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

Protocol: CE01-203

STATISTICAL ANALYSIS PLAN

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1 DOCUMENT HISTORY

Version	Date of Issue	Summary of Changes
1.0	June 30, 2017	Original finalized copy
1.1	May 14, 2018	Edits to address early termination of trial

2 PURPOSE OF THE ANALYSIS PLAN

The purpose of this statistical analysis plan (SAP) is to give a brief overview of the study design and study objectives for Cempra, Inc. study CE01-203, outline the types of analyses and presentations of data relevant to the study objectives, and to provide a detailed description of the method in which the statistical analyses will be conducted to meet protocol objectives.

The scope of this plan applies primarily to the evaluation of the safety and efficacy objectives of the study as presented in the clinical protocol. The analyses of pharmacokinetic (PK) data will be conducted according to the PK data analysis plan contained as an appendix to this document. The SAP is based on the study protocol (Protocol CE01-203) and the electronic Case Report Form (eCRF) that were in effect at the date this SAP was finalized. An update to this SAP may be necessary if the protocol and/or eCRF are updated in a manner that affect the planned analyses. The Duke Clinical Research Institute (DCRI) on behalf of the sponsor (Cempra, Inc.) will conduct all statistical analyses detailed in this SAP.

It is intended that all statistical analyses specified in the protocol will be performed. However, it is conceivable that due to the manner in which the study unfolds, some scheduled analyses may not be performed. In addition, study conditions or analysis results may suggest the need for additional statistical analyses of the collected study data. In either case, deviations from the planned statistical analysis will be fully described in the final clinical study report. Furthermore, any additional analyses performed beyond those specified in the protocol or this SAP will be descriptive in nature and will not include hypothesis testing for the purposes of inferential conclusions.

In March 2018, the CE01-203 trial was terminated, because the sponsor discontinued development of Solithromycin. As a result of the early termination, the final number of enrolled participants was fewer than one quarter of the originally-planned sample size of 400. In consultation with the study investigators and the sponsor, the planned statistical analyses laid out in this SAP were curtailed due to the limited sample size particularly within age subgroups.

3 STUDY OVERVIEW

The overall study design and objectives are summarized in the following sections. The reader is referred to the study protocol and eCRFs for details of study conduct and data collection.

3.1 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 adolescents (12 to 17 years inclusive) and children (≥2 months to <12 years of age) with suspected or confirmed Community-acquired Bacterial Pneumonia (CABP).

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 intravenously (IV) or by mouth (PO) in capsules or suspension formulation, with dosing based on a combination of weight and age. The treatment assignment will be open-label. Subjects will be treated for 5 days with oral solithromycin, 7 days with IV or IV-to-oral solithromycin, or for 5 to 10 days with comparator antibiotics (duration of comparator antibiotic per investigator discretion). Subjects will have daily assessments on days of treatment as detailed in the Protocol, and undergo a follow-up visit on last day of therapy (+48 hours). Subjects will be followed for the occurrence of Adverse Events (AEs) for 16 days (±4 days) after randomization, and Serious Adverse Event (SAE) monitoring will occur up to 28 days (±4 days) post randomization. PK samples will be collected to assess solithromycin disposition at specified time points. A blinded clinical signs and symptoms assessment will occur at Screening, and clinical outcomes will be assessed by a blinded health care provider at each site on the Day 3 to 4 visit (early clinical response), the Last Day of Treatment Visit (end-of-treatment response), and at the Day 16 Follow-Up visit (16 ±4 days post-randomization). 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.

3.2 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

3.3 Sample Size and Randomization

Approximately 400 subjects ≥2 months to 17 years of age inclusive, with CABP will be enrolled. Subjects will be randomized (3:1) into two 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 United States. Enrollment will occur simultaneously for all age groups for which information to inform the dosing regimen is available.

The sample size of 300 in the solithromycin group is based on the ability to observe an SAE at a frequency higher than 1% (see Table 1).

Table 1 Probability of Observing at Least 1 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% confidence interval (CI) for safety. If 1 subject has an AE, then the 95% CI (exact binomial) for incidence of that AE within the subject population of 300 subjects is 0.01%, 1.8% (see Table 2).

Table 2 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

The above estimates assume that all 300 subjects assigned to the solithromycin arm will be evaluable for safety and do not account for the possibility that a subject may be excluded from the safety analysis, for example because she/he did not receive any study drug, or withdrew consent prior to completing follow up evaluations for safety.

