 77°F) for up to 12 hours or stored refrigerated for up to 24 hours before use; the bag **should not be frozen at any time**. Room light exposure is allowed during preparation, storage, and patient administration.

Solithromycin powder for suspension and the reconstituted suspension should be stored at a controlled room temperature of 15°C to 25°C (59°F to 77°F) and protected from light and moisture. The suspension should be used within 10 days of reconstitution.

Comparator study drug should be stored per the recommendations noted on the products drug label.

9.5 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized separately within each age group in a 3:1 ratio of solithromycin to comparator antibiotics using blocked randomization. The randomization schedule will be generated by Duke Clinical Research Institute (DCRI) team (or designee) using the clinical database randomization module. Subjects randomized into the study will be assigned the treatment corresponding to the next available number in the respective stratum of the computer-generated randomization schedule. The subject will only be randomized after the inclusion and exclusion criteria are verified.

9.6 Blinding

This study will be open-label with a blinded health care professional designated as a subinvestigator at each site. The blinded subinvestigator will be responsible for conducting the clinical outcome (efficacy) assessments.

9.7 Receipt of Supplies

Upon receipt of the study drug, the pharmacist or designated study site personnel will visually inspect the shipment and verify the drug information, quantity, and condition of the kits received. The Study Drug Transmittal and Receipt Form will be completed, signed by the pharmacist or designated study site personnel, and forwarded to Cempra Pharmaceuticals (or its designee). The original signed form should be filed with the inventory/drug accountability records.

9.8 Study Drug Accountability

9.8.1 Overall

It is the responsibility of the investigator to ensure that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor and available to regulatory agencies for inspection at any time.

9.8.2 Study Drug Handling and Return

Upon the completion or termination of the study, and upon written authorization from Cempra or its representative, all unused and/or partially used study drug should be returned or destroyed at the investigational site, as specified by Cempra. It is the investigator's responsibility to ensure that Cempra or its representative has provided written authorization that procedures for proper disposal

of the study drug have been established, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed of until fully accounted for by the Cempra monitor (or designee).

10 STUDY ASSESSMENTS AND PROCEDURES

Assessments and procedures will be performed at the time points indicated below.

10.1 Baseline or Screening Study Procedures (Day -3 to -1)

The following evaluations will be obtained and recorded on the eCRF (as applicable) after the ICF and assent (if applicable) is signed. Laboratory tests, non-pharmacologic procedures, and imaging studies that are considered standard of care and that were performed within 72 hours prior to the first dose of study drug may be used for screening procedures.

1. Demographics (date of birth, sex, race, ethnicity)
2. Inclusion/exclusion criteria determination as described in Sections 8.1 and 8.2.
3. Significant past and present medical/illness history (medical history diagnoses included in current admission/emergency/urgent care note)
4. Physical examination including height; weight; head, eyes, ears, nose, throat (HEENT); heart, lungs, abdomen, skin, and extremities.
5. Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
6. Chest x-ray; if a subject is outpatient and starting on oral therapy, an x-ray is not required
7. Obtain study-required safety labs as described in Section 10.4.1.1.
8. Document standard-of-care safety labs as described in Section 10.4.1.2.
9. Document microbiology assessments as described in Section 10.4.2.
10. Document radiological imaging as described in Section 10.4.3.
11. Document non-pharmacologic treatments as described in Section 10.4.3.
12. Pregnancy test in females of childbearing potential
13. Record all prior and concomitant medications other than antibiotics taken within 72 hours prior to first dose of study drug and all antibiotics taken within 7 days prior to first dose of study drug.
14. Perform clinical outcomes assessment as described in Section 10.6.
15. Randomization

10.2 Treatment Period Procedures

10.2.1 Treatment Days up to Last Day of Treatment

1. Every effort should be made to obtain safety labs 72 hours (± 24 hours) after the first dose to include ALT, AST, alkaline phosphatase, total and direct bilirubin, and WBC with

differential. A separate study sample is not required if these labs are obtained at 72 hours (± 24 hours) after the first dose per standard of care.

2. Document physical examination if available per standard of care on the day of clinical outcome assessment only.
3. Document vital signs if available per standard of care on the day of clinical outcome assessment only.
4. Document standard-of-care safety labs as described in Section 10.4.1.
5. Document microbiology assessments as described in Section 10.4.2.
6. Document radiological imaging as described in Section 10.4.3.
7. Document non-pharmacologic treatments on the day of clinical outcome assessment only as described in Section 10.4.3.
8. If the screening visit for females occurred more than 24 hours before receiving the study drug, a pregnancy test will be performed prior to first dose of study drug.
9. Review and record concomitant medications as described in Section 8.3.
10. Administer study drug. If the subject is an outpatient and receiving study drug orally, a dosing diary is included on the capsule blister pack and the label for the suspension. This diary should be completed for each dose taken and brought back to each visit for review and accountability.
11. Obtain PK samples as described in Section 10.4.3.
12. Review and record any AEs and SAEs as described in Section 12.1.
13. Perform clinical outcomes assessment once on days 3–5 (ECR) if the subject is available. A return visit is not required to perform the outcomes assessment.

10.2.2 Last Day of Treatment (+48 Hours)

1. Perform physical examination on the last day of dosing or within 48 hours after the last dose.
2. Obtain vital signs on the last day of dosing or within 48 hours after the last dose.
3. Perform safety labs as described in Section 10.4.1. Safety labs must be collected on the last day of dosing or within 48 hours after the last dose. A separate study sample is not required if safety labs above are obtained on the last day of dosing or within 48 hours after the last dose per standard of care.
4. Document microbiology assessments as described in Section 10.4.2.
5. Document radiological imaging as described in Section 10.4.3.
6. Document non-pharmacologic treatments as described in Section 10.4.3.
7. Review and record concomitant medications as described in Section 8.3.
8. Administer study drug and active comparator. If the subject is an outpatient and receiving study drug orally, a dosing diary is included on the capsule blister pack and the label for

the suspension. This diary should be completed for the last day of treatment and the diary should be returned to the study site at this visit for review and accountability.

9. Obtain PK samples as described in Section 10.4.3.
10. Review and record any AEs and SAEs as described in Section 12.1.
11. Perform clinical outcomes assessment

10.3 Follow-up Procedures

10.3.1 Day 16 Post Randomization (± 4 days)

1. Every effort should be made to obtain safety labs Day 16 (± 4 days) after the first dose to include ALT, AST, alkaline phosphatase, total and direct bilirubin, and WBC with differential. A separate study sample is not required if these labs are obtained at Day 16 (± 4 days) after the first dose per standard of care.
2. Perform physical examination including weight, HEENT, heart, lungs, abdomen, skin, and extremities.
3. Perform vital signs (blood pressure, heart rate, respiratory rate, and temperature).
4. Document standard-of-care safety labs as described in Section 10.4.1.
5. Document microbiology assessments as described in Section 10.4.2.
6. Document radiological imaging as described in Section 10.4.3.
7. Document non-pharmacologic treatments as described in Section 10.4.3.
8. Review and record any AEs and SAEs as described in Section 12.1. Every effort should be made to bring the subject back for follow up, but SAEs must be collected via phone/other media if the subject is unable or unwilling to return.
9. Perform clinical outcomes assessment.

10.3.2 Day 28 Post Randomization (± 4 days)

1. Every effort should be made to obtain safety labs Day 28 (± 4 days) after the first dose to include ALT, AST, alkaline phosphatase, total and direct bilirubin, and WBC with differential. A separate study sample is not required if these labs are obtained at Day 28 (± 4 days) after the first dose per standard of care.
2. Review and record any SAEs as described in Section 12.1. Every effort should be made to bring the subject back for follow up, but SAEs must be collected via phone/other media if the subject is unable or unwilling to return.

10.4 Laboratory Determinations

10.4.1 Safety Laboratory Tests

Safety laboratories will include hemoglobin, hematocrit, WBC with differential, platelet count, blood urea nitrogen, calcium, serum creatinine, potassium, sodium, AST, ALT, ALP, total and direct bilirubin, and albumin.

10.4.1.1 Study-Required Safety Laboratories

All safety laboratory tests with values that become clinically significantly abnormal (as determined by the investigator) during the study should be repeated until the values return to baseline or normal values. If clinically significant abnormal laboratory values do not return to baseline or normal values within a reasonable period, the etiology should be identified and the medical monitor notified. For children <2 years of age, no more than 4 to 5 mL of whole blood for research purposes will be collected (including safety laboratories and PK samples), whereas for subjects aged ≥ 2 years, no more than 10 mL of whole blood will be collected. For infants < 7 kg, no more than 3 mL/kg will be drawn for research purposes during the study. In countries where micro laboratory equipment is not available, whole blood for research purposes in children < 2 years of age should not exceed 2.4 mL/kg.

Laboratory samples will be analyzed by a certified laboratory at the scheduled times. Laboratories in the U.S. will be required to have Clinical Laboratory Improvement Amendments certifications.

10.4.1.2 Standard-of-Care Safety Laboratories

A separate study sample is not required if safety labs are obtained per standard of care. If multiple laboratory tests are obtained within 72 hours of first dose of study drug, record test results closest to administration of study drug.

Laboratory samples will be analyzed by each clinical site's local laboratory.

10.4.2 Microbiology Assessments

Results of microbiology assessments performed in accordance with routine standard of care will be recorded on the study eCRF. These include all cultures from cerebrospinal fluid, pleural fluid, blood, urine (catheter or suprapubic tap), and sputum, as well as molecular and serologic tests for *M. pneumoniae* and *C. pneumoniae*.

10.4.3 Pharmacokinetic Determinations

Solithromycin concentrations will be measured in plasma. Pharmacokinetics samples will be processed at a central lab using a validated bioanalytical assay. These data will be reviewed periodically during the study. Two PK samples (150 μ L per sample) will be collected on Day 1. Additional PK samples (150 μ L per sample) will be collected at varying time points on Days 3 to 7 (maximum of 6 PK samples taken total). Every effort should be made to collect at least 2 PK samples on Day 1 and additional PK samples on Days 3 to 7. Table 10 below provides the optimal sampling collection windows for solithromycin according to route of administration. Every effort should be made to collect PK samples during the time windows provided; however, samples obtained outside of the sampling windows are acceptable. Lack of collection of samples or collection outside the optimal windows will not be considered protocol deviations. No more than 6 PK samples will be collected per subject. For subjects switched from an IV to oral formulation, the oral sampling scheme can be used following all subsequent oral doses.

Table 10 Optimal Pharmacokinetics Sampling Windows Following Dose Administration

Intravenous Time after dose	Oral Time after dose
Prior to dosing (within 1 hour) ^a	Prior to dosing (within 1 hour) ^a
End of infusion (within 10 minutes)	0.5–1.5 hours
2–4 hours	2–4 hours
8–10 hours	8–10 hours
16–18 hours	16–18 hours
20–<24 hours	20–<24 hours

a. Only applicable to Days 3 to 7 PK samples.

10.5 Radiological Imaging and Non-pharmacologic Treatment/Procedures

Chest x-rays and CT scan of the chest will be recorded on the study eCRF. Surgeries and non-pharmacologic procedures of interest performed in accordance with routine standard of care will be recorded on the study eCRF. Surgeries of interest include surgeries of the chest and chest wall, such as pleural tube placement and video assisted thoracoscopic surgery.

10.6 Clinical Efficacy Outcomes Assessments Time Points

Clinical outcomes assessments will be performed by a blinded investigator at the study site. At each time point, the site blinded investigator will evaluate signs and symptoms and record physical findings of CABP. These assessments will include cough, difficulty breathing, purulent sputum production, chest pain, grunting, hypotension, tachycardia, tachypnea, and evidence of pulmonary consolidation (further details are in the Blinded Investigator Plan). If symptoms and physical exam findings are available in the medical record per standard of care, these can be used for the clinical outcomes assessments.

Clinical efficacy outcomes assessments will be performed at the following time points:

- A baseline assessment of signs, symptoms, and physical exam findings will be completed at screening
- Clinical improvement on the last day of treatment (+48 hours) (primary efficacy endpoint)
- Clinical improvement on Day 3 or 4. If the subject is discharged from the hospital prior to Day 3, assessment may be recorded on Day 2. A return visit is not required to perform this assessment if the subject has been discharged prior to the assessment.
- Clinical cure during SFU at 16 days (+/-4 days) post-randomization (secondary efficacy endpoint). This assessment will be conducted if information is available per standard of care and may be recorded from the medical record via phone/other media.

10.7 Clinical Improvement Definition (Early Clinical Response and End-of-Treatment Response)

Clinical improvement is defined as improvement of at least 1 of the presenting signs and symptoms of CABP with no deterioration in any presenting sign or symptom of CABP, no development of new sign or symptom of CABP, and no requirement for additional or alternative antimicrobial therapy.

10.8 Clinical Cure Definition (Day 16 Post Randomization [± 4 Days])

Clinical cure is defined as resolution of all presenting signs and symptoms of CABP (excluding cough), no development of new sign or symptoms of CABP, and no requirement for alternative antimicrobial therapy.

10.9 Signs and Symptoms of CABP

- Cough
- Difficulty breathing
- Production of purulent sputum
- Chest pain
- Grunting
- Hypotension
- Tachycardia defined as follows:
 - 2 months to <24 months: ≥ 160 beats/min
 - 24 months to <10 years: ≥ 140 beats/min
 - ≥ 10 years: ≥ 100 beats/min
- Tachypnea, defined as follows:
 - 2 months to <12 months: ≥ 50 breaths/min
 - 12 months to <5 years: ≥ 40 breaths/min
 - ≥ 5 years: ≥ 20 breaths/min
- Physical exam consistent with pulmonary consolidation

11 STUDY AND SUBJECT DISCONTINUATION

A clear distinction will be made between subjects who discontinue study drug dosing and those who withdraw or are withdrawn from the study. Only those subjects who are lost to follow-up, are unwilling to comply with protocol procedures, or who withdraw consent and/or refuse any further contact with respect to the study will be withdrawn from the study. Subjects discontinued from study drug dosing and/or withdrawn for the study will not be replaced, regardless of the reason.

11.1 Screening Failures

Subjects who sign and date the ICF and assent (if applicable) but who fail to meet the inclusion and exclusion criteria are defined as screen failures. A screening log, which documents the subject's initials and reason(s) for screen failure, is to be maintained by the Investigator for all screen failures. A copy of the log should be retained in the Investigator's study files. Screen failures will not be added to the eCRF.

11.2 Discontinuation from Study Drug

A subject may have study drug prematurely discontinued for any of the following reasons:

- Safety, including AEs or development of clinically significant laboratory abnormalities. The subject must be followed clinically until the event is resolved or deemed stable.
- Clinical failure or lack of efficacy.
- Subject wishes to withdraw consent for reasons other than an adverse experience.
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol.
- Investigator discretion.
- Sponsor request.

Any subject who prematurely discontinues study drug should be encouraged to complete the study through the last study visit. The Last Day of Treatment procedures will be performed the day (+48 hours) the study drug is discontinued.

11.3 Withdrawal from Study

A subject may be withdrawn from the study for any of the following reasons:

- Subject wishes to withdraw consent for reasons other than an adverse experience
- Subject wishes to withdraw consent due to an adverse experience
- Subject is lost to follow-up
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol
- Investigator discretion
- Sponsor request

11.4 Study Site Discontinuation

Reasons for discontinuation of the study at an investigational site may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Investigator request to withdraw from participation
- Sponsor decision
- Serious and/or persistent non-compliance by the investigator with the protocol, the clinical research agreement, and/or applicable regulatory guidelines in conducting the study
- Institutional review board (IRB)/independent ethics committee (IEC) decision to terminate or suspend approval for the investigation or the investigator
- Investigator fraud (altered data, omitted data, or manufactured data)
- Recommendation from the DMC

12 SAFETY ASSESSMENTS

Safety assessments will include attention to relevant changes in physical examinations, clinical condition, vital signs, and safety laboratory tests that are identified as occurring after the ICF and assent (if applicable) are signed regardless of relationship to study drug. Any study team member may conduct safety assessments.

12.1 Adverse Events

An AE is any untoward medical occurrence associated with the use of a study drug in humans, whether or not considered drug related. An AE can be a clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human being participating in a clinical study with study drug or comparator, regardless of causal relationship. A “pre-existing” condition is one that is present prior to study drug administration and is reported as part of the subject’s medical history. A pre-existing condition should be reported as an AE only if the frequency, intensity, or character of the pre-existing condition worsens during the course of the study.