3.4 Study Drug Administration and Duration of Treatment

Solithromycin will be administered IV or PO within each age group according to Table 3. Study drug is administered approximately every 24 hours and at approximately the same time each day (±4 hours). Study drug can be taken without regard to food. IV Solithromycin is infused over approximately 60 minutes (±20 minutes). Dosing variations within 10% of the calculated IV or suspension dosing are not considered protocol deviations. A subject can be converted from the IV

to an oral formulation following 1 or more IV doses. In the event of a patient switching from IV to oral formulation after experiencing a study-drug related adverse event associated with the IV formulation (e.g., infusion pain) the action taken with study drug may be recorded as "study drug not changed" if full protocol-defined dosing continues with a different formulation.

Table 3 Solithromycin Administration Route and Formulation by Age Group

Age	Routes	Formulations	Solithromycin Cohort
12 to 17 years	PO	Capsules	12 to17 y, PO Capsule
	PO	Suspension	12 to 17 y, PO Suspension
	IV	Solution	12 to17 y, IV
6 to <12 years	PO	Capsules	6 to <12 y, PO Capsule
	PO	Suspension	6 to <12 y, PO Suspension
	IV	Solution	6 to <12 y, IV
2 to <6 years	PO	Suspension	2 to <6 y, PO Suspension
	IV	Solution	2 to <6 y, IV
2 mo to <2 years	PO	Suspension	2 mo to <2 y, PO Suspension
	IV	Solution	2 mo to <2 y, IV

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 if weight <40 kg 800 mg if weight ≥ 40 kg	10 mg/kg if weight <40 kg 400 mg if weight ≥ 40 kg
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 (Max 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

Switch from 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
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.

Drug formulation and administration route will be decided upon by investigator discretion. Subjects starting with IV dosing may be switched to oral dosing at any time at the clinical discretion of the investigator. Under Protocol version 3.0 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 a total of 7 days of solithromycin treatment.

The comparator therapy drug, dose and mode of administration will be selected by the treating provider from those listed in the Study Protocol. The treating provider will make a selection of therapy according to subject weight and geographic region of enrollment, and will be consistent with current treatment recommendations for CABP in children as well as standard of care at the site. Subjects must receive 5 to 10 days of treatment with comparator. The exact duration of treatment may be determined at the investigator's discretion.

In the event that a subject is on an IV comparator medication and switches to an oral formulation of a different comparator drug (IV – PO switch), this will not be counted as a premature discontinuation of drug and will not be counted as an efficacy failure unless the site specifically enters that the initial drug was prematurely discontinued. In the event that a subject changes from a PO comparator medication to an IV formulation, or changes specific comparator drug within the first 5 days but remains taking the same formulation (ie changes from one IV drug to another IV drug, or one PO drug to another PO drug), this will be counted as a premature discontinuation of drug and efficacy failure. If a patient prematurely discontinues comparator drug then all dosing of other medications following the initial drug will be recorded as Concomitant Medications (not as further Comparator Arm dosing).

4 DATA SOURCES

At each study site data will be entered on the eCRFs stored on IBM Clinical Development (run by Merge Healthcare, an IBM company). Normal ranges for local laboratory measures will be received directly from laboratories and will be integrated with the clinical database. One master list of randomized trial arm assignments will be uploaded to IBM Clinical Development from DCRI Statistics. Subject data which is downloaded from IBM Clinical Development or received from DCRI Data Export Services will include the randomization assignment. Solithromycin plasma concentrations will be received from a central laboratory and will be integrated with the clinical database. Prior to database lock, programmed computer edit checks will be run against the database to identify discrepancies and verify reasonableness of the data. Queries to resolve discrepancies will be generated and resolved by the sites. Periodically, DCRI Statistics will receive or download from DCRI Data Export Services the eCRF database as Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM version 3.1.3) datasets. CDISC Analysis Data Model (ADaM version 2.1) datasets will be created by DCRI Statistics for production of tables, figures, and listings. All planned reporting will be based off of CDISC datasets, but in the case of emergent safety data some reporting may occur from the raw eCRF data. Table 4 summarizes the variables and time points when measurements are made during the patient assessment period.

Table 4 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	

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)
Serious adverse event assessment	X	X	X	X	X
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 to10 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.

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 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 *Chlamydophila 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 (± 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)

5 STATISTICAL ISSUES

5.1 General Analysis Conventions

Descriptive Statistics: For continuous and pseudo-continuous variables, the number of observations, mean, standard deviation, median, twenty-fifth percentile, seventy-fifth percentile, minimum and maximum will be provided. For binary yes/no, categorical, and/or ordinal variables a simple count and percent or tally will be provided. Other statistics may be considered if necessary.

Baseline: The latest recorded measurement available prior to first dose of study drug.

Age Group: Analysis presented "by age group" will use the categories "12 -17 years, inclusive", "6 - <12 years", "2 - <6 years", and "2 months - <2 years."

Consolidated Age Group: Analysis presented "by consolidated age group" will use the categories "2 months - <6 years" and "6 years – 17 years."

Drug Route: Analysis presented "by drug route" will categorize Solithromycin patients receiving capsule or suspension formulations of Solithromycin as "PO" and IV solution as "IV," based on the initial (Day 1) administration route of study drug. Comparator patients will not be categorized by drug route due to the possibility of multiple administration routes being utilized concurrently.

5.2 Documentation Convention

The statistical analyses described in this SAP as well as production of tables, listings and figures will be performed using SAS®, version 9.4 or higher (SAS Institute, Cary, NC). Additional statistical software may be used as needed.

5.3 Verification of Results

All tables, listings, and graphs will be verified and reviewed before considered final. The verification process will ensure that the numbers are produced by a statistically valid method and that the execution of the computations is correct. Qualified statisticians or statistical programmers employed by the DCRI (an affiliate of the Duke University School of Medicine) who have not been previously involved in the production of the original programming will perform the verification procedures. Methods of verification will include independent programming, prior to issuance of the draft statistical report, of all analysis datasets/ADaM and comparison to data listings. Tables, listings and graphs will be reviewed for accuracy, consistency with this analysis plan, consistency within tables/listings/graphs, and consistency with corresponding output. Once verification is complete, all documentation of the verification process will be filed in a statistical programming documentation notebook as required by the Statistical Standard Operations Procedures of the DCRI.

5.4 Handling of Missing Data

Efforts will be made to minimize the occurrence of missing data. However, the general approach will be to use only data which are complete with regard to the variable(s) and timepoint(s) being analyzed for descriptive summaries, or for the evaluation of safety and efficacy endpoints. In the case of a patient withdrawing or being lost (unrelated to documented AE or SAE), the denominator for rates of AE and SAE occurrence will remain as the complete Safety Population.

6 ANALYSIS POPULATIONS

Randomized population: All subjects who were enrolled and randomized in the study will be included in the analysis population for evaluating efficacy. This population will be used for analyses of efficacy.

Safety population: All subjects who receive at least one dose of study drug (solithromycin or active comparator) will be included in the analysis population for evaluating safety. This population will be used for analyses of safety.

PK population: All subjects who receive at least one dose of solithromycin (regardless of randomization assignment) and had at least one evaluable PK sample will be included in the analysis population for evaluating PK.

6.1 Methods of Analysis

Intention to treat (ITT): Subjects will be grouped for analysis according to their randomized allocation (solithromycin or active comparator) and initial solithromycin cohort (Table 3) where possible, regardless of whether the allocated therapy was administered, or switched (e.g., from IV-to-oral solithromycin), and regardless of compliance, protocol deviations, withdrawal, or anything else that occured once randomized. For efficacy analyses the ITT grouping of subjects will be applied to the randomized population. For safety analyses the ITT grouping of subjects will be applied to the safety population.

> *Note:* Hypothetically, a subject could be randomized to one arm and switch immediately to the other arm before the first dose. However, in practice, such switching did not occur. Therefore it is reasonable for the safety analyses (restricted to the safety population) to also group patients according to their randomized treatment assignment, which will be equivalent to grouping them according to the treatment that they initially received after being randomized.

7 SUBJECT DISPOSITION

This analysis will be performed on the randomized population. The number of subjects receiving any amount of study drug (safety population), completing study drug administration, number who withdrew from the study or discontinued from study drug early, and the number who completed the trial will be summarized by treatment arm, by age group, and by treatment arm stratified within age group. The timing and reasons for early discontinuation of study drug and/or withdrawal from the study will be summarized. The number of subjects with major protocol deviations will be summarized and listed. Additionally, a summary will be provided of subjects enrolled and randomized in each country.