Laboratory abnormalities are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. However, a clinically significant laboratory abnormality (e.g. detected on clinical chemistry or hematology) that is independent from the underlying medical condition and that requires medical or surgical intervention, or leads to study drug interruption or discontinuation, will usually be considered an AE.

Lack of efficacy/clinical failure is captured as an efficacy measure and in general will not be considered an AE.

Adverse events will be collected from the time of signing of the informed consent until 28 days post-randomization. In addition, the investigator (or designee) should seek to elicit any clinical or objective reactions by specific questioning (“How have you been feeling?”) and, as appropriate, by examination. Information on all AEs should be recorded on the eCRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. The component parts of the diagnosis may be listed for verification. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality.

To avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology on the eCRF and on the medical record rather than in the subject’s own words. Each AE will also be described in terms of duration (start and stop date and times), severity, association with the study drug, action(s) taken, and outcome.

12.1.1 Serious Adverse Events

An AE or suspected adverse reaction is considered serious if, in the view of the investigator or sponsor, it results in any of the following outcomes:

- Death: “Death” is an outcome and is NOT the AE. In the event of death, the cause of death should be recorded as the AE. The only exception is “sudden death” when the cause is unknown.
- Life-threatening AE: Places the subject at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Subject hospitalization or prolongation of hospitalization. A “planned” hospitalization for study procedures or preexisting conditions is NOT an SAE.
- Congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in in subject hospitalization, or the development of drug dependency or drug abuse.

Serious AEs will be collected from the time of signing of informed consent until 28 (\pm 4) days after randomization. All SAEs, regardless of the investigator’s assessment of causal relationship to study drug, must be reported by the investigator or qualified designee within 24 hours of the site’s knowledge of the event, and a copy of the initial SAE report must be received within 1 business day.

The report must include an assessment of whether there is a reasonable possibility that the study drug caused the event. “Reasonable possibility” means there is evidence to suggest a causal relationship between the study drug and the AE.

12.1.1.1 Reporting of SAEs

All SAEs must be reported to APCER Life Sciences preferably by email within 24 hours of the site’s knowledge of the event. APCER contact information:

APCER Email: Safety.Cempra@apcerls.com

Fax: 888-264-1449

Phone: 888-998-7256

12.1.2 Follow-up of SAEs

When additional relevant information becomes available, the investigator will record follow-up information according to the same process used for reporting the initial event as described above. The investigator will follow all SAEs until resolution, stabilization, or the event is otherwise explained.

All SAEs will be followed until resolution, stabilization, until otherwise explained, or until the last subject completes the final follow-up, whichever occurs first.

12.1.3 Other Reportable Events

Reports of overdose (with or without an AE), inadvertent or accidental exposure, and known pregnancy should be forwarded in the same time frame as an SAE.

Overdose occurs when a subject is administered or has taken a dose greater than the intended or scheduled dose specified by the protocol.

All pregnancies occurring during the study must be followed for information regarding the course of pregnancy, delivery, and condition of the newborn. Follow-up should be provided by the investigator to the medical monitor in a timely manner.

Monitoring of liver laboratory tests

Monitoring of liver laboratory tests of special interest (AST, ALT, and direct bilirubin) will be conducted throughout the study. Three levels of monitoring will be performed:

Weekly monitoring: Each week, data entered in the eCRF will be downloaded to identify any child enrolled in the study with a) normal AST, ALT, or direct bilirubin at baseline AND at least $2 \times \text{ULN}$ on any of these laboratory tests at any study visit post baseline and b) any child meeting laboratory criteria for Hy's Law. These data will be provided to the DCRI medical monitor and the sponsor for review.

Quarterly monitoring: Each quarter, summary data of children enrolled in the study with a) normal AST, ALT, or direct bilirubin at baseline AND at least $3 \times \text{ULN}$ on any of these laboratory tests at any study visit post baseline and b) any child meeting laboratory criteria for Hy's Law will be provided to the DMC chair for review. Actions by the DMC chair will be described in the DMC meeting minutes.

Biannual monitoring: Twice per year, all data pertaining to liver laboratory tests will be presented to the DMC for review. This includes the data presented quarterly as well as listings of all laboratory tests at every visit.

12.1.4 Severity of Adverse Events

AE severity will be graded based on the following:

- | | |
|------------------|---|
| Mild: | Transient or mild discomfort; no medical intervention/therapy required |
| Moderate: | Mild-to-moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required |
| Severe: | Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalizations possible |

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity assessment changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

12.2 Assessment of Causal Relationship

The investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

- **Unrelated:** There is not a reasonable possibility that the drug caused the event.
- **Related:** There is a reasonable possibility that the drug caused the event; “reasonable possibility” means there is evidence to suggest a causal relationship between the study drug and the AE.

12.3 Action Taken

For each reported AE, the investigator must document the action taken according to the following criteria:

- No action taken
- Non-pharmacologic treatment
- Pharmacologic treatment
- Discontinued from study drug
- Discontinued from study
- New or prolonged hospitalization

12.4 Adverse Event Outcome

For each reported AE, the investigator must document the outcome according to the following criteria:

- Recovered
- Ongoing
- Unknown
- Death

12.5 Expedited Safety Reports to Health Authorities

Sponsor or designate will be responsible for reporting expedited and periodic safety reports to health authorities in accordance with the requirements of individual countries.

For SAEs that require expedited regulatory reporting in the U.S. under 21 Code of Federal Regulations (CFR) 312.32(c)(1), the sponsor will notify the FDA and all participating investigators in a written IND safety report.

13 DATA MANAGEMENT

Study data will be entered into eCRFs at the study sites (Section [15.7](#)). Prior to database lock, programmed computer edit checks will be run against the database to check for discrepancies and reasonableness of the data. All issues resulting from the computer-generated checks as well as manual data review will be resolved prior to database lock.

14 STATISTICAL ASSUMPTIONS

14.1 Statistical Methods and Planned Analyses

14.1.1 Endpoints

The primary endpoints for safety will be:

- The proportion of subjects with TEAEs
- The proportion of subjects with therapy not tolerated. Therapy not tolerated will be defined as discontinuation of drug treatment due to a related AE.

Secondary endpoints include efficacy of solithromycin or active comparator as evidenced by clinical response (see Section 10.7) and population PK of solithromycin.

14.1.2 Sample Size

Subjects will be randomized 3:1 (solithromycin 300: comparator 100), stratified by age, with at least 40 subjects randomized per age group. The sample size of 300 in the solithromycin group is based on the ability to observe an SAE at a frequency higher than 1% (Table 11).

Table 11 Probability of Observing at Least one Subject with a Serious Adverse Event

	Possible Serious Adverse Event Incidence with 5 Days of Dosing				
Number of Subjects	0.1%	0.25%	0.5%	1%	2%
100	0.095	0.22	0.39	0.63	0.87
200	0.18	0.39	0.63	0.87	0.98
300	0.26	0.53	0.78	0.95	>0.99

In addition, this sample size will provide reasonable estimates and 95% CI for safety. If 1 subject has an AE, then the 95% CI (exact binomial) for that AE within the subject population of 300 subjects is 0, 1.8% (see Table 12).

Table 12 Proportion of Subjects with Adverse Events and 95% CI

Number of Events	Proportion	95% CI
0	0	0, 0.012
1	0.003	0.0001, 0.018
2	0.007	0.001, 0.024
3	0.010	0.002, 0.029

14.1.3 Safety Analysis

For the primary safety endpoints, the frequency and percentage of subjects with AEs and therapy not tolerated will be determined and 95% CIs calculated. Summaries will be calculated by treatment group for the overall safety population and stratified by age group.

Additional safety analyses include summaries of AEs, descriptive statistics of laboratory values, descriptive statistics of vital signs, and frequency distributions of abnormal physical examinations. Laboratory data, such as hematology and serum chemistry data, as well as safety data will be analyzed. Summary statistics for changes from baseline and shift tables will be presented. Continuous laboratory measurements will be described at each visit using descriptive statistics (mean, median, etc.); observed values and changes from baseline will be summarized. Laboratory tests reflective of liver toxicity (e.g., ALT, AST) will be further summarized in terms of the most extreme values and largest changes from baseline (in the appropriate direction) observed from start of study drug through the end of therapy. All analyses will include summaries for both treatment and active comparator.

Additional details of safety analyses will be included in the Statistical Analysis Plan (SAP).

14.1.4 Pharmacokinetic Analysis

A population PK analysis will be performed using non-linear mixed effects modeling in NONMEM. Data will be reviewed during the study to evaluate the PK of solithromycin in pediatric CABP patients. The influence of covariates on PK parameters will be explored. Monte Carlo simulations will be used to evaluate optimal drug exposure. The relationship between drug exposure and safety events will be evaluated by calculating the proportion of subjects with AEs and SAEs at different exposure levels.

14.1.5 Efficacy Analysis

Efficacy will be evaluated as a binary variable representing clinical improvement on the last day of treatment, as a binary variable representing early clinical improvement on treatment days 3 and 4, and as a binary variable representing clinical cure on Day 16 (± 4 days) post-randomization. The frequency and percentage of subjects achieving each efficacy endpoint will be determined, and a 95% CI calculated. Summaries will be calculated by treatment group for the overall ITT population (and microITT population if the data is sufficient to provide meaningful analysis) and stratified by age group. This study is not powered for comparison of efficacy endpoints between treatment groups. Additional details of efficacy analyses will be included in the SAP.

14.2 Quality Assurance

Accurate, consistent, and reliable data and reporting will be ensured through the use of standard practices and procedures.

15 ADMINISTRATIVE ASPECTS

15.1 Compliance with Regulatory Requirements

This study will be conducted in compliance with the protocol and all regulatory requirements, in accordance with GCP, including ICH Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

15.2 Institutional Review Board or Independent Ethics Committee Approval

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB/IEC for approval. IRB/IEC approval of the protocol, informed consent document, and any advertisement used to recruit study subjects must be obtained before the study may be initiated.

The principal investigator is responsible for keeping the IRB/IEC advised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The principal investigator is also responsible for notifying the IRB/IEC of all unanticipated risks involving human subjects that occur during the study. Notwithstanding the foregoing, studies funded by the Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, Department of Health and Human Services (“BARDA”), which include this study, require immediate notice to Cempra and the CRO of any issues that could affect the safety of the human subjects.

15.3 Informed Consent/Assent

Prior to any study-related procedures, the investigator or designee will obtain from the participant and/or participant’s legally authorized representative (i.e., parent/legal guardian) a signed and dated written study consent/authorization consistent with FDA/ICH regulations and the HIPAA (Health Insurance Portability and Accountability Act) Privacy Rule. Children will have the study explained to them as well in an understandable way, and their refusal to take part will be honored. Children old enough to be able to sign their name will sign an assent form. HIPAA Privacy Rule authorization language will be included in the informed consent/authorization form (where the informed consent and authorization are combined into 1 document) and must be IRB approved prior to study implementation. When applicable (such as in the state of California), the document of Bill of Rights will be attached to the ICF so that the participants can read and understand the same. The original signed consent/assent for each participating subject shall be filed with records kept by the investigator. A copy of the informed consent/assent document must be provided to the participant’s legally authorized representative and participant (as applicable).

15.4 Confidentiality

Personal study subject data collected and processed for the purposes of this study should be managed by the principal investigator and his/her staff with adequate precautions to ensure the confidentiality of those data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors and other authorized agents of sponsor and the clinical research organization (CRO), the IRB/IEC approving this research, and the FDA, as well as any other applicable regulatory authorities, will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentation of the results of this study at meetings or in publications, the subject identities will remain confidential.

15.5 Compensation, Insurance and Indemnity

Information regarding compensation, insurance, and indemnity is addressed in the Clinical Trial Research Agreement.

15.6 Protocol Amendment

If a protocol has been filed with regulatory agencies or submitted to an IRB/IEC and requires changes, a protocol amendment must be written. Any changes to the protocol will be made by the sponsor. All amendments will be sent to the study sites who are then responsible for submitting the amendment to their IRB/IECs for approval.

15.7 Case Report Forms: Electronic

An eCRF will be used to record all subject data specified by this protocol. The eCRF must be completed by designated and trained study personnel. The eCRF will be electronically signed by the principal investigator or a subinvestigator (listed on the Form FDA 1572). It is the responsibility of the principal investigator to ensure the eCRFs are completed in an accurate and timely manner. The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change and person making change). At the completion of the study, the sponsor will be provided with the per-subject eCRF in an individual subject profile on disk or other electronic medium.

15.8 Source Document Maintenance

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondence, computer printouts, laboratory data, and drug accountability records. All source documents produced in this study will be maintained by the investigators and made available for inspection by sponsor representatives, the FDA, or other regulatory authorities.

15.9 Study Monitoring Requirements

Site visits will be conducted by an authorized Cempra Pharmaceuticals representative (the monitor) to inspect study data, subject medical records, and eCRFs in accordance with ICH guidelines, GCPs, and the respective U.S. or national regulations and guidelines, as applicable. It will be the monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRFs.

The investigator will permit representatives of the sponsor, the FDA, and/or respective health authorities to inspect facilities and records relevant to this study.

15.10 Study File Management

It is the responsibility of the principal investigators to ensure that the study file at the site is maintained. The study file will contain, but not be limited to:

1. Investigator's brochure (including updated or revised versions)
2. Final study protocol
3. Protocol amendments (if applicable)
4. Fully executed Clinical Trial Agreement
5. Investigator manual (if applicable)
6. ICF (blank)
7. Revised ICFs and/or all addenda (blank)
8. Copy of signed U.S. FDA Form 1572
9. Department of Health and Human Services number for IRB or other documentation of IRB/IEC compliance with FDA
10. Curricula vitae (CV) of principal investigators and subinvestigators
11. Financial disclosure information provided to the sponsor
12. A list of the IRB/IEC members and their qualifications, as well as a description of the IRB processes
13. If the principal investigator is a member of the IRB/IEC, documentation stating he/she did not vote on the study
14. Documentation of IRB/IEC approval of protocol, consent form, any protocol amendments, and any consent form revisions
15. Annual IRB/IEC updates and approvals
16. All correspondence between the principal investigator, IRB/IEC, and sponsor (or designee)
17. Copies of all IND Safety Reports submitted to the FDA or other regulatory agencies and IRB/IEC correspondence documenting their submission (if applicable)
18. Laboratory certifications/normal laboratory value ranges
19. Screening log
20. Clinical research associate monitoring log
21. Drug accountability records and invoices for receipt/return of study drug
22. Protocol signature page
23. Laboratory director's CV and medical/professional license, if available

15.11 Study Completion

The sponsor requires that the following data and materials be on file at the study site before a study can be considered completed or terminated:

1. Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
2. eCRFs properly completed by appropriate study personnel and electronically signed and dated by the principal investigator
3. Complete drug accountability records (drug inventory log and an inventory of returned or destroyed clinical material)
4. Copies of protocol amendments and IRB/IEC approval/notification, if appropriate
5. A summary of the study prepared by the principal investigator (an IRB/IEC summary letter is acceptable)

15.12 Audits

During the course of the study, or after completion of the study, each study site may be subject to an audit by a sponsor quality assurance auditor (or an auditor appointed by the sponsor or its authorized representative) and/or an inspector from the FDA and/or other regulatory authority. Every attempt will be made to notify the principal investigator in writing in advance of the audit.

15.13 Retention of Records

The sponsor follows U.S. regulations and ICH guidelines in its retention policy.

U.S. IND regulations (21 CFR 312.62) require that records and documents pertaining to the conduct of this study and the distribution of study drugs, including eCRFs, consent forms, laboratory test results, and medication inventory records be kept on file by the principal investigator for 2 years after a marketing application is approved for the drug for the indication for which it is being studied. If no application is filed or approved, these records must be kept for 2 years after the investigation has been discontinued and the FDA has been notified. ICH guidelines indicate that documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. If there is a country or institutional policy that specific records and documents be retained for a longer period than described above, the applicable sites must comply with those policies in addition to U.S. and ICH policies. No study records should be destroyed without prior authorization from the sponsor.

15.14 Disclosure of Data

The principal investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the names of principal investigators, their addresses,

qualifications and extent of involvement. It is understood that the investigator is required to provide the sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by the FDA and other regulatory authorities, by the sponsor, and by the IRB as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Subject medical information obtained during the course of this study is confidential, and disclosure to third parties other than those noted above is prohibited.

15.15 Financial Disclosure

The FDA Financial Disclosure by Clinical Investigators (21 CFR 54) regulations require Sponsors to obtain certain financial information from investigators participating in covered clinical studies; each principal investigator and subinvestigator is required to provide the required financial information before participating in the study and to promptly update Cempra Pharmaceuticals with any relevant changes to this information throughout the course of the clinical study and for up to 1 year after its completion. This rule applies to all investigators and subinvestigators participating in covered clinical studies to be submitted to the FDA in support of an application for marketing approval.

15.16 Publication Policy

The publication policy is outlined in more detail the Clinical Trial Agreement.

Studies funded by BARDA, in whole or in part, including this study, shall acknowledge such funding when issuing statements, press releases, and other documents. For purposes of this section, "publication" is defined as an issue of printed material offered for distribution or any communication or oral presentation of information, including any manuscript or scientific meeting abstract. The principal investigator agrees to accurately and factually represent the work conducted under this protocol in all press releases. Any publication containing data generated under this protocol must be submitted for BARDA review no fewer than 30 calendar days for manuscripts and 15 calendar days for abstracts before submission for public presentation or publication.

Misrepresenting protocol results or releasing information that is injurious to the integrity of BARDA may be construed as improper conduct. Press releases shall be considered to include the public release of information to any medium, excluding peer-reviewed scientific publications. Publications are required to include: (1) the percentage and dollar amounts of the total program or project costs financed by BARDA and; (2) the percentage and dollar amount of the total costs financed by nongovernmental sources. The principal investigator shall ensure that Cempra and CRO receive an advance copy of any press release related to the study no fewer than 5 working days prior to the issuance of the press release. Funding support shall be acknowledged in all such publications substantially as follows:

"This project has been funded in whole or in part with federal funds from BARDA, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, Department of Health and Human Services, under Contract No. HHS0100201300009C."

For each Institution and Investigator conducting the Study or a portion thereof outside of the United States, Institution and Investigator acknowledge and agree that (i) the Study and all other activities to be performed hereunder will be supported by funding provided, and will be performed in support of Sponsor's performance of its obligations, under Contract No. HHS0100201300009C ("Prime Award"), entitled "*SOLI- Solithromycin Pediatric Development Program*", awarded by the United States Government through the Office of Acquisitions Management, Contracts and Grants ("Prime Sponsor"), and that, therefore, certain obligations are required of Sponsor's subcontractors (including Institution and Investigator) and, notwithstanding anything to the contrary in the Clinical Trial Agreement, or any other clinical study agreement, clinical trial agreement, investigator agreement, or the like executed by Institution or Investigator with respect to the Study, (ii) the terms and conditions of the Protocol and the Clinical Trial Agreement are subject to the terms included as Appendix B, attached hereto and fully incorporated herein, and, without limitation of the foregoing, to those provisions of the Prime Award incorporated herein, and, in the event of any conflict between those terms included as Appendix B and the terms and conditions of the Protocol, the Clinical Trial Agreement, or any other clinical study agreement, clinical trial agreement, investigator agreement, or the like executed by Institution or Investigator with respect to the Study, the terms of Appendix B shall govern to the extent of such conflict.

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Appendix A Protocol Amendments

Amendment #3 29 November 2017

Rationale for Amendment

Amendment 3 revised the oral suspension Solithromycin concentration from 320mg/5mL to 275mg/5mL and removed the 160mg/5mL concentration. In addition, a new exclusion criteria was added for an evaluation of renal failure [End Stage Renal Disease (dialysis requiring) OR severe renal impairment (defined as serum creatinine > 1.5 fold ULN for age).], a section was added to improve clarity of SAE reporting and the Cempra sign-off for the protocol was changed from Brian Jamieson, MD to Robert M Hernandez, PhD.

Language has been modified in some sections to improve the clarity of the protocol requirements and procedures, and to correct minor typographical errors. Typographic corrections, including grammatical and punctuation errors, are not shown in this rationale.

New/revised text is in ***bolded italics***. Deletions are identified by ~~strikethrough~~.

SIGNATURE PAGE

~~Brian Jamieson, MD~~ ***Robert Hernandez, PhD***
~~Sr. Director, Clinical Research~~ ***Operations***

2 Synopsis

Changes made in accordance with the revisions described below.

Inclusion Criteria

4...History of and/or documented fever (rectal, ***temporal, ear, or oral temperature $\geq 38^{\circ}\text{C}$ or axillary temperature $\geq 37.5^{\circ}\text{C}$) or hypothermia (rectal, ***temporal***, ear, or oral temperature $< 35^{\circ}\text{C}$ or axillary temperature $< 34.5^{\circ}\text{C}$) . . .***

Exclusion Criteria

14. End Stage Renal Disease (dialysis requiring) OR severe renal impairment (defined as serum creatinine > 1.5 fold ULN for age).

Test Product

~~...Azithromycin IV/PO or erythromycin lactobionate IV or erythromycin PO may be added to any of the treatment regimens above.~~ ***Azithromycin is also acceptable as a first line of treatment. . .***

Table 1 foot note

- g ~~Local laboratory; includes hemoglobin, hematocrit, white blood cell count with differential, platelet count, blood urea nitrogen, calcium, serum creatinine, potassium, sodium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, and albumin.~~

Local laboratory; includes hemoglobin*, hematocrit*, white blood cell count with differential*, platelet count*, blood urea nitrogen*, calcium*, serum creatinine, potassium*, sodium*, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase*, total and direct bilirubin, and albumin*. If laboratories with * designation are not obtained, it will not result in a protocol deviation.

7.3 Study Drug and Administration

... Subjects requiring an oral dosage form other than capsules will receive suspension formulation, provided at ~~160 mg/5 mL and 320~~ **275 mg/5 mL** strengths . . .

... Azithromycin IV/PO or erythromycin lactobionate IV or erythromycin PO may be added to any of the treatment regimens above. ***Azithromycin is also acceptable as a first line of treatment.***

..

8.1 Inclusion Criteria

4...History of and/or documented fever (rectal, ***temporal***, ear, or oral temperature $\geq 38^{\circ}\text{C}$ or axillary temperature $\geq 37.5^{\circ}\text{C}$) or hypothermia (rectal, ***temporal***, ear, or oral temperature $< 35^{\circ}\text{C}$ or axillary temperature $< 34.5^{\circ}\text{C}$) . . .

8.2 Exclusion Criteria

14. End Stage Renal Disease (dialysis requiring) OR severe renal impairment (defined as serum creatinine > 1.5 fold ULN for age).

9.1 Solithromycin (CEM-101)

... Detailed instructions for the reconstitution of the powder for oral suspension to ~~320~~ **275 mg/5 mL** and ~~160 mg/5 mL~~ will be listed in the pharmacy manual . . .

12.1.1 Serious Adverse Events

... All SAEs, regardless of the investigator's assessment of causal relationship to study drug, must be reported by the investigator or qualified designee within 24 hours of the site's knowledge of the event, and a copy of the initial SAE report must be received within 1 business day. ~~All SAEs will be reported to the Medical Monitor (or designee) within 24 hours of occurring.~~

12.1.1.1 Reporting of SAEs

All SAEs must be reported to APCER Life Sciences preferably by email within 24 hours of the site's knowledge of the event. APCER contact information:

APCER Email: Safety.Cempra@apcerls.com

Fax: 888-264-1449

Phone: 888-998-7256

Amendment #2 16 December 2016

Rationale for Amendment

Amendment 2 incorporates additional safety laboratory evaluations along with new and updated dosing information for all 3 formulations of solithromycin.

Safety laboratories, including ALT, AST, ALP, total and direct bilirubin, and eosinophil count have been added at 72 hours (± 24 hours), Day 16 (± 4 days), and Day 28 (± 4 days). The Day 28 (± 4 days) visit evaluates safety laboratories approximately 3 weeks after completion of dosing, and replaces the Day 36 (± 4 days) visit. Data pertaining to liver laboratory evaluations will be reviewed on a regularly scheduled basis (Section 12.1.3) and presented to the DMC.

Solithromycin suspension dosing information, including the dosage rationale, has been added for all age groups. The IV dose has been updated to 8 mg/kg (maximum 400 mg) for all age groups based on additional Phase 1 pediatric PK data. PK/PD simulations based on adult CABP patient data have been reassessed following an FDA recommendation to remove the loading dose on the first oral dosing day after IV administration; the loading dose did not appear to be required for efficacy but did increase the potential for ALT elevations and could be associated with dosing errors. Consequently, the oral loading dose after IV dosing has been replaced by the daily oral maintenance dose (10 mg/kg; maximum 400 mg). A loading dose will be employed only on the first day of oral only dosing (20 mg/kg; maximum 800 mg).

The duration of dosing with solithromycin will be 5 days with oral only dosing, and 7 days with IV only or IV to oral dosing; previously the duration was 5 to 7 days for all formulations. Five-day oral and 7-day IV and IV to oral regimens of solithromycin were demonstrated to be non-inferior to moxifloxacin in the Phase 3 adult pneumonia studies (CE01-300 and CE01-301). Comparator duration of dosing will continue to be per standard of care.

The minimum weight requirement of 60 kg for solithromycin capsule dosing in the 12 to 17 year old age group has been removed. This is supported by PK modeling efforts from Phase 1 studies as well as by safety data from more than 100 adult patients <60 kg who received solithromycin in completed pneumonia studies (Cempra Phase 3 studies and Toyama Phase 2 study).

“Clinical failure or lack of efficacy” has been added as a reason for discontinuation from study drug, and “withdrawal of consent due to an adverse experience” has been added as a reason for discontinuation from study. These additional reasons will better categorize patient disposition.

Language has been modified in some sections to improve the clarity of the protocol requirements and procedures, and to correct minor typographical errors. Typographic corrections, including grammatical and punctuation errors, are not shown.

New/revised text is in ***bolded italics***. Deletions are identified by ~~strikethrough~~.

SIGNATURE PAGE

~~Mike Cinoman~~ **Brian Jamieson, MD**
Sr. Director, Pediatric Clinical Research

2. SYNOPSIS

Changes made in accordance with the revisions described below.

Planned Number of Investigational Sites: Approximately **90** ~~60~~

Clinical Phase: 2/3, to be conducted in the U.S. and up to **approximately 7** additional countries in other regions of the world, ~~including Europe~~

Methodology

~~“...capsules or suspension formulation based on age and weight.”~~

Subject Participation

~~... up to 40~~ **32** days.

- Up to ~~40~~ **32** days of adverse event (AE and serious AE (SAE) monitoring (~~36~~ **28** ...

Exclusion Criteria

8...In addition, the following drugs may not be co-administered with solithromycin in this trial due to the potential for adverse drug-drug interaction: digoxin, colchicine, midazolam, quinidine, ergotamine, dihydroergotamine, **rivaroxaban, apixaban, dabigatran, edoxaban**, cisapride, cyclosporine, sildenafil, astemizole, and alfentanil.

Test Product

Dose and Mode of Administration: Solithromycin will be administered IV or PO according to the tables below. **If dosing begins with oral therapy, the Day 1 dose will be a loading dose. No loading doses are used with IV solithromycin administration or if switched to oral administration.** ~~Note that oral dosing, either as initial exposure to solithromycin with capsules or suspension or as follow-on therapy to prior IV dosing, is initiated with a single (PO) loading dose. An IV-to-PO switch can occur after the first IV dose. No loading doses are used with IV solithromycin administration.~~ Subjects starting with oral therapy will receive 5 to 7 days of solithromycin treatment and those starting with IV therapy (regardless of if and when they switch to oral therapy) will receive 5 to 7 days of solithromycin treatment.

Age (years)	Route	Formulation	Loading dose (Max dose: 800 mg) ^a	Daily maintenance dose (Max dose: 400 mg) ^a
12 to 17	PO	Capsules ^b	800 mg	400 mg
12 to 17	PO	Suspension	TBD	TBD
12 to 17	IV	Solution	No loading dose	6 mg/kg
6 to <12	PO	Capsules ^b	TBD	TBD
6 to <12	PO	Suspension	TBD	TBD
6 to <12	IV	Solution	No loading dose	7 mg/kg
2 to <6	PO	Suspension	TBD	TBD
2 to <6	IV	Solution	No loading dose	TBD
2 mo to <2	PO	Suspension	TBD	TBD
2 mo to <2	IV	Solution	No loading dose	TBD

a. The maximum oral loading dose is 800 mg, and the maximum IV or oral maintenance dose is 400 mg.

b. The capsule dose is rounded upwards to the nearest 200 mg.

c. The adult dose should be administered unless the subject weighs <40 kg, in which case they receive 20 mg/kg on Day 1 and 10 mg/kg on Days 2-5. Minimum weight for using capsules is 60 kg. All smaller subjects should receive suspension if dosing orally.

Capsule Dosing Regimens

Age (years)	Weight	Route	Formulation	Day 1 (Max dose: 800 mg)	Days 2 to 5 (Max dose: 400 mg)
6 to 17	>30 kg	PO	Capsules	800 mg	400 mg
	>20 to 30 kg	PO	Capsules	600 mg	400 mg
	≤20 kg	PO	Capsules	400 mg	200 mg

Suspension Dosing Regimens

Age (years)	Route	Formulation	Day 1 (Max dose: 800 mg)	Days 2 to 5 (Max dose: 400 mg)
12 to 17	PO	Suspension	20 mg/kg (800 mg)	10 mg/kg (400 mg)
6 to <12	PO	Suspension	20 mg/kg	10 mg/kg
2 to <6	PO	Suspension	20 mg/kg	10 mg/kg
2 mo to <2	PO	Suspension	20 mg/kg	10 mg/kg

Intravenous Dosing Regimens

Age (years)	Route	Formulation	Days 1 to 7 (Maximum dose: 400 mg)
12 to 17	IV	Solution	8 mg/kg
6 to <12	IV	Solution	8 mg/kg
2 to <6	IV	Solution	8 mg/kg
2 mo to <2	IV	Solution	8 mg/kg

Intravenous to Oral Dosing Regimens

Age (years)	Route	Oral Formulation	Day 1 to Last IV Dosing Day (Max dose: 400 mg)	First Oral Dosing Day to Day 7 (Max dose: 400 mg) ^a
12 to 17	IV/PO	Suspension or Capsules	8 mg/kg	10 mg/kg (400 mg)
6 to <12	IV/PO	Suspension or Capsules	8 mg/kg	10 mg/kg
2 to <6	IV/PO	Suspension	8 mg/kg	10 mg/kg
2 mo to <2	IV/PO	Suspension	8 mg/kg	10 mg/kg

a. The adult dose should be administered unless the subject weighs <40 kg, in which case they receive 10 mg/kg on the first oral dosing day through Day 7. The capsule dose is rounded upwards to the nearest 200 mg.

Comparator Therapy

Addition of expanded gram-positive coverage to treatment and comparator groups will be allowed if empiric therapy for methicillin-resistant *Staphylococcus aureus* is desired per local standard of care. Oral step-down therapy should be informed by antimicrobial testing.

Pharmacokinetics:

The table below provides the optimal plasma sampling collection windows for solithromycin according to route of administration. Every effort should be made to collect at least 2 PK samples on Day 1 and at least 2 PK samples on days 3 through 7 during these windows (not to exceed 6 samples total); however, samples obtained outside of the sampling windows are acceptable and will not be considered protocol deviations.

Lack of collection of samples will also not be considered protocol deviations.

Statistical Methods and Data Analysis

... changes in study drug dosing, relationship to study drug, and outcome. Laboratory determinations performed by local laboratories including hematology values (hemoglobin, hematocrit, WBC count ***and differential, and*** platelet count, ~~and differential~~) and serum chemistry values ...

... Population PK methodologies using nonlinear mixed effects modeling in NONMEM will be used to analyze the concentration data. ***Data will be reviewed during the study to evaluate PK of solithromycin in pediatric CABP patients.***

Added footnote 'i', changed the 36 day follow-up visit to a 28 day follow-up visit, and added liver enzymes and a white blood cell count with differential to all visits in Table 1 Schedule of Assessments

5 INTRODUCTION

... The PK of both intravenous (IV) and oral solithromycin in adolescents and children ~~is currently under investigation~~ ***has been investigated.*** In both the completed and ongoing PK studies of solithromycin in adolescents and children ...