8 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

This analysis will be performed on the safety population. Demographic and baseline characteristics including age, sex, height, weight, race, and ethnicity, are evaluated prior to initiation of study drug. Demographic and baseline characteristics will be summarized with descriptive statistics by randomized treatment arm, and consolidated age group.

9 STUDY DRUG ADMINISTRATION

Study drug administration will be summarized in the safety population, by treatment arm, and by treatment arm stratified within consolidated age group. Subjects randomized to solithromycin will also be presented by age group and formulation. Summaries will include a frequency distribution of number of days of drug administration, summary statistics forsolithromycin daily dosing amount,and frequency of active comparator antibiotics. Aggregate summaries of treatment discontinuation will be presented. For solithromycin, a subject will be considered to be prematurely discontinued if drug dosing ceases with <5 days on drug for patients starting on PO therapy, and <7 days on drug for patients starting on IV therapy. For active comparator a subject will be considered to be prematurely discontinued if drug dosing ceases with <5 days on drug, or if discontinuation is precipated by occurrence of an AE . For the purpose of counting days on drug, any date which contains at least a partial dose will be counted. In earlier versions of the protocol (versions 1.0-2.0), 5 to 7 days of solithromycin IV therapy was allowed. For patients enrolled under those protocol versions, premature discontinuation will be determined as <5 days on drug.

For solithromycin subjects, study drug exposure information will be listed, including administered weight-adjusted dose (mg/kg), start and stop date, number of days of dosing, number of days dosing required by protocol which was in effect at the site at the time, loading dose information if applicable, and formulation. For active comparator subjects, details about the active comparator (drug name, dose, dosing frequency), the start date/stop date, and number of days of dosing will be listed.

10 DATA ANALYSIS

10.1 Safety Evaluations

New events that occur or pre-existing conditions that worsen through frequency or intensity will be reported as AEs or SAEs. The investigator will provide date of onset and resolution, intensity, frequency, action(s) 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 [BUN], calcium, serum creatinine, potassium, sodium, AST, ALT, alkaline phosphatase, total and direct bilirubin, and albumin) are required by the protocol within 72 hours prior to the first dose, and on the last day of study drug. In addition, investigators are asked to make every effort to obtain safety labs (to include aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, and white blood cell count with differential) 72 hours (±24 hours) after the first dose, at the Day 16 and Day 28 post-randomization visits (implemented in Protocol version 3.0).

10.2 Primary Safety and Tolerability Endpoints

Primary safety endpoints will be the proportion of subjects in the safety population experiencing a TEAE and the proportion of subjects in the safety population discontinuing study drug due to a related AE. Discontinuation from related AE counts will be created by using any discontinuation from related AE documented in the study drug discontinuation page and the AE data for a subject. The first safety endpoint will be evaluated through the Day 28 visit (28 days ±4 days after randomization). This will be a composite of TEAEs through Day 16 visit and TESAEs through Day 28 visit. The second safety endpoint will be evaluated through the last day of study drug dosing.

For the primary safety end points, the frequency and percentage of subjects with at least one treatment emergent adverse event, and the frequency and percentage of subjects discontinuing study drug due to a related AE, will be determined. Ninety-five percent Clopper-Pearson (exact) confidence intervals will be calculated for each incidence of occurrence by treatment arm. Summaries will be calculated by treatment arm for the overall safety population, by treatment arm stratified within age group, and within age group and formulation for the solithromycin arm. Patient-level information for adverse events and subjects discontinuing study drug due to a related AE will be listed. For this analysis subjects will be grouped according to their randomized treatment arm assignment (intent-to-treat analysis).

10.3 Additional Safety Analyses

Additional safety analyses include summaries of AEs, descriptive statistical summaries of abnormal laboratory values, frequency distributions and shift tables summarizing abnormal laboratory values, graphs of lab values and vital signs, and summaries of concomitant medications as well as prior medications. Pregnancy test results and non-pharmacological treatments will be listed but not summarized. These analyses will be presented in the safety population using intent-to-treat analysis. Summaries will be produced by treatment arm, drug route, and consolidated age groups (2 months - <6 years, 6 years – 17 years inclusive) with the exception of lab graphs and

shift tables. The lab graphs and shift tables will be summarized by treatment arm, with all age groups combined. Safety data will also be listed by treatment arm, age group, formulation (for solithromycin patients only), and subject, with relevant information such as values, normal ranges, and severity presented.