5.2.2.2.5 Pediatric Subjects

Solithromycin PK in adolescents (12 to <17 years) and children (<12 years) following oral (capsules, suspension) and intravenous administration was further investigated in a phase 1, open-label, multi-center study (protocol CE01-120). ***As of July 31, 2016, 10 patients aged 12 to 17 years (all received IV solithromycin), 33 patients 6 to <12 years (8 IV, 9 oral capsules and 16 oral suspension), 15 patients 2 to <6 years (8 IV and 7 oral suspension) and 23 patients <2 years (8 IV and 15 oral suspension) have been enrolled. Population pharmacokinetic modeling was used to determine the dosing regimens for oral and intravenous dosing from the data collected.*** Intravenous data collected in this study supported the use of a 6 and 7 mg/kg intravenous daily dose (no loading dose required) in adolescents (12 to <17 years) and children (6 to <12 years), respectively. These doses resulted in a median (range) Day 3-5 C_{max} and AUC_{0-24} of 2.3 µg/mL (1.2-7.7) and 12.3 µg*h/mL (8.2-19.9) in adolescents, and 2.8 µg/mL (1.0-8.1) and 10.6 µg*h/mL (2.7-18.4) in children, respectively. These estimates are comparable to adult median (range) values of 2.7 µg/mL (2.1-3.5) for C_{max} and 13.7 µg*h/mL (6.1-22.3) following 400 mg of daily dosing.

5.2.3 Summary of Efficacy

Three randomized, double-blind efficacy studies in CABP with oral solithromycin have been completed. One open-label efficacy study in GC with single dose oral solithromycin has been completed.

The Phase 2 oral CABP study (CE01-200) compared 5-day regimens of solithromycin (800 mg×1 on Day 1 followed by 400 mg QD on Days 2-5) and levofloxacin (750 mg QD Days 1-5). One hundred thirty-two patients were enrolled and randomized (1:1) to solithromycin or

levofloxacin. A total of 132 patients were randomized; 65 were randomized to receive solithromycin and 67 were randomized to receive levofloxacin.

In the ITT population at TOC, clinical success was observed in 55 (84.6%) patients randomized to receive solithromycin and 58 (86.6%) patients randomized to receive levofloxacin. In the CE population, clinical success was observed in 46 (83.6%) patients who received solithromycin and 54 (93.1%) patients who received levofloxacin. Early clinical success at Day 3 (according to the proposed Biomarkers Consortium criteria) was observed for 47 (72.3%) and 48 (71.6%) patients in the solithromycin and levofloxacin groups, respectively.

~~Phase 2 studies have been conducted in CABP and uncomplicated urogenital gonorrhea. A global, randomized, double-blind phase 3 study in CABP subjects has been successfully completed. A second phase 3 study has completed enrollment; data analysis is pending. A phase 3 study in gonorrhea is also currently enrolling.~~

~~Solithromycin demonstrated 100% efficacy in a phase 2 trial that evaluated single oral doses (1000 mg and 1200 mg) for treatment of uncomplicated gonorrhea, as evidenced by positive gonorrhea cultures (GCs) at baseline, with negative cultures at 1-week follow-up.~~

~~Solithromycin demonstrated comparable efficacy and safety to oral levofloxacin in a phase 2 CABP trial.~~

The Phase 3 CABP Studies CE01-300 and CE01-301, were randomized, double-blind, active-controlled, multi-center, non-inferiority studies with moxifloxacin as the active comparator.

In the oral Study CE01-300, the dosing regimen of solithromycin evaluated was 800 mg as a single 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 in CE01-300 was 400 mg QD on Days 1 through 7.

In the IV to oral Study CE01-301, all patients in both treatment groups received IV treatment on Day 1. Patients continued on IV treatment during the 7-day treatment course until predefined oral switch criteria related to clinical improvement were met and the Investigator felt it was appropriate to transition the patient to oral drug. Patients remained on IV treatment for the full 7 days if they did not meet the oral switch criteria or at the Investigator's discretion. The dosing regimen, whether IV to oral or IV only was 7 days. Patients randomized to solithromycin received 400 mg IV as a single dose on Day 1 and on all subsequent IV dosing days. For patients who transitioned to oral treatment in the solithromycin group, the first oral dose of solithromycin following IV therapy was 800 mg administered as a single dose, followed by 400 mg oral QD for the remainder of the study drug administration period. Moxifloxacin was administered as a 400 mg QD dose whether it was an IV or oral dosing day.

Solithromycin demonstrated non-inferiority to moxifloxacin in the treatment of CABP in each Phase 3 study.

5.2.3.1 Primary Efficacy Outcome: Early Clinical Response (ECR)

Table 6-15 provides a summary of the primary efficacy outcome, ECR in the ITT population, in the individual and pooled Phase 3 CABP studies. ECR was defined as improvement at 72 hours (Day 4) after the first dose of study drug in at least 2 of the following 4 cardinal symptoms of CABP: cough, dyspnea/shortness of breath, chest pain due to pneumonia and difficulty with sputum production.

Solithromycin and moxifloxacin ECR responder rates in the ITT population were similar in each Phase 3 study and in the pooled studies, approximately 78 to 79% of patients. Solithromycin was non-inferior to moxifloxacin for the ECR outcome in each study and in the pooled studies. The lower limit of the 95% confidence interval (CI) around the treatment difference in responder rates (solithromycin minus moxifloxacin) was greater than the prespecified NI boundary of -10%.

Table 4 Primary Efficacy Outcome: Early Clinical Response in Individual Phase 3 Studies and Pooled Studies

Early Clinical Response	Study CE01-300		Study CE01-301		Pooled Phase 3 Studies	
	Solithromycin Oral (N=425) n (%)	Moxifloxacin Oral (N=431) n (%)	Solithromycin IV to Oral (N=434) n (%)	Moxifloxacin IV to Oral (N=429) n (%)	Solithromycin Pooled (N=859) n (%)	Moxifloxacin Pooled (N=860) n (%)
Responder	332 (78.1)	336 (78.0)	344 (79.3)	342 (79.7)	676 (78.7)	678 (78.8)
Difference (95% CI)	0.16 (-5.6,5.9)		-0.46 (-6.1,5.2)		-0.16 (-4.0,3.7)	
Nonresponder	93 (21.9)	95 (22.0)	90 (20.7)	87 (20.3)	183 (21.3)	182 (21.2)
Nonresponder	81 (19.1)	83 (19.3)	76 (17.5)	78 (18.2)	157 (18.3)	161 (18.7)
Indeterminate	12 (2.8)	12 (2.8)	14 (3.2)	9 (2.1)	26 (3.0)	21 (2.4)

Source Data: pooled CE01-300 and CE01-301 data

CI=confidence interval; N=number of patients in the ITT population; n=number of patients within a specific category.

Notes: The time window for determining early clinical response was 72h -12/+36h for CE01-300 and 72h -13/+36h for CE01-301). Difference=For studies CE01-300 and CE01-301, difference in responder rates (solithromycin minus moxifloxacin). For the pooled Phase 3 studies, the weighted (by study) difference in responder rates is presented. Percentages were calculated as 100 x (n/N). For studies CE01-300 and CE01-301, the CI was calculated using an unadjusted continuity corrected Z-test. For the pooled Phase 3 studies, the CI was stratified (for study) and calculated using the method of Miettinen and Nurminen with the inverse variance of the difference used as stratum weights. Per the ISE SAP, patients from Site 710 in Study 300 were excluded from all pooled results, unless otherwise noted.

ECR in the clinically evaluable (CE-ECR) population in each study was consistent with the results observed for the primary efficacy analysis in the ITT population. In the pooled studies, the ECR responder rates in the CE-ECR population were 81.5% in the solithromycin group compared with 82.0% in the moxifloxacin group. Consistent results were observed in each study.

In subgroup analyses in the ITT population, a consistent effect was observed for ECR responder rates by geographic region and in demographic subpopulations, e.g., age, weight, gender and ethnicity.

Subpopulation analyses were also conducted for characteristics related to baseline disease severity. Responder rates and treatment differences were consistent in analyses of patients classified as PORT II (treatment difference: 1.14; 95% CI: -5.1, 7.3) or PORT III/V (treatment difference: -0.93; 95% CI: -5.9, 4.0). No differences in responder rates were noted based upon prior history of asthma/COPD or receipt a single dose of a short-acting antibiotic within 7 days prior to randomization.

A phase 3 study (Study CE01-300) of the efficacy and safety of oral solithromycin for treatment of moderate-to-moderately severe CABP (Pneumonia Patient Outcomes Research Team [PORT] II-IV classification) in comparison with oral moxifloxacin has been completed. In this double-blind, randomized controlled trial, subjects were randomized 1:1 to receive oral solithromycin (single 800 mg dose on Day 1, followed by 400 mg once daily on Days 2 through Day 5 (total duration of dosing 5 days) or oral moxifloxacin, 400 mg once daily, Days 1 through Day 7 (total duration of dosing, 7 days), with evaluations at Baseline, Day 4 to assess early clinical response (ECR), Day 7, Days 12–17 (short term follow-up [SFU] visit), and Day 28 (long term follow-up). An ECR was defined as improvement in at least 2 of 4 cardinal symptoms (cough, chest pain, dyspnea, sputum production) without worsening in any. Success at SFU was determined by investigators. Primary objectives were demonstration of non-inferiority (10% NI margin) at ECR in the intent-to-treat (ITT) population (Food and Drug Administration [FDA] guidance) and at SFU in the ITT and clinically evaluable (CE) populations (European Medicines Agency guidance).

Eight hundred and sixty subjects from 16 countries were randomized (ITT population); 856 received at least 1 dose of study drug (safety population), 426 received solithromycin. Among all subjects, 90% met key study inclusion and exclusion criteria without confounding diagnoses and within pre-specified protocol windows for follow-up (CE population). The mean age of solithromycin subjects was 58.5 years, with 36.4% \geq age 65, versus 56.7 years with 31.6% \geq age 65 for moxifloxacin.

Solithromycin was non-inferior to moxifloxacin in the ITT in ECR (78.2 versus 77.9%) and SFU success (84.5 versus 86.6%) and in the CE SFU success (88.1 versus 91.3%). Comparative ECR success for solithromycin was more favorable among the pre-defined subgroup of subjects \geq age 75 (83.9 vs 69.8%). Solithromycin demonstrated comparable safety to moxifloxacin in the occurrence of AEs (36.6 versus 35.6%), study drug-related AEs (10.1 versus 12.5%), SAEs (6.6 versus 6.3%; none attributed to study drug) and deaths (1.4 in both groups). Grade 4 ALTs ($>8 \times$ upper limit of normal [ULN]) were observed in 5 moxifloxacin subjects and 2 solithromycin subjects. Two episodes of *Clostridium difficile* diarrhea were diagnosed, both in moxifloxacin recipients.

Final efficacy results from 2 phase 3 trials: 1) IV to oral solithromycin (versus moxifloxacin) in CABP, and 2) Single-dose oral solithromycin for uncomplicated genitourinary gonococcal infection (versus intramuscular ceftriaxone + oral azithromycin) are pending.

5.2.4 Summary of Safety

As of 30 April 2016, more than 2000 subjects and patients received systemic exposure to solithromycin. The major source of safety data are the two Phase 3 pivotal studies in patients with CABP (n=856).

5.2.4.1 Overview of Adverse Events

Macrolides, as a class, are well-tolerated and widely utilized. The most common AEs reported with the use of existing macrolides are GI, such as diarrhea, nausea and vomiting; others include headache and dizziness.

Oral solithromycin has been well tolerated, the most common AEs being mild GI events in Phase 1 and 2 trials. The most common AEs in the Phase 1 IV trials were related to infusion site tolerability; there were no other unique AEs relative to events reported in oral trials.

Infrequent reports of local and systemic allergic reactions have occurred with oral and IV solithromycin, including anaphylaxis, urticaria, erythema and maculopapular rashes.

The AE profile of the 5-day CABP regimen compared favorably with that of levofloxacin in the Phase 2 CABP trial. In the Phase 3 oral CABP study, solithromycin demonstrated a similar AE profile to that of moxifloxacin. In the Phase 2 GC study, the most common AEs were mild GI disorders, primarily diarrhea and nausea. Although both doses were acceptably tolerated, treatment-related GI AEs occurred less frequently with the 1000 mg dose than with 1200 mg.

In the Phase 3 oral CABP study, 6 (1.4%) patients in the solithromycin group and 6 (1.4%) patients in the moxifloxacin group died during the study. None of the SAEs resulting in death was considered related to study drug. A total of 28 (6.6%) patients in the solithromycin group and 27 (6.3%) patients in the moxifloxacin group reported at least 1 non-fatal SAE. No patient in either treatment group had an SAE that was considered related to study drug. The most common AEs observed in patients receiving solithromycin were headache (4.5%) and diarrhea (4.2%).

In the Phase 3 IV to oral CABP study, 5 (1.2%) patients in the solithromycin group and 7 (1.6%) patients in the moxifloxacin group died during the study. None of the SAEs resulting in death was considered related to study drug. A total of 30 (6.9%) patients in the solithromycin group and 2 (5.4%) patients in the moxifloxacin group reported at least 1 non-fatal SAE. Only 3 SAEs were considered related to study drug by the investigators (urticaria and anaphylactic reaction in 1 patient each in solithromycin and anaphylactic reaction in 1 moxifloxacin patient). The most frequently reported infusion site related TEAEs were infusion site pain (10.4%), infusion site phlebitis (10.0%) and infusion related reaction (6.5%). Infusion site related TEAEs were mostly mild or moderate in intensity and infrequently led to discontinuation of study drug or withdrawal from the study (in 1 moxifloxacin and 10 solithromycin patients). Apart from infusion site related events, the most common AEs observed in patients receiving solithromycin were diarrhea (5.9%) and headache (4.2%).

~~Overall, in the 13 oral Phase 1 studies, solithromycin was generally well tolerated in healthy adults when administered in single doses up to 1600 mg, in multiple doses of 200, 400, and 600 mg~~

administered QD for 7 days; in multiple doses of 400 mg administered QD for 5 days; as a loading dose regimen of 800 mg on Day 1 followed by 400 mg QD on Days 2 to 5; and when co-administered with digoxin (a P-gp substrate), and when co-administered with a CYP3A4 substrate (midazolam), inhibitor (ketoconazole), or inducer (rifampin). The most common AEs were GI disorders (primarily mild diarrhea and nausea) and nervous system disorders (primarily headache and dysgeusia). Most AEs were mild in severity.

In initial IV phase 1 studies (CE01-104, CE01-116 and CE01-118), the most common AEs reported after single IV doses were general disorders and administrative site conditions (infusion-related pain) followed by nervous system disorders (headache, dysgeusia), with the majority mild in severity.

One subject who received 800 mg IV for 3 days in study CE01-116 had a marked ($8\times\text{ULN}$) ALT elevation. One subject in a phase 1 IV study designed to reach the maximally tolerated dose (CE01-116) had a clinically significant ALT elevation to $8\times\text{ULN}$ after receiving 3 daily doses of 800 mg IV. Across all 3 completed IV studies, 8 other subjects had Grade 1 elevations in ALT ($<2\times\text{ULN}$) and 1 had a Grade 2 elevation of ALT to $2.4\times\text{ULN}$ (1 received multiple 200mg doses, and 7 received multiple 400mg doses). These 9 subjects' ALT elevations were asymptomatic, transient, reversible, and not associated with bilirubin elevation. The subject with the marked ALT elevation had notable drug accumulation with high solithromycin plasma concentrations ($5\text{--}8\text{ }\mu\text{g/mL}$); exposures of this magnitude have not been reached in any study with oral solithromycin and are not expected with 400mg IV infusions.

Study CE01-121 evaluated a single vial formulation of solithromycin, containing 400 mg solithromycin lyophilized with 3 amino acids as buffering agents. Both central and peripheral venous administration of multiple 400mg daily doses for 7 days were assessed, and 2 peripheral infusion durations, 30 and 60 minutes, were tested.