10.3.1 Adverse Events

AEs (as defined in section 12.1 of Protocol) will be collected from the time of signing the informed consent and assent (if applicable) through 16 days (±4 days) after randomization. SAEs will be collected through 28 days (±4 days) after randomization. AEs will be tabulated by using the Medical Dictionary for Regulatory Activities (MedDRA v18.1) system organ class and preferred term. The treatment emergent adverse event (TEAE) is defined as any AE that has an onset on or after the first dose of either study drug, or any pre-existing AE that increases in severity after dosing with either study drug. Adverse events will be tabulated to show the number of subjects with at least one AE, number of subjects with at least one TEAE, and the number of subjects that experienced each individual count of AEs and TEAEs (e.g., number of subjects with 2 AEs, number of subjects with 3-4 AEs, etc.). Additional summaries will be created for infusion site events as well as TEAEs excluding these infusion site events.

10.3.2 Laboratory Data

Descriptive statistics will be generated for post-baseline abnormal laboratory data, such as hematology and serum chemistry values. Additionally, shift tables will be presented. The shift tables tabulate the number of lab values determined to be "Normal" and "Abnormal" at baseline and post-baseline timepoints. The classifications on shift tables will categorize lab values as "Normal" when they are in an acceptable range, using a combination of clinician judgment specific to each lab test, and the local lab reference ranges (see below). Laboratory values outside the normal range will be graded on the Labs Listing as 1x, 2x, 3x, 5x or 10x the upper limit (or .5x, 1x the lower limit) of normal value based on appropriate increases or decreases. Lab tests reflective of liver toxicity (ALT, AST, and Total and Direct Bilirubin) will be further summarized in terms of the most extreme values and largest increases from baseline observed from the start of study drug through Day 16 Post-Randomization (± 4 days). Laboratory data will also be summarized graphically to show the magnitude and changes in individual subject values over time relative to normal ranges.

Laboratory Name	**Clinically Pertinent Normal Range**
Blood Urea Nitrogen [BUN]	(0, Site Specific ULN)
Calcium	(Site Specific LLN, Site Specific ULN)
Serum Creatinine	(0, Site Specific ULN)
Potassium	(Site Specific LLN, Site Specific ULN)
Sodium	(Site Specific LLN, Site Specific ULN)

AST	(0, Site Specific ULN)
ALT	(0, Site Specific ULN)
Alkaline Phosphatase	(0, Site Specific ULN)
Total Bilirubin	(0, Site Specific ULN)
Direct Bilirubin	(0, Site Specific ULN)
Albumin	(Site Specific LLN, ∞)
Hemoglobin	(Site Specific LLN, ∞)
Hematocrit	(Site Specific LLN, ∞)
WBC Count	(Site Specific LLN, Site Specific ULN)
Platelet Count	(Site Specific LLN, Site Specific ULN)
Neutrophils	(Site Specific LLN, Site Specific ULN)
Lymphocytes	(Site Specific LLN, Site Specific ULN)
Monocytes	(Site Specific LLN, Site Specific ULN)
Eosinophils	(Site Specific LLN, Site Specific ULN)
Basophils	(Site Specific LLN, Site Specific ULN)
C-reactive protein	(0, Site Specific ULN)
Procalcitonin	(0, Site Specific ULN)

10.3.3 Vital Signs

Vital sign data plots will be produced to graphically display data summaries. Each vital sign that is presented will include the time windows “Baseline”, “Day 1”, “Day 2-7 Combined”, and “Day 8-10 Combined.”

10.3.4 Prior and Concomitant Medications

Prior and concomitant medication use will be tabulated by generic drug name. Prior medications and concomitant medications generic name and anatomic therapeutic chemical classification (ATC) level will be coded using the September 2015 version of the World Health Organization Drug Dictionary (WHODD) Enhanced.

10.3.5 Pregnancy Tests

Pregnancy test results at baseline and any other reported will be listed for female participants of child-bearing potential.

10.4 Secondary Efficacy/Clinical Outcomes

Evaluation of clinical signs and symptoms of CABP, requirement for additional or alternative antimicrobial therapy, and efficacy will be performed by a blinded investigator or designee at the site. Outcomes will be assessed at the following time points:

- Baseline clinical signs and symptoms assessment
- Clinical improvement on Day 3 - 4. If the subject is discharged from the hospital prior to Day 3, assessment may be recorded on Day 2.
- Clinical improvement on the last day of treatment (+48 hours)
- Clinical cure during short-term follow up at 16 days (± 4 days) after 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 or other media.