Forty subjects were enrolled (30 solithromycin/ 10 placebo). Twenty subjects received multiple doses (7 daily doses) of 400 mg via a peripheral IV line, and 5 received 7 daily doses of 400 mg via PICC. Five subjects received a single 800mg IV dose of solithromycin given over 40 minutes to evaluate the safety of supratherapeutic plasma concentrations.

Infusion-site pain was the most common AE reported. Seven subjects discontinued the study drug or the study due to infusion-related AEs (6 subjects due to infusion-site pain and 1 subject due to phlebitis). Adverse events appeared to be correlated with the duration of multiple dosing.

Five of 25 subjects receiving multiple 400mg doses of solithromycin had 1.1 to $<2\times\text{ULN}$ elevations in ALT, and 2 subjects had 1.1 to $<2\times\text{ULN}$ elevations in AST. A $4.5\times\text{ULN}$ AST elevation (173 U/L) was observed on Day 12 in a subject who received 6 daily doses of 400 mg solithromycin infused peripherally over 60 minutes. It had declined on Day 15 and returned to a normal level (28 U/L) on Day 36.

One subject (PICC line cohort) had a $1.8\times\text{ULN}$ total bilirubin elevation, mildly elevated AST ($1.2\times\text{ULN}$), and elevated direct bilirubin ($1.5\times\text{ULN}$) on Day 12. This subject had an elevated total bilirubin ($1.2\times\text{ULN}$) at baseline, and at discharge (Day 9) had a normal ALT, AST, total bilirubin, and direct bilirubin.

Two of the 5 subjects who received a single 800 mg dose solithromycin over 40 minutes experienced an AE. The most common AE was infusion-related pain. One subject receiving solithromycin had a 1.1 to $<1.5 \times \text{ULN}$ elevation of direct bilirubin.

In the phase 2 CABP study (CE01-200), solithromycin was administered to 64 adult subjects as a loading dose of 800 mg on Day 1 followed by 400 mg QD on Days 2 to 5. The percentage of subjects who experienced ≥ 1 treatment-emergent AE (TEAE) during the study was 29.7% in the solithromycin group and 45.6% in the levofloxacin (comparator) group. The majority of AEs were GI disorders and of mild or moderate intensity. The most frequently reported GI AEs with solithromycin were diarrhea (7.8%) and nausea (1.6%). Two subjects randomized to solithromycin in this study had SAEs, neither attributed to study drug (1 elderly subject with multiple medical sequelae following a fall with humerus fracture and a second subject with persistent chest pain requiring hospitalization). There was 1 death in the study, a subject randomized to receive levofloxacin, who died with pulmonary embolism.

In the phase 2 GC study, 59 adult subjects received a single dose of 1200 or 1000 mg solithromycin. Mild diarrhea and nausea were the most commonly reported AEs and were less frequent after the 1000mg dose.

In the phase 3 oral CABP study (CE01-300), solithromycin was administered to 424 adult subjects (among 860 enrolled) as a loading dose of 800 mg on Day 1, followed by 400 mg QD on Days 2 through Day 5. The percentage of subjects who experienced ≥ 1 TEAE during the study was 36.6% in the solithromycin group and 35.6% in the moxifloxacin (comparator) group. The most commonly reported AE was headache, occurring in 4.5% of solithromycin recipients (and in 2.5% of moxifloxacin recipients), of mild severity in the majority. Gastrointestinal AEs were also common, with diarrhea, nausea, and emesis reported by 4.2, 3.5 and 2.4% of solithromycin recipients, respectively. Diarrhea and nausea were more commonly reported by moxifloxacin recipients, while emesis was reported by 10 subjects in each arm of the trial. These GI disorders were of mild or moderate intensity, and were rarely treatment limiting. Serious AEs were reported for 6.6% of solithromycin recipients (and 6.3% of moxifloxacin recipients). None was considered study drug related. Among these SAEs, a wide range of medical outcomes anticipated during or following an episode of pneumonia were observed, including acute myocardial infarction, congestive heart failure, empyema, cerebrovascular accident, renal dysfunction, and respiratory failure. In addition, conditions which mimicked pneumonia (resulting in the subject's enrollment) were also reported as SAEs, including pulmonary malignancy and tuberculosis. The mortality rate in both arms of the study was 1.4%, an overall figure below that which would be predicted by the PORT score profile of the study population.

In the phase 3 IV to oral CABP study (CE01-301), solithromycin was administered in daily IV doses of 400 mg. When clinical stability is achieved, subjects could switch to oral solithromycin dosing, receiving an initial dose of 800 mg on the first oral dosing day, followed by oral dosing with 400 mg each day. The total duration (by IV or IV/oral dosing) of treatment was 7 days. This study has been completed and unblinded. However, at this time, data are currently being analyzed and all results would be considered preliminary.

Solithromycin, like most antibiotics and like all macrolide antibiotics, has been associated with hepatic aminotransferase elevations. In the pooled Phase 3 CABP trials, ALT elevations to $>3\times\text{ULN}$, $>5\times\text{ULN}$ and $>10\times\text{ULN}$ were seen in 7.2%, 2.4% and 0.1% of solithromycin recipients compared to 3.6%, 1.0% and 0.2% of moxifloxacin recipients. Elevations of ALT to $>3\times\text{ULN}$ were 5.4% in the oral study and 9.1% in the IV to oral study. These elevations were typically asymptomatic, not associated with bilirubin elevation and readily reversible, with improvement in many cases seen during continued dosing. There have been no Hy's Law cases.

Multiple lines of evidence point to an exposure-response relationship for ALT elevation with increasing solithromycin exposure.

In the pooled Phase 3 CABP studies, rates of bilirubin elevation to levels $>\text{ULN}$ were comparable between solithromycin and moxifloxacin (4.3% vs 4.0%, respectively), and elevations $>2\times\text{ULN}$ were uncommon ($<0.5\%$) in both treatment groups. Solithromycin was more frequently associated with alkaline phosphatase elevation to $>1.5\times\text{ULN}$ than moxifloxacin (5.2% versus 2.9%, respectively), consistent with the potential to induce mild degrees of cholestasis, as has been observed with older macrolides and other antibiotics.

Solithromycin was generally well tolerated in subjects with cirrhosis of Child Pugh Class A, B and C severity in a controlled Phase 1 trial. In the Phase 3 CABP studies, the overall incidence of AEs was similar among subjects with and without hepatic impairment. ALT elevation to $>5\times\text{ULN}$ occurred with identical frequency among patients with and without hepatic impairment (2.4%), and AST elevation $>5\times\text{ULN}$ occurred in 1 patient with baseline hepatic impairment.

Analysis of ALT elevation by patient characteristics including age, sex, race, history of chronic liver disease and concomitant exposure to statins have not revealed a population at particular risk for these events.

While solithromycin can cause asymptomatic, reversible ALT elevation and mild degrees of cholestasis, the overall liver safety profile of clinically important events was comparable to moxifloxacin and may be comparable to the older macrolides.

When solithromycin is taken for longer than 7 days, rare cases of jaundice and itching have occurred. These events were reversible after solithromycin treatment was stopped.

~~Hepatic transaminase elevations have been commonly observed with macrolides, and reports of cholestatic hepatitis (generally reversible) and rarely, hepatic failure, have been reported after their use.~~

~~The most extensive subject experience with solithromycin dosing has been obtained from the phase 3 oral CABP trial (CE01-300). ALT elevation (of any grade, $>1.1\times\text{ULN}$) occurred in 123 subjects (29%). Grade 1 ($1.1\times\text{ULN}$ to $<2.0\times\text{ULN}$) and grade 2 ($2.0\times\text{ULN}$ to $<3.0\times\text{ULN}$) comprised the majority of these episodes (102/424, 24.5%). Nineteen subjects (4.6%) had grade 3 elevation ($3.0\times\text{ULN}$ to $<8.0\times\text{ULN}$) of ALT, and 2 subjects (0.5%) had grade 4 ALT elevation ($>8.0\times\text{ULN}$). In the 2 grade 4 ALT elevation episodes, there was evidence of cholestasis (with elevated ALP), without elevation of bilirubin. No subject had treatment-emergent ALT and bilirubin elevation consistent with Hy's Law criteria, and there was no evidence of hepatic~~

~~synthetic dysfunction in any subject. Across all studies, there have been no cases of concomitant bilirubin and hepatic transaminase elevations meeting Hy's Law criteria, including in the ongoing IV to oral phase 3 CABP trial (data not summarized herein, as the study remains blinded).~~

~~Macrolides have been associated with QT prolongation and risk for torsades de pointes. In March 2013, the U.S. FDA warned the public that azithromycin may cause fatal heart rhythm disturbances. Unlike the older macrolides, however, solithromycin does not prolong the QT interval (as summarized in Section 5.2.2.2).~~

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. A thorough QT study of solithromycin was negative, demonstrating that solithromycin does not have a propensity to prolong the QT interval in a clinically significant manner in healthy subjects.

In the pooled Phase 3 CABP studies, cardiac AEs were observed more frequently in moxifloxacin recipients (4.7%) than solithromycin recipients (3.0%). Most of these events reflected the underlying chronic diseases of enrolled patients in the context of the severe physiologic stress of CABP and were not considered study drug related.

The thorough QT study revealed that healthy subjects with supratherapeutic exposure to solithromycin experience an increase in heart rate. The exact mechanism for this effect is unknown, although a variety of receptors and cardiac channels have been evaluated in vitro. However, in the Phase 3 studies, the central tendency for observed heart rate was a decline from baseline over time comparable to that observed with moxifloxacin, as the physiologic stressors of CABP diminished with response to therapy. Fewer patients receiving solithromycin than moxifloxacin experienced a potentially clinically significant tachycardia (> 120 bpm) that was associated with an increase over baseline of ≥ 15 bpm (1.3% and 1.8%, respectively).

In the Phase 3 studies, categorical changes from baseline in the QTcF interval of > 30 msec occurred less frequently with solithromycin (16.7%) than with moxifloxacin (28.0%). Post-baseline changes resulting in a QTcF > 500 msec occurred in $< 1\%$ of patients in both treatment groups. Based on these data and the results of the thorough QT study, it is clear that solithromycin does not present intrinsic QT prolongation risks. However, as a CYP3A4 inhibitor, solithromycin may pose secondary risk of QT prolongation through inhibition of metabolism of other QT-prolonging drugs.

~~A plasma concentration effect analysis of data from the TQT study showed that the increase in heart rate was concentration dependent. An effect on heart rate with the IV, IV/oral, and therapeutic regimens planned for CABP would be expected to be modest. In subjects with CABP, who may have an elevated baseline heart rate associated with their infection and other physiologic stressors, mean heart rate has declined with solithromycin therapy. In study CE01-300, among solithromycin-treated subjects, mean heart rate at baseline was 90.1 bpm, with decreases from baseline on Days 2, 4, and 7 of 9.0, 8.0, and 10.1 bpm. In contrast, among moxifloxacin-treated subjects, mean heart rate at baseline was 93.2 bpm, with mean decreases on these days of 13.9, 14.1, and 14.2 bpm. Reported AEs associated with elevated heart rate (including the terms: sinus tachycardia, supraventricular tachycardia, tachycardia, and atrial fibrillation) occurred in $< 1.0\%$ of solithromycin recipients.~~

~~Solithromycin does not contain a pyridine moiety in its side chain, unlike telithromycin. The pyridine moiety has been shown to significantly inhibit nicotinic acetylcholine (nACh) receptor subtypes in vitro. This inhibition may be associated with certain AEs observed with telithromycin that are unusual for the macrolide class. All solithromycin clinical studies will continue to carefully monitor for these atypical AEs, and subjects with known myasthenia gravis will continue to be excluded from clinical studies.~~

5.4 Rationale for Dosing Regimen

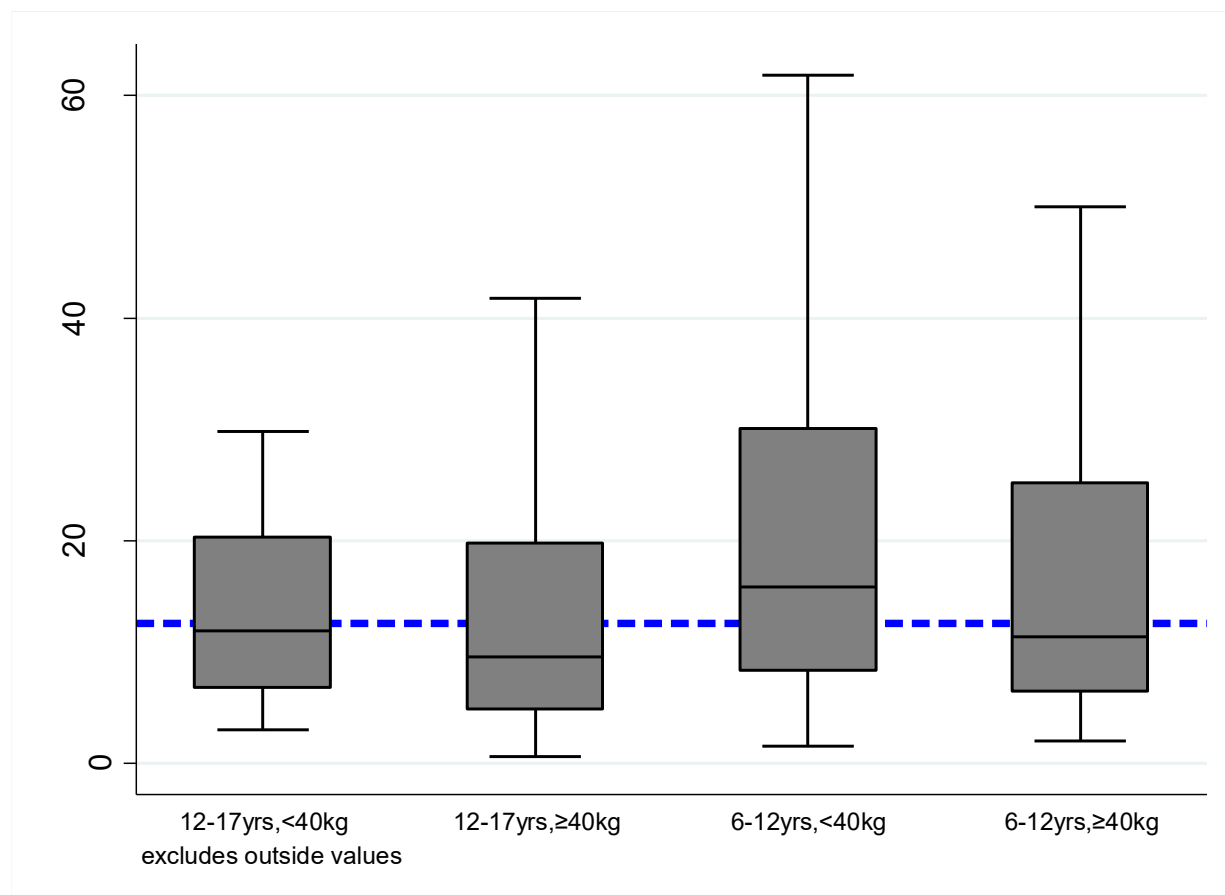
... The dosing regimens for each age group and each of the 3 formulations (capsule, IV infusion, and suspension) ~~are being~~ *were* determined in phase 1 studies in children.

~~To date, data are available from phase 1 pediatric studies (CE01-119 and CE01-120) to identify optimal dosing following capsule and intravenous solithromycin administration in adolescents 12 to 17 years of age and children 6 to <12 years of age. As noted in Section 5.2.2.2 and Table 2 above, data from 13 adolescents receiving capsule administration demonstrated that >90% of adolescents achieved therapeutic exposures, and that PK estimates were in the range of observed adult values following an the recommended adult regimen (800 mg Day 1, 400 mg on Days 2-5). In this adolescent PK study, the majority of subjects received the recommended adult regimen, with variable exposure estimates and safety profile.~~

Data from two phase 1 studies in children (N=92) were merged and used to develop a population PK model that informs dosing for this study for all formulations. A two compartment model with linear elimination characterized the solithromycin data following both oral (capsule and suspension) and intravenous administration. To account for the growth effects, actual body weight was included in the model using allometric scaling. Using the final model, Monte Carlo simulations were performed to identify pediatric dosing that matches adult exposure (area under the concentration versus time curve from 0 to 24 hours and maximal drug concentrations after multiple doses) observed in the phase 3 program.

The selected dosing regimen for adolescents (12-17 years) receiving solithromycin via oral administration (capsules or suspension) was 800 mg on Day 1 and 400 mg on Days 2-5 if they weight ≥ 40 kg. For subjects 12 to 17 years and < 40 kg, a capsule dosing regimen of 20 mg/kg on Day 1 (800 mg maximum) and 10 mg/kg on Days 2-5 (400 mg maximum) was selected based on simulated exposure (Figure 2). Suspension dosing for adolescents was selected based on data obtained from a bioequivalence study in adults between capsules and suspension and the similar bioavailability estimates obtained for both formulations in the population PK model.

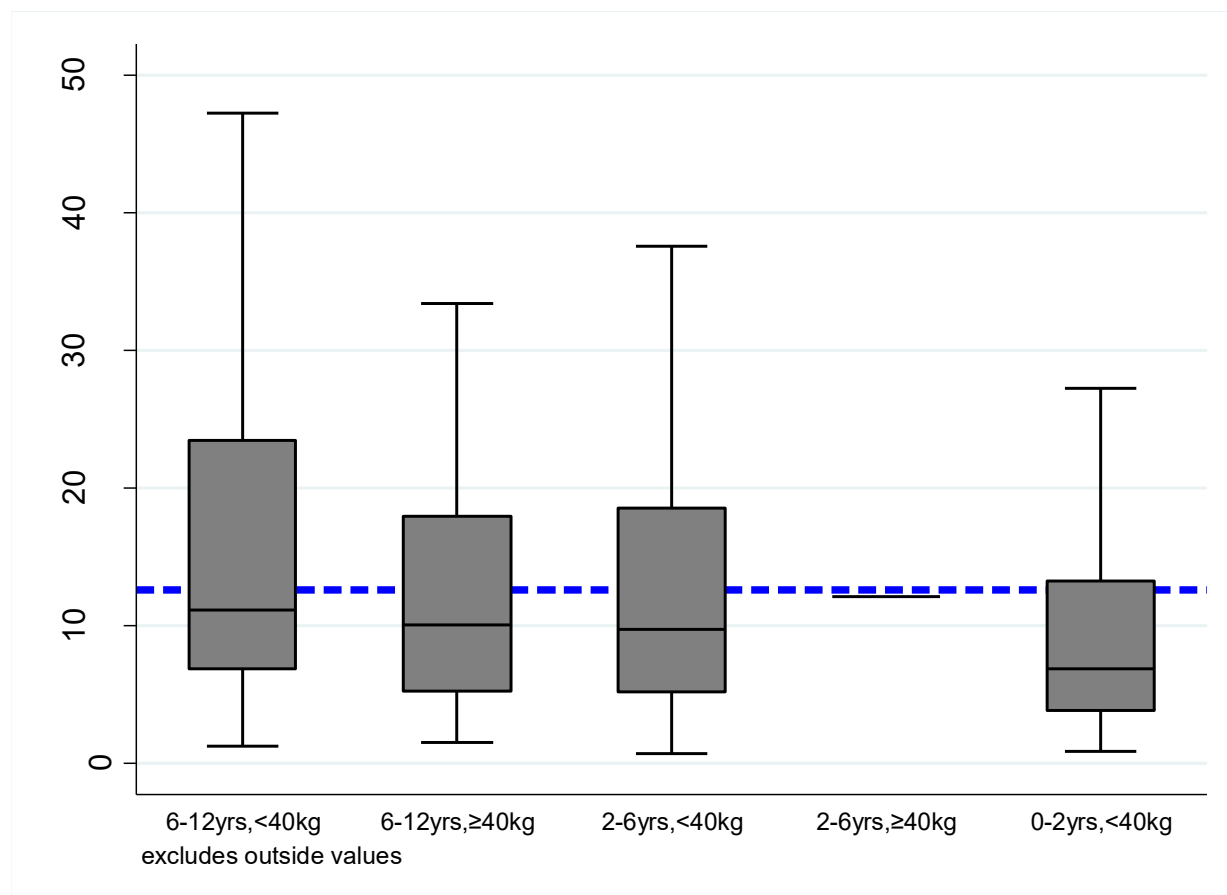
Figure 2 **Simulated Day 5 Exposure following a capsule dose of 20 mg/kg on Day 1 and 10 mg/kg on Days 2-5**



Note: Doses rounded upward to the nearest 200 mg. The dashed line represents an adult Day 4 AUC_{0-24} of 12.6 mcg*h/mL.

For the suspension dosing for children <12 years of age, a dose of 20 mg/kg on Day 1 (800 mg maximum) and 10 mg/kg on Days 2-5 (400 mg maximum) resulted in a comparable simulated Day 5 AUC_{0-24} across pediatric age groups (Figure 3). Although the median simulated exposure appears to be lower in the 0-2 years age group, the simulated exposure was within the range observed in adults and it's possible that the observed values may be higher due to immature CYP3A4 metabolism in this age group.

Figure 3 Simulated Day 5 Exposure following a suspension dose of 20 mg/kg on Day 1 and 10 mg/kg on Days 2-5



Note: The dashed line represents an adult Day 4 AUC_{0-24} of 12.6 mcg*h/mL. There is only one subject in the 2-6 years ≥ 40 kg category

*Intravenous daily dosing of 8 mg/kg resulted in comparable simulated Day 5 AUC_{0-24} across all pediatric age groups: median (standard deviation) 14.4 mcg*h/mL (23.4) for 12-17 years; 14.1 mcg*h/mL (25.4) for 6-<12 years; 11.0 mcg*h/mL (26.0) for 2-<6 years; and 9.4 mcg*h/mL (19.1) for 0-<2 years. The adult exposure used for matching purposes was 12.6 mcg*h/mL. Then in the follow-up study, CE01-120, an intravenous dose of 6 mg/kg daily resulted in median (range) C_{max} and AUC_{0-24} estimates of 2.3 μ g/mL (1.2-7.7) and 12.3 μ g*h/mL (8.2-19.9), respectively, in six adolescents (12 to <17 years). In children (6 to <12 years), C_{max} and AUC_{0-24} estimates were 2.8 μ g/mL (1.0-8.1) and 10.6 μ g*h/mL (2.7-18.4) following 7 mg/kg daily dosing. These estimates are comparable to adult median (range) values of 2.7 μ g/mL (2.1-3.5) for C_{max} and 13.7 μ g*h/mL (6.1-22.3) following 400 mg of daily dosing. Data for younger age groups and oral formulations are in development.*

Because of the complete efficacy extrapolation approach to determination of efficacy in the pediatric population, the **duration of study** dosing drug regimens are similar to those in adults. Oral-only dosing is for 5 to 7 days, with a loading dose on the first day. Intravenous-only and IV-to-oral dosing are for 5 to 7 days **duration**, with a loading dose given the first day of oral dosing.

7.3 Study Drug Dosage and Administration

Solithromycin will be administered IV or PO according to Tables 4 **5 through 8** below. No loading doses are used with IV solithromycin administration **or if switched to oral administration**. An IV-to-PO switch can occur after the first IV dose. ~~Note that oral dosing either as initial exposure to solithromycin with capsules or suspension, or as follow on therapy to prior IV dosing, is initiated with a single (PO) loading dose.~~ Subjects starting with oral therapy will receive 5 ~~to 7~~ days of solithromycin treatment, and those starting with IV therapy (regardless of if and when they switch to oral therapy), will receive 5 ~~to 7~~ days of solithromycin treatment.

Table 4 Study Design by Age Group

Age (years)	Route	Formulation	Loading dose (Max dose: 800 mg) ^a	Daily maintenance dose (Max dose: 400 mg) ^a
12 to 17	PO	Capsules ^b	800 mg	400 mg
12 to 17	PO	Suspension	TBD	TBD
12 to 17	IV	Solution	No loading dose	6 mg/kg
6 to <12	PO	Capsules ^b	TBD	TBD
6 to <12	PO	Suspension	TBD	TBD
6 to <12	IV	Solution	No loading dose	7 mg/kg
2 to <6	PO	Suspension	TBD	TBD
2 to <6	IV	Solution	No loading dose	TBD
2 mo to <2	PO	Suspension	TBD	TBD
2 mo to <2	IV	Solution	No loading dose	TBD

a. The maximum oral loading dose is 800 mg, and the maximum IV or oral maintenance dose is 400 mg.

b. The capsule dose is rounded upwards to the nearest 200 mg.

c. The adult dose should be administered unless the subject weighs <40 kg, in which case they receive 20 mg/kg on Day 1 and 10 mg/kg on Days 2-5. Minimum weight for using capsules is 60 kg. All smaller subjects should receive suspension if dosing orally.

For subjects receiving the capsule formulation, 200 mg solithromycin capsules will be used to provide the absolute dose of either 200 mg, 400 mg or 800 mg. ***The capsule dose will be rounded upwards to the nearest 200 mg, not to exceed an 800 mg loading dose and 400 mg maintenance dose.*** Study drug should be swallowed with water approximately every 24 hours and at approximately the same time each day (±4 hours). Study drug can be taken without regard to food.

Table 5 Capsule Dosing Regimens

Age (years)	Weight	Route	Formulation	Day 1 (Max dose: 800 mg)	Days 2 to 5 (Max dose: 400 mg)
6 to 17	>30 kg	PO	Capsules	800 mg	400 mg
	>20 to 30 kg	PO	Capsules	600 mg	400 mg
	≤20 kg	PO	Capsules	400 mg	200 mg

Subjects requiring an oral dosage form other than capsules will receive suspension formulation, provided at 160 mg/5 mL and 320 mg/5 mL strengths, to achieve the age-appropriate mg/mL and solithromycin dose. ***Any dosing variations within 10% of the calculated suspension dose is not considered a deviation.***

Table 6 Suspension Dosing Regimens

Age (years)	Route	Formulation	Day 1 (Max dose: 800 mg)	Days 2 to 5 (Max dose: 400 mg)
12 to 17	PO	Suspension	20 mg/kg (800 mg)	10 mg/kg (400 mg)
6 to <12	PO	Suspension	20 mg/kg	10 mg/kg
2 to <6	PO	Suspension	20 mg/kg	10 mg/kg
2 mo to <2	PO	Suspension	20 mg/kg	10 mg/kg

No loading doses are used with IV solithromycin administration. Intravenous solithromycin should be infused over approximately 60 minutes (± 20 minutes) approximately every 24 hours (± 4 hours). Changes to the infusion duration should be discussed with the study medical monitor prior to study drug administration. *Any dosing variations within 10% of the calculated IV or suspension dose is not considered a deviation.*

Table 7 Intravenous Dosing Regimens

Age (years)	Route	Formulation	Days 1 to 7 (Maximum dose: 400 mg)
12 to 17	IV	Solution	8 mg/kg
6 to <12	IV	Solution	8 mg/kg
2 to <6	IV	Solution	8 mg/kg
2 mo to <2	IV	Solution	8 mg/kg

A subject can be converted from the IV to an oral formulation following 1 or more IV doses. *The first oral dose will be 10 mg/kg with a maximum of 400 mg.* ~~No loading doses are used with IV solithromycin administration. Note that oral dosing, either as initial exposure to solithromycin with capsules or suspension, or as follow-on therapy prior to IV dosing, is initiated with a single (oral) loading dose.~~

Table 8 Intravenous to Oral Dosing Regimens

Age (years)	Route	Oral Formulation	Day 1 to Last IV Dosing Day (Max dose: 400 mg)	First Oral Dosing Day to Day 7 (Max dose: 400 mg) ^a
12 to 17	IV/PO	Suspension or Capsules	8 mg/kg	10 mg/kg (400 mg)
6 to <12	IV/PO	Suspension or Capsules	8 mg/kg	10 mg/kg
2 to <6	IV/PO	Suspension	8 mg/kg	10 mg/kg
2 mo to <2	IV/PO	Suspension	8 mg/kg	10 mg/kg

a. The adult dose should be administered unless the subject weighs <40 kg, in which case they receive 10 mg/kg on the first oral dosing day through Day 7. The capsule dose is rounded upwards to the nearest 200 mg.

7.5 Age Group Initiation

Enrollment will occur simultaneously for all age groups ~~for which information to inform the dosing regimen is available.~~

8.2 Exclusion Criteria

8. ...In addition, the following drugs may not be co-administered with solithromycin in this trial due to the potential for adverse drug-drug interaction: digoxin, colchicine, midazolam, quinidine, ergotamine, dihydroergotamine, *rivaroxaban*, *apixaban*, *dabigatran*, *edoxaban*, cisapride, cyclosporine, sildenafil, astemizole, and alfentanil.

9.1 Solithromycin (CEM-101)

Solithromycin suspension contains aspartame and patients with phenylketonuria should be aware that the suspension contains 78 µg of phenylalanine (as a component of aspartame) per mL.

9.4 Study Drug Storage Conditions

The oral capsules will...*Daily temperature logs must be kept at the clinical site and all temperature excursions during storage must be reported to Cempra GCP QA to obtain approval for continued use.*

Once prepared, the reconstituted vials *should be used within 2 hours when can be stored at room temperature for up to 24 hours*; they should not be refrigerated or frozen. *Room light exposure is allowed.* Once the reconstituted solithromycin solution has been added to the saline bag, the infusion solution in the saline bag can be kept at room temperature (15°C to 25°C; 59°F to 77°F) for up to 12 hours *or stored refrigerated for up to 24 hours before use* the bag should not be refrigerated or frozen *at any time. Room light exposure is allowed during preparation, storage, and patient administration.*

10.2.1 Treatment Days up to Last Day of Treatment

1. *Every effort should be made to obtain safety labs 72 hours (±24 hours) after the first dose to include ALT, AST, alkaline phosphatase, total and direct bilirubin, and WBC with differential. A separate study sample is not required if these labs are obtained at 72 hours (±24 hours) after the first dose per standard of care.*

10. Administer study drug and active comparator.

10.2.2 Last Day of Treatment (+48 Hours)

3. Perform safety labs *as described in Section 10.4.1.*

10.3.1 Day 16 Post Randomization (±4 days)

1. *Every effort should be made to obtain safety labs Day 16 (±4 days) after the first dose to include ALT, AST, alkaline phosphatase, total and direct bilirubin, and WBC with differential. A separate study sample is not required if these labs are obtained at Day 16 (±4 days) after the first dose per standard of care.*
8. Review and record any AEs and SAEs as described in Section 12.1. *Every effort should be made to bring the subject back, but SAEs must be collected via phone/other media if the subject is unable or unwilling to return.*

10.3.2 Day 36-28 Post Randomization (± 4 days)

1. *Every effort should be made to obtain safety labs Day 28 (± 4 days) after the first dose to include ALT, AST, alkaline phosphatase, total and direct bilirubin, and WBC with differential. A separate study sample is not required if these labs are obtained at Day 28 (± 4 days) after the first dose per standard of care.*
2. *Review and record any SAEs as described in Section 12.1. Every effort should be made to bring the subject back for follow up, but SAEs must be collected via phone/other media if the subject is unable or unwilling to return.*

~~Review and record any SAEs as described in Section 12.1. Every effort should be made to bring the subject back, but SAEs must be collected via phone/other media if the subject is unable or unwilling to return.~~

10.4.1 Safety Laboratory Tests

Safety laboratories will include hemoglobin, hematocrit, WBC *with differential*, platelet count, blood urea nitrogen, calcium, serum creatinine, potassium, sodium, AST, ALT, ALP, total and direct bilirubin, and albumin.

10.4.2 Microbiology Assessments

Results of microbiology assessments performed in accordance with routine standard of care will be recorded on the study eCRF. These include all cultures from *cerebrospinal fluid, pleural fluid, blood, urine (catheter or suprapubic tap), and sputum* ~~sterile body fluids~~, as well as molecular and serologic tests for *M. pneumoniae* and *C. pneumoniae*.

10.4.3 Pharmacokinetic Determinations

~~Solithromycin and metabolite~~ concentrations will be measured in plasma. Pharmacokinetics samples will be processed at a central lab using a validated bioanalytical assay. *These data will be reviewed periodically during the study.* . .