Efficacy will be quantified as a binary variable at each timepoint listed above using the algorithm specified in Appendix 2. Clinical improvement is defined as improvement (compared to baseline) of at least 1 of the presenting signs and symptoms of CABP with no deterioration in any presenting sign or symptom of CABP (compared to baseline), no development of new sign or symptom of CABP, and no requirement for additional or alternative antimicrobial therapy. 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 antimicrobial therapy. Clinical improvement and cure will be determined using the specific signs and symptoms data recorded on the eCRF, as well as a separate question on the eCRF concerning additional antimicrobial therapy. These questions will be completed by the blinded investigator (or potentially unblinded investigator in the case of screening evaluation), who will be supplied with information according to the blinded investigator plan.

Efficacy will be evaluated in the randomized population, and subjects will be evaluated in the treatment group to which they were randomized regardless of actual treatment received (Intention-To-Treat analysis). The main analysis of efficacy at each time point will include subjects with efficacy evaluated at that time point (complete case analysis). The frequency and percentage of subjects achieving each efficacy end point will be determined, and a 95% Clopper-Pearson (exact) confidence interval calculated. Summaries will be calculated by treatment arm for the overall randomized population and by treatment arm stratified within consolidated age group. This study is not powered for comparison of efficacy end points between treatment groups.

10.5 Standard of Care Evaluations

Evaluations that are collected as part of the standard of care will be recorded. These may include microbiology evaluations (all cultures from sterile body fluids, as well as molecular and serologic tests for *M. pneumoniae* and *C. pneumoniae*), radiological imaging of the chest, including chest x-ray or CT scan, and surgeries and non-pharmacological procedures of interest (including surgeries of the chest and chest wall such as pleural tube placement, video assisted thoracoscopic surgery, and surgical procedures of the head and neck). These evaluations will be presented in listings and will be summarized by treatment arm.

11 INTERIM DMC DATA REVIEW

- To monitor the safety and tolerability of solithromycin in the CE01-203 trial, 4 interim data monitoring committee (DMC) meetings are planned to review accumulating data. Interim review meetings will occur at ~6 month intervals, at ~ 6, 12, 18, and 24 months after the initial meeting. The following data will be listed and/or summarized for the DMC. Data completeness to date

- Demographic data, baseline characteristics (such as underlying conditions, suspected/identified/confirmed bacterial infection, etc.) and enrollment trends.
- Subjects who have discontinued prematurely from the study and/or study drug: listing of all such subjects including date of discontinuation and reason discontinued by site
- Study drug exposure data
- Prior and Concomitant medication
- Vital signs
- Laboratory data, relative to corresponding lab normals will be listed. Additionally, a summary of lab abnormalities and grade will be presented in table format.
- All serious adverse events
- All adverse events
- Treatment emergent adverse events
- Aggregate summaries for safety labs and vital signs
- PK data, if available and needed in the evaluation of safety
- Efficacy data, if needed in the evaluation of safety
- Additional data may be added as request by the DMC

Summaries will be aggregated for the DMC as described in above sections of this SAP for relevant data elements, for example, by treatment arm and by treatment arm within consolidated age group, as sample size of accumulating data allows. Details of the DMC operations and responsibilities are laid out in the DMC Charter.

12 TABLES, FIGURES, AND LISTINGS SHELLS

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14.5 Efficacy Data

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16.2.2 Patient Disposition

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16.2.3 Demographics and Other Baseline Characteristics

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16.2.4 Study Drug Exposure

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[1] This output will present the 4 age groups (2 Months - <2 Yrs, 2 - <6 Yrs, 6 - <12 Yrs, 12 – 17 Yrs) as well as the two treatment arms (All Subjects Soli, All Subjects Comparator) for a total of 6 categories of subjects.
[2] This output will present the 8 categories: 2 Months - <2 Yrs Soli., 2 Months - <2 Yrs Comparator, 2 - <6 Yrs Soli., 2 - <6 Yrs Comparaor, 6 - <12 Yrs Soli., 6 - <12 Yrs Comparator, 12 – 17 Yrs Soli., 12 – 17 Yrs Comparator.