10.5 Radiological Imaging and Non-pharmacologic Treatment/Procedures

. . . Surgeries of interest include surgeries of the chest and chest wall, such as pleural tube placement and video assisted thoracoscopic surgery. ~~Surgical procedures of the head and neck area will also be needed.~~

10.6 Clinical Efficacy Outcomes Assessments Time Points

Clinical outcomes assessments will be performed by a blinded investigator at the study site. At each time point, the site blinded investigator will evaluate *signs and symptoms* and record physical findings of CABP. *These assessments will include cough, difficulty breathing, purulent sputum production, chest pain, grunting, hypotension, tachycardia, tachypnea, and evidence of pulmonary consolidation (further details are in the Blinded Investigator Plan).* If symptoms and physical exam findings are available in the medical record per standard of care, these can be used for the clinical outcomes assessments.

- A baseline assessment of signs, symptoms, and physical exam findings will be completed at screening

10.8 Clinical Cure Definition (Day 16 Post Randomization [\pm 4 Days])

Clinical cure is defined as resolution of all presenting signs and symptoms of CABP (excluding cough), no development of new sign or symptoms of CABP, and no requirement for ~~additional~~ *alternative* antimicrobial therapy.

11.2 Discontinuation from Study Drug

A subject may have study drug prematurely (~~prior to 5 to 7 oral doses days or 5 to 7 IV or IV/oral doses~~) discontinued for any of the following reasons:

- Safety, including AEs or development of clinically significant laboratory abnormalities. The subject must be followed clinically until the event is resolved or deemed stable.
- Clinical failure or lack of efficacy.
- Subject wishes to withdraw consent for reasons other than an adverse experience.
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol.
- Investigator discretion.
- Sponsor request.

Any subject who prematurely discontinues study drug should be encouraged to complete the study through the last study visit. *The Last Day of Treatment procedures will be performed the day (+48 hours) the study drug is discontinued.*

11.3 Withdrawal from Study

- *Subject wishes to withdraw consent due to an adverse experience*

11.4 Study Site Discontinuation

- *Recommendation from the DMC*

12.1 Adverse Events

Laboratory abnormalities are not considered AEs unless they are associated with clinical signs or symptoms, or require medical intervention. However, a clinically significant laboratory abnormality (e.g. detected on clinical chemistry or hematology) that is independent from the underlying medical condition and that requires medical or surgical intervention, or leads to study drug interruption or discontinuation, will usually be considered an AE.

Lack of efficacy/clinical failure is captured as an efficacy measure and in general will not be considered an AE.

~~A laboratory abnormality that is considered clinically significant by the investigator (e.g., a change detected on clinical chemistry or hematology) that is independent from the underlying medical condition, requires medical or surgical intervention, or leads to study drug discontinuation will be considered an AE.~~

12.1.1 Serious Adverse Events

- Death
“Death” is an outcome and is NOT the AE. In the event of death, the cause of death should be recorded as the AE. The only exception is “sudden death” when the cause is unknown.
- Subject hospitalization or prolongation of hospitalization. A “planned” hospitalization for study procedures or preexisting conditions is NOT an SAE.

...

Serious AEs will be collected from the time of signing of informed consent until 36 28 (± 4) days after randomization.

12.1.3 Other Reportable Events

Monitoring of liver laboratory tests

Monitoring of liver laboratory tests of special interest (AST, ALT, and direct bilirubin) will be conducted throughout the study. Three levels of monitoring will be performed:

Weekly monitoring: each week, data entered in the eCRF will be downloaded to identify any child enrolled in the study with a) normal AST, ALT, or direct bilirubin at baseline AND at least 2×ULN on any of these laboratory tests at any study visit post baseline and b) any child meeting laboratory criteria for Hy’s Law. These data will be provided to the DCRI medical monitor and the sponsor for review.

Quarterly monitoring: each quarter, summary data of children enrolled in the study with a) normal AST, ALT, or direct bilirubin at baseline AND at least 3×ULN on any of these laboratory tests at any study visit post baseline and b) any child meeting laboratory criteria for Hy’s Law will be provided to the DMC chair for review. Actions by the DMC chair will be described in the DMC meeting minutes.

Biannual monitoring: twice per year, all data pertaining to liver laboratory tests will be presented to the DMC for review. This includes the data presented quarterly as well as listings of all laboratory tests at every visit.

14.2.2 Endpoints

The primary endpoints for safety will be:

- a. The proportion of subjects with *TEAEs*

14.1.4 Pharmacokinetic Analysis

A population PK analysis will be performed using non-linear mixed effects modeling in NONMEM. *Data will be reviewed during the study to evaluate the PK of solithromycin in pediatric CABP patients.*

Amendment #1 19 January 2016

Rationale for Amendment

Amendment 1 adds dosing information, including the dosage rationale, for the 6-12 year old intravenous solithromycin age cohort, based on analysis of PK data from an ongoing Phase 1 study.

To help ensure the integrity of randomization, follow-up visits are now based on date randomized instead of date of last treatment.

A microbiological intent to treat population has been defined, to capture information on baseline pathogens if obtained per standard of care, and will represent an additional analysis population if there are sufficient numbers of subjects in this population in which to conduct a meaningful analysis.

IV amoxicillin/clavulanic acid has been added as a comparator since it is a common antibiotic used in many countries as an appropriate treatment in pediatric patients with CABP.

The use of diaries for outpatients who receive oral study drug has been added to help monitor compliance and drug accountability when drug is taken outside a healthcare setting.

The two available suspension concentrations are described.

Language required by the BARDA contract for sites outside the US has been added.

Language has been modified in some sections to improve the clarity of the protocol requirements and procedures, and to correct minor typographical errors. Typographic corrections, including grammatical and punctuation errors, are not shown.

New/revised text is in ***bolded italics***. Deletions are identified by ~~strikethrough~~.

Protocol Synopsis

Changes made in accordance with the revisions described below.

Rationale: There is a growing body of efficacy and safety data on solithromycin in adults, ~~it and solithromycin~~ was shown to be non-inferior to moxifloxacin in ***an adult*** Phase 3 trial in CABP.

Subject Participation:

- Up to 40 days of adverse event (AE) and serious AE (SAE) monitoring (~~treatment phase plus up to 30 days post completion of therapy~~ ***36 ± 4 days*** will be reported)

Test Product:

Age (years)	Route	Formulation	Loading dose (Max dose: 800 mg) ^a	Daily maintenance dose (Max dose: 400 mg) ^a
12 to 17	PO	Capsules ^b	800 mg	400 mg
12 to 17	PO	Suspension	TBD	TBD
12 to 17	IV	Solution	No loading dose	6 mg/kg
6 to <12	PO	Capsules ^b	TBD	TBD
6 to <12	PO	Suspension	TBD	TBD
6 to <12	IV	Solution	No loading dose	7 mg/kg
2 to <6	PO	Suspension	TBD	TBD
2 to <6	IV	Solution	No loading dose	TBD
2 mo to <2	PO	Suspension	TBD	TBD
2 mo to <2	IV	Solution	No loading dose	TBD

Comparator Therapy:**Children ≥2 months to <5 years of age:**

- Ceftriaxone IV **OR**
- Ampicillin IV (~~United States~~) **or** amoxicillin IV (~~Rest of the World~~)
- Amoxicillin-clavulanic acid (PO **or IV**) **or** amoxicillin PO

Children 5 to 17 years of age (inclusive):

- Ceftriaxone IV **OR**
- Ampicillin IV (~~United States~~) **or** amoxicillin IV (~~Rest of the World~~) **OR**
- Amoxicillin-clavulanic acid PO **or IV or** amoxicillin PO

Azithromycin IV/PO or erythromycin lactobionate IV or erythromycin PO may be added to any of ~~the three~~ treatment regimens above.

	United States	Rest of the World
Amoxicillin-clavulanic acid	-	Children >4kg but < 40kg: amoxicillin component 25 mg/kg intravenously every 8 hours [1000 mg max dose] Children ≥ 40 kg: amoxicillin component 1000 mg intravenously every 8 hours

Intravenous-to-oral switch:

Subjects receiving an IV comparator drug (~~i.e. ceftriaxone, ampicillin~~) in any age group may be switched . . .

Statistical Methods and Data Analysis

Efficacy population: All subjects who are randomized.

Safety population: All subjects who receive at least 1 dose of study drug.

PK population: All subjects who receive at least 1 dose of solithromycin and have at least 1 evaluable PK sample.

MicroITT population: Randomized subjects who have a microbiologically confirmed baseline pathogen.

Safety:

New events that occur or pre-existing conditions that worsen in frequency or intensity will be reported as AEs or SAEs. AEs will be reported for ~~14-16~~ days and SAEs for ~~30-36~~ days ~~following the end of therapy~~ ***post-randomization***. . .

Efficacy:

The primary efficacy endpoint is defined as clinical improvement on the last day of treatment (end of treatment response), and the secondary efficacy endpoints are defined as early clinical response at Days 2-4 and clinical success (i.e., cure) at the short-term follow-up visit (~~14-16~~ days [\pm 4 days] ~~following the end of therapy~~ ***post-randomization***).

Table 1 Schedule of Assessments and Procedures

Column heading modified: Day ~~16~~ ~~10 Last Day of Treatment~~ ***Post Randomization*** (\pm 4 days)

Column heading modified: Day ~~36~~ ~~30 Last Day of Treatment~~ ***Post Randomization*** (\pm 4 days)

Footnote v modified: Day 16 post ~~10 End of Treatment~~ ***randomization*** response (cure)

Section 5.2.3 Summary of Efficacy

Final efficacy results ~~are not yet available~~ from 2 ongoing phase 3 trials: 1) IV-to-oral solithromycin (versus moxifloxacin) in CABP, and 2) Single-dose oral solithromycin for uncomplicated genitourinary gonococcal infection (versus intramuscular ceftriaxone + oral azithromycin) ***are pending***.

Section 5.2.2.2.5 Pediatric Subjects

Added the rationale for the dosing regimen:

Solithromycin PK in adolescents (12 to <17 years) and children (<12 years) following oral (capsules, suspension) and intravenous administration was further investigated in a phase 1, open-label, multi-center study (protocol CE01-120). Intravenous data collected in this study supported the use of a 6 and 7 mg/kg intravenous daily dose (no loading dose required) in adolescents (12 to <17 years) and children (6 to <12 years), respectively. These doses resulted in a median (range) Day 3-5 C_{max} and AUC_{0-24} of 2.3 $\mu\text{g/mL}$ (1.2-7.7) and 12.3 $\mu\text{g}\cdot\text{h/mL}$ (8.2-19.9) in adolescents, and 2.8 $\mu\text{g/mL}$ (1.0-8.1) and 10.6 $\mu\text{g}\cdot\text{h/mL}$ (2.7-18.4) in children, respectively. These estimates are comparable to adult median (range) values of 2.7 $\mu\text{g/mL}$ (2.1-3.5) for C_{max} and 13.7 $\mu\text{g}\cdot\text{h/mL}$ (6.1-22.3) following 400 mg of daily dosing.

Section 5.2.4 Summary of Safety

In the adolescent oral phase 1 study (CE01-119), 12 AEs were reported, of which 9, . . .

In the ~~ongoing~~ phase 3 IV-to-oral CABP study (CE01-301), solithromycin ~~was~~ is administered in daily IV doses of 400 mg. When clinical stability is achieved, subjects ~~could may~~ switch to oral solithromycin dosing, receiving an initial dose of 800 mg on the first oral dosing day, followed by oral dosing with 400 mg each day. The total duration (by IV or IV/oral dosing) of treatment ~~was~~ is 7 days. ***This study has been completed and unblinded. However, at this time, data are currently being analyzed and all results would be considered preliminary.*** ~~This trial remains blinded and is ongoing, therefore rates of events are not summarized herein. To date, approximately 600 subjects have been enrolled, and an estimated 300 subjects have received solithromycin. The (blinded) AE and SAE profile from this study appears similar to that from study CE01-300, with the addition of infusion-related AEs that were not observed in that (oral dosing only) study.~~

Section 5.4 Rationale for the Dosage Regimen

To date, data are available from phase 1 pediatric studies (CE01-119 and CE01-120) to identify optimal dosing following capsule and intravenous solithromycin administration in adolescents 12 to 17 years of age ***and children 6 to <12 years of age.*** . .

Then in the follow-up study, CE01-120, an intravenous dose of 6 mg/kg daily resulted in median (range) C_{max} and AUC_{0-24} estimates ***of*** 2.3 mcg/mL (1.2-7.7) and 12.3 $\mu\text{g}\cdot\text{h/mL}$ (8.2-19.9), respectively, in six adolescents ***(12 to <17 years). In children (6 to <12 years), C_{max} and AUC_{0-24} estimates were 2.8 $\mu\text{g/mL}$ (1.0-8.1) and 10.6 $\mu\text{g}\cdot\text{h/mL}$ (2.7-18.4) following 7 mg/kg daily dosing. These estimates are comparable to adult median (range) estimates values of 2.7 $\mu\text{g/mL}$ (2.1-3.5) for C_{max} and 13.7 $\mu\text{g}\cdot\text{h/mL}$ (6.1-22.3) following 400 mg of daily dosing. Data for younger age groups and oral formulations are in development.***

Section 7.1 Duration of Subject Participation

The duration of subject participation from signing the informed consent form (ICF) will be approximately 40 days (includes up to 10 days of study drug/comparator drug administration, a follow-up visit at ~~10~~ 16 days [\pm 4 days] after the last day of study dose ***randomization***, AE monitoring for ~~10~~ 16 (\pm 4) days, and SAE monitoring for ~~30~~ 36 (\pm 4) days after the last dose of study drug ***post-randomization***). Adverse event monitoring ~~30~~ 36 days after the last dose of study drug ***randomization*** can be conducted by telephone/other media visit. The study duration from first subject first visit until last subject last visit will be approximately 24 months.

Section 7.3 Study Drug Dosage and Administration

Table 4 Study Design by Age Group:

Age (years)	Route	Formulation	Loading dose (Max dose: 800 mg) ^a	Daily maintenance dose (Max dose: 400 mg) ^a
12 to 17	PO	Capsules ^b	800 mg	400 mg
12 to 17	PO	Suspension	TBD	TBD
12 to 17	IV	Solution	No loading dose	6 mg/kg
6 to <12	PO	Capsules ^b	TBD	TBD
6 to <12	PO	Suspension	TBD	TBD
6 to <12	IV	Solution	No loading dose	7 mg/kg
2 to <6	PO	Suspension	TBD	TBD
2 to <6	IV	Solution	No loading dose	TBD
2 mo to <2	PO	Suspension	TBD	TBD
2 mo to <2	IV	Solution	No loading dose	TBD

Subjects requiring an oral dosage form other than capsules will receive suspension formulation, provided at ~~32~~ **160** mg/5 mL and ~~48~~ **320** mg/5 mL strengths, to achieve the age-appropriate mg/mL *and solithromycin* dose.

Children ≥2 months to <5 years of age:

- Ceftriaxone IV **OR**
- Ampicillin IV (~~United States~~) **or** amoxicillin IV (~~Rest of the World~~)
- Amoxicillin-clavulanic acid PO **or IV** **or** amoxicillin PO

Children 5 to 17 years of age (inclusive):

- Ceftriaxone IV **OR**
- Ampicillin IV (~~United States~~) **or** amoxicillin IV (~~Rest of the World~~) **OR**
- Amoxicillin-clavulanic acid PO **or IV** **or** amoxicillin PO

	United States	Rest of the World
Amoxicillin-clavulanic acid	-	Children >4kg but < 40kg: amoxicillin component 25 mg/kg intravenously every 8 hours [1000 mg max dose] Children ≥ 40 kg: amoxicillin component 1000 mg intravenously every 8 hours

Section 7.5 Age Group Initiation

Enrollment of subjects in all age groups will occur simultaneously. *will occur simultaneously for all age groups for which information to inform the dosing regimen is available.*

Section 9.1 Solithromycin (CEM-101)

... The inactive ingredients for all formulations will be listed in the pharmacy manual. *Detailed instructions for the reconstitution of the powder for oral suspension to 320 mg/5ml and 160 mg/5 ml will be listed in the pharmacy manual.*

Section 9.2 Comparator

Comparator antibiotics may be administered “off the shelf” at the doses described above based on age range, *local availability, and local treatment preferences*. Comparator antibiotic preparation will be performed per local standard of care.

Section 9.4 Study Drug Storage Conditions

... Once prepared, *the reconstituted vials can be stored at room temperature for up to 24 hours; they should not be refrigerated or frozen. Once the reconstituted solithromycin solution has been added to the saline bag, the infusion solution in the saline bag can be kept at room temperature (15°C to 25°C; 59°F to 77°F) for up to 12 24 hours; the bags should not be refrigerated nor frozen after reconstitution.* ...

Section 10.2.1 Treatment Days up to Last Day of Treatment

9. Administer study drug and active comparator. *If the subject is an outpatient and receiving study drug orally, a dosing diary is included on the capsule blister pack and the label for the suspension. This diary should be completed for each dose taken and brought back to each visit for review and accountability.*

Section 10.2.2 Last Day of Treatment

9. Administer study drug and active comparator. *If the subject is an outpatient and receiving study drug orally, a dosing diary is included on the capsule blister pack and the label for the suspension. This diary should be completed for each dose taken and brought back to each visit for review and accountability.*

Section 10.2.1 Day 10 16 Post Last Day of Treatment Randomization (±4 days)

Section 10.2.2 Day 30 36 Post Last Day of Treatment Randomization (±4 days)

Section 10.4.1.1 Study-Required Safety Laboratories

... For infants <7 kg, no more than 3 mL/kg will be drawn for research purposes during the study. *In countries where micro laboratory equipment is not available, whole blood for research purposes in children < 2 years of age should not exceed 2.4 mL/kg.*

Section 10.7 Clinical Cure Definition (Day ~~10~~ 16 Post ~~Last Day of Treatment~~ Randomization [± 4 days])

Section 12.1 Adverse Events

A laboratory abnormality that is considered clinically significant by the investigator (e.g., a change detected on clinical chemistry or hematology) that is independent from the underlying medical condition, requires **medical** or surgical intervention, or leads to study drug discontinuation will be considered an AE.

Adverse events will be collected from the time of signing of the informed consent until ~~10~~ 16 days after the last dose of study drug post-randomization . . .

Section 12.1.1 Serious Adverse Events

Serious AEs will be collected from the time of signing of informed consent until ~~30~~ 36 (± 4) days after the last dose of study drug **randomization**.

Section 14.1.5 Efficacy Analysis

Efficacy will be evaluated as a binary variable representing clinical improvement on the last day of treatment, as a binary variable representing early clinical improvement on treatment days 3 and 4, and as a binary variable representing clinical cure on Day ~~10~~ 16 (± 4 days) after the end of therapy post-randomization. The frequency and percentage of subjects achieving each efficacy endpoint will be determined, and a 95% CI calculated. Summaries will be calculated by treatment group for the overall ITT population (**and microITT population if the data is sufficient to provide meaningful analysis**) and stratified by age group. This study is not powered for comparison of efficacy endpoints between treatment groups. Additional details of efficacy analyses will be included in the SAP.

Section 15.16 Publication Policy

Added the following text along with the addition of Appendix B for clarification for sites outside of the United States:

For each Institution and Investigator conducting the Study or a portion thereof outside of the United States, Institution and Investigator acknowledge and agree that (i) the Study and all other activities to be performed hereunder will be supported by funding provided, and will be performed in support of Sponsor's performance of its obligations, under Contract No. HHS0100201300009C ("Prime Award"), entitled "SOLI- Solithromycin Pediatric Development Program", awarded by the United States Government through the Office of Acquisitions Management, Contracts and Grants ("Prime Sponsor"), and that, therefore, certain obligations are required of Sponsor's subcontractors (including Institution and Investigator) and, notwithstanding anything to the contrary in the Clinical Trial Agreement, or any other clinical study agreement, clinical trial agreement, investigator agreement, or the like executed by Institution or Investigator with respect to the Study, (ii) the terms and conditions of the Protocol and the Clinical Trial Agreement are subject to the terms included as Appendix B, attached hereto and fully incorporated herein, and, without limitation of the foregoing, to those

provisions of the Prime Award incorporated herein, and, in the event of any conflict between those terms included as Appendix B and the terms and conditions of the Protocol, the Clinical Trial Agreement, or any other clinical study agreement, clinical trial agreement, investigator agreement, or the like executed by Institution or Investigator with respect to the Study, the terms of Appendix B shall govern to the extent of such conflict.

Added both Appendix A and Appendix B to the protocol to support the protocol amendment #1 changes and the BARDA terms for sites outside of the United States.

Appendix B BARDA-Related Terms for Sites Outside of the United States

1. Investigator and Institution acknowledge that the Study and other activities to be performed hereunder will be supported by funding provided, and will be performed in support of Sponsor's performance of its obligations, under Contract No. HHS0100201300009C ("Prime Award"), entitled "*SOLI- Solithromycin Pediatric Development Program*", awarded by the United States Government through the Office of Acquisitions Management, Contracts and Grants ("Prime Sponsor"), and that, therefore, certain obligations are required of Sponsor's subcontractors (including Institution and Investigator). The Parties agree that the terms and conditions of the Protocol and the Clinical Trial Agreement are in alignment with and subject to the following terms, and, without limitation of the foregoing, to those provisions of the Prime Award incorporated herein.
2. Compliance with U.S. Federal Acquisition Regulation ("FAR") 52.245-1, Alternate II with respect to U.S. Government Property is required. Accordingly, title to property having a value less than US \$5000 purchased with funds provided under the Clinical Trial Agreement vests in Investigator or Institution, as applicable, upon acquisition if approval of the U.S. government contracting officer concerning the Prime Award is obtained prior to acquisition. Upon written request of Investigator or Institution, as applicable, Sponsor will use commercially reasonable efforts to assist Investigator or Institution, as applicable, in obtaining such consent. Consistent with the Prime Award, title to equipment having a value above US \$5000 and purchased with funds provided under the Clinical Trial Agreement shall vest in the U.S. Government. Investigator and Institution shall comply with the provisions of U.S. Department of Health and Human Services ("DHHS") publication, "Contractor's Guide for Control of Government Property" with respect to any applicable property or equipment purchased by Investigator or Institution, as applicable, with funds provided under the Clinical Trial Agreement, and Investigator or Institution, as applicable, agrees to maintain records related to such equipment and the ownership, maintenance, care, and use thereof.
3. In addition to all other reporting and notification requirements set forth in the Clinical Trial Agreement or this Appendix B, the Investigator and Institution will immediately disclose to Sponsor in writing formal findings of noncompliance with any law, regulation or other term or condition incorporated into the Clinical Trial Agreement and receipt of notices of suit or litigation or other formal adversary proceedings, or any formal discovery requests, related to the Study, the conduct thereof, or the Clinical Trial Agreement regarding any aspect of the Investigator or Institution. Neither Investigator nor Institution shall use funds provided under the Clinical Trial Agreement during a clinical hold to fund the clinical studies that are on hold. Neither Investigator nor Institution shall enter into any new financial obligations related to clinical activities for the clinical trial on clinical hold. Neither Investigator nor Institution shall use funds provided under the Clinical Trial Agreement to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug.
4. Neither Investigator nor Institution shall (i) directly or indirectly pay or promise to pay, or authorize the payment of any money, or give, promise to give or authorize the giving of anything of value to any person or entity, whether governmental, quasi-governmental or private, to obtain or retain business or secure improper advantage for Chiltern or for Sponsor or (ii) to lobby any legislative bodies within the United States. Neither Investigator nor Institution shall directly or indirectly receive or solicit any money or anything of value from any person or entity, whether governmental, quasi-governmental or private, in order to secure

an improper advantage to such person or entity. Neither Investigator nor Institution will take any action which could render Chiltern or Sponsor liable under any other applicable laws for the prevention of fraud, corruption, racketeering, money laundering and/or terrorism. Institution and Investigator acknowledge that United States Executive Orders and Laws, including but not limited to E.O. 13224 and P.L. 107-56, prohibit transactions with, and the provision of resources and support to, individuals and organizations associated with terrorism. It is the legal responsibility of the Institution and Investigator to ensure compliance with these Executive Orders and Laws. This clause must be included in all subcontracts issued under the Clinical Trial Agreement.

5. Investigator and Institution shall apply to it and Research Staff the conflicts of interest policy of [*Sponsor*] OR [*Institution*], and Investigator and Institution (i) certify that, if agreeing to apply Institution's conflict of interest policy, that such policy complies with 45 CFR Part 94 and (ii) agree that all such entities and individuals shall be subject to, and comply with, such policy, in each case, to the extent such policy relates to "financial conflicts of interest" as defined in 45 CFR Part 94.3 for disclosing significant financial interests that are directly related to Investigator's work for Sponsor in accordance with 45 CFR Part 94. Investigator shall report any financial conflict of interest to Sponsor by written notice and email. Any financial conflicts of interest identified shall subsequently be reported by Sponsor to U.S. National Institutes of Health ("NIH"). Such report shall be made before expenditure of funds authorized in the Clinical Trial Agreement or within 45 days of any subsequently identified financial conflict of interest.
6. To the extent the Prime Award and related applicable United States law, rule, and regulation (the "BARDA Provisions") require that any results, data, information, know-how, analyses, reports, inventions (whether or not patentable), deliverables, or intellectual property rights (including but not limited to patent rights) that were to be owned by Sponsor pursuant to the Clinical Trial Agreement are instead to be owned by Institution or Investigator (or instead can be owned by Institution or Investigator, in lieu of the US Government, pursuant to an election of title thereto by Institution or Investigator under applicable law or regulation) (such results, data, information, know-how, analyses, reports, inventions, deliverables, and intellectual property rights, "Subject IP"):
 - i. Institution and Investigator agree to take such steps as may be necessary to ensure they own and retain title to Subject IP, instead of the US Government, subject to any rights the US Government may have therein under the BARDA Provisions;
 - ii. Institution and Investigator hereby grant Sponsor and its affiliates a perpetual, irrevocable, world-wide, royalty-free, fully-paid, transferable, exclusive license, with rights of sublicense, under Subject IP to make, have made, use, sell, offer for sale, import, export, and otherwise practice Subject IP for any and all purposes;
 - iii. Institution and Investigator shall, if and as requested by Cempra and at Cempra's expense, (i) use reasonable efforts to obtain such waivers or permissions from the US Government as may be necessary to permit the assignment of all of Subcontractor's right, title, and interest in Subject IP to Cempra or any designee thereof and (ii) upon receipt of such waivers and/or permissions, assign all of Institution's and Investigator's right, title, and interest in such Subject IP to Cempra or any designee thereof without requirement or obligation of any further payment or consideration; and

- iv. clauses i., ii., and iii. above shall not apply to, or have any effect on, any allocation of rights between Sponsor, Institution, and Investigator with respect to any results, data, information, know-how, analyses, reports, inventions (whether or not patentable), deliverables, or intellectual property rights (including but not limited to patent rights) except to the extent such allocation conflicts with that required by the BARDA Provisions (i.e., if the BARDA Provisions do not apply to any particular intellectual property or do not conflict with the other applicable terms of the Clinical Trial Agreement or this Protocol).
7. Notification is hereby given that Investigator, Institution, and their employees are subject to criminal penalties for violation of certain United States laws concerning privacy to the same extent as employees of the US Government. Investigator, and Institution shall assure that each of its employees knows the prescribed rules of conduct and that each is aware that he or she can be subjected to criminal penalty for violation of such laws. Institution and Investigator shall follow guidance concerning certain United States privacy laws.
8. Prior to conducting the Study, Investigator and Institution certify that they have an appropriate and current Federal Wide Assurance of Protection for Human Subjects (or other applicable assurance) on file with the United States Department of Health and Human Services and will provide a copy of such assurance upon request. The performance of the Study hereunder shall be subject to, and Investigator and Institution shall comply with, such Federal Wide Assurance number # _____.
9. Neither investigator nor Institution shall use any funds supplied under the Clinical Trial agreement to pay any person for influencing or attempting to influence an officer or employee of any agency, a member of the United States Congress, an officer or employee of the United States Congress, or an employee of any member of the United States Congress in connection with any of the following: the awarding of any United States government contract; the making of any United States government grant; the making of any United States government loan; the entering into of any cooperative agreement with the United States government; or the modification of any United States government contract, grant, loan, or cooperative agreement. No funding provided under the Clinical Trial Agreement shall be used for publicity or propaganda purposes, for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support or defeat legislation pending before the United States Congress, or any state or local legislature. No funding provided under the Clinical Trial Agreement shall be used to pay the salary or expenses of any contract or grant recipient, or agent acting for such recipient, related to any activity designed to influence legislation or appropriations pending before the United States Congress, or any state or local legislature.
10. Anyone who becomes aware of the existence or apparent existence of fraud, waste and abuse in BARDA-funded programs is encouraged to report such matters to the United States' Department of Health and Human Services' Inspector General's Office in writing or on the Inspector General's Hotline. The toll free number is 1-800-HHS-TIPS (1-800-447-8477). All telephone calls will be handled confidentially. The e-mail address is Htips@os.dhhs.gov and the mailing address is:

Office of Inspector General
Department of Health and Human Services
TIPS HOTLINE
P.O. Box 23489
20026

11. No information related to data obtained under this Protocol or Clinical Trial Agreement shall be released or publicized without the prior written consent of the Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, United States Department of Health and Human Services ("BARDA"). Institution and Investigator will acknowledge US government funding when issuing statements, press releases, requests for proposals, bid solicitations and other documents. Institution and Investigator are required to state: (1) the percentage and dollar amounts of the total program or project costs financed with US government funding and; (2) the percentage and dollar amount of the total costs financed by non-US government sources. Contract support shall be acknowledged in all such publications, and any publicizing or any release of any information related to the work performed under the Clinical Trial Agreement or the Clinical Trial Agreement itself, substantially as follows:

"This project has been funded in whole or in part with United States federal funds from the Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, Department of Health and Human Services, under Contract No. HHS0100201300009C".

12. Investigator and Institution specifically agree, to the extent applicable to the Clinical Trial Agreement, the Protocol, and the services performed or goods provided thereunder, that the applicable regulations set forth in the following tables entitled, "U.S. Federal Acquisition Regulations" and "U.S. Department of Health and Human Services Acquisition Regulations Clauses" respectively, shall flow-through and apply to it, its affiliates, and Research Staff or other employees, agents, representatives, or subcontractors of Institution or Investigator.

Except as otherwise provided, as used in the cited clauses, "Government" and "Contracting Officer" shall refer to "Sponsor" and "authorized Sponsor representative," respectively, and "Contractor" or "Offeror" shall refer to Investigator and Institution. Without limiting the generality of the foregoing sentence, as used in 52.246-9, "Government" and "Contracting Officer" shall refer to "Government" and "Contracting Officer," respectively, and Investigator and Institution shall have all rights and obligations of a "Contractor" under such provisions. Any reference in a FAR or a U.S. Department of Health and Human Services Acquisition Regulations ("HHSAR") clause to "Subcontractor" shall mean lower-tier subcontractor(s) to Investigator and/or Institution, as applicable, in instances where flow through to such lower-tier subcontractors is required under the FAR or HHSAR.

U.S. Federal Acquisition Regulations

52.209-6	Protecting the Government's Interests When Subcontracting With Contractors Debarred, Suspended, or Proposed for Debarment (Contracts Over \$30,000)
52.222-21	Prohibition of Segregated Facilities
52.222-37	Employment Reports on Special Disabled Veterans, Veterans of the Vietnam Era, and Other Eligible Veterans (Contracts over \$100,000)
52.222-50	Combating Trafficking in Persons
52.223-18	Encouraging Contractor Policy to Ban Text Messaging While Driving
52.224-2	Privacy Act
52.225-13	Restrictions on Certain Foreign Purchases
52.227-11	Patent Rights - Ownership by the Contractor (Note: In accordance with FAR 27.303(b)(2), paragraph (e) is modified to include the requirements in FAR 27.303(b)(2)(i) through (iv). The frequency of reporting in (i) is annual.
52.245-1 Alt. II	Government Property, Alternate II (Jun 2007) (but references to "Government" shall not be changed to mean "Contractor")
52.246-9	Inspection of Research and Development (Short Form)
52.247-63	Preference for U.S.-Flag Air Carriers

U.S. Department of Health and Human Services Acquisition Regulations Clauses

HHSAR CLAUSE NO.	CLAUSE TITLE
352.223-70	Safety and Health
352.224-70	Privacy Act
352.231-70	Salary Rate Limitation
352.270-6	Restriction on use of Human Subjects