A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Lefamulin (BC-3781) Versus Moxifloxacin (With or Without Adjunctive Linezolid) in Adults With Community-Acquired Bacterial Pneumonia

Protocol: NAB-BC-3781-3101

AMENDED

STATISTICAL ANALYSIS PLAN

STATISTICAL ANALYSIS PLAN APPROVAL

Protocol: NAB-BC-3781-3101

Version 2.0

Anita F. Das, PhD
Project Statistician

01 Sept 2017
Date

Leanne Gasink, MD
Senior Director, Clinical Development and
Medical Affairs
Nabriva Therapeutics AG

1 Sept 2017
Date

Lisa Goldberg
Senior Director, Clinical Development
Nabriva Therapeutics AG

1 Sept 2017
Date

AMENDMENT: 30 AUG 2017

The Amended SAP includes changes to better describe planned analyses, clarifications and corrections to analyses and definitions. Added text is **bolded**; deleted text is ~~struck through~~. Corrections of typographical errors and minor wording updates are not included in the summary below.

Section 4.0 PATHOGEN IDENTIFICATION Baseline is defined as the 24-hour period prior to the administration of the first dose of study drug **and the 24 hours after the first dose of study drug**. A pathogen identified from a respiratory (pleural fluid, bronchoalveolar lavage (BAL), sputum), blood for culture, urine, nasopharyngeal or oropharyngeal specimen collected at baseline is considered a baseline pathogen. An atypical pathogen identified by serology is considered a baseline pathogen if the baseline sample is collected in the 24-hour period prior to **or the 24 hours after** the administration of the first dose of study drug. ~~If no specimen (ie, respiratory culture, blood culture, blood for serology, urine, nasopharyngeal or oropharyngeal) is collected in the 24-hour period prior to the first dose of study drug or no pathogen is identified from the specimen prior to the first dose of study drug, a specimen obtained within 24 hours after the first dose of study drug which identifies a pathogen will be considered baseline.~~ Post-baseline is defined as ~~after the first dose of study drug. In those cases where a specimen obtained within the 24 hours after the first dose of study drug is considered baseline, post-baseline is defined as~~ the period starting 24 hours after the first dose of study drug. A pathogen identified from a specimen collected post-baseline is considered a post-baseline pathogen. Only pathogens identified by culture of the sputum, BAL, pleural fluid or blood are considered post-baseline pathogens.
Section 4.1 "Typical" Respiratory Pathogens The best Gram stain reading from the central read of a central laboratory Gram stained respiratory specimen and the central read of the local/regional laboratory Gram stained respiratory specimen will be used to determine the adequacy of the specimen for pathogen determination. **If the Gram stain reading from the central read of a central laboratory Gram stained respiratory specimen and the central read of the local/regional laboratory Gram stained respiratory specimen have the same ranking, the central read of a central laboratory Gram stained respiratory specimen will be considered the best Gram stain.**

Section 4.2 "Atypical" Respiratory Pathogens

Mycoplasma pneumoniae

- Between baseline and convalescent (LFU Visit) specimens, a 4-fold or greater increase in *M. pneumoniae* IgG serum antibody titer to ≥1:160; or
- ~~A single *M. pneumoniae* IgM titer ≥1:20; or~~

Chlamydophila pneumoniae

- Between baseline and convalescent (LFU Visit) specimens, a 4-fold or greater increase in *C. pneumoniae* IgG serum antibody titer; or
- ~~A single *C. pneumoniae* IgM titer ≥1:10; or~~

Section 5.6 Clinically Evaluable (CE) Analysis Sets

2. Completed the visit within the protocol mandated window:
   - For the CE-EOT Analysis Set:
     - Completed the EOT Visit **on the day of last dose of study drug or** within 2 days after the last dose of study drug.
6. Received the correct study drug ~~for all doses~~, based on randomization assignment**, for all active doses taken.**
9. Subjects who have ~~CABP caused by a pathogen known to be resistant to any of the study drugs,~~ pneumonia attributable to etiologies other than community-acquired pneumonia, a noninfectious cause of pulmonary infiltrates or confirmed pleural empyema at Screening but discovered post-baseline will be excluded from the CE Analysis Sets.

Section 5.7 Microbiologically Evaluable (ME) Analysis Sets

The ME Analysis Sets (ME-EOT, ME-TOC and ME-LFU) will consist of all subjects who meet criteria for inclusion in both the microITT and the CE-EOT (ME-EOT) Analysis Set, the CE-TOC (ME-TOC) Analysis Set or the CE-LFU (ME-LFU) Analysis Set. **Subjects who have CABP caused *only* by a pathogen(s) resistant to moxifloxacin or lefamulin will be excluded from the ME Analysis Sets. Resistance is defined as: 1) a pathogen resistant to moxifloxacin or non-susceptible to lefamulin based on susceptibility results from the central laboratory, or 2) a pathogen in the *Enterobacteriaceae* family or a non-fermenting Gram-negative pathogen (with the exception of *Legionella pneumophila* and *Moraxella catarrhalis*), unless susceptibility data from the central laboratory is available and indicates the pathogen is susceptible to both moxifloxacin (Table 9) and lefamulin (Table 10).**

Section 5.9 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set will consist of all subjects in the mITT Analysis Set who have at least one pharmacokinetic sample analyzed.

Section 6.1 Primary Efficacy Outcome: Early Clinical Response

Section 6.2.3 Early Clinical Response Plus Improvement in Vital Signs

- Received a concomitant antibiotic (other than adjunctive linezolid for subjects randomized to the moxifloxacin treatment group) for the treatment of CABP up through the assessment of the cardinal symptoms of CABP, or if no assessment was completed, up to 120 hours after the first dose of study drug **(or randomization if the subject did not receive study drug)**; or

Section 6.2.3 Early Clinical Response Plus Improvement in Vital Signs

- Improvement in vital signs (ie, body temperature, blood pressure, heart rate, respiratory rate), if abnormal at baseline. Improvement is defined as returning to normal. If vital signs are normal at baseline (ie, not abnormal as per the definitions below), none can have worsened. Abnormal vital signs are defined as:
  - Fever: defined as body temperature >38.0°C (100.4°F) measured orally, >38.5°C (101.3°F) measured tympanically, ~~or~~ >39.0°C (102.2°F) measured rectally **or >37.5°C (99.5°F) by axillary measurement**
- Did not show an improvement in vital signs. Improvement is defined as the following:
  - Body temperature 35.0 to 38.0°C (95.0 to 100.4°F) measured orally, 35.5 to 38.5°C (95.9 to 101.3°F) measured tympanically, ~~or~~ 36.0 to 39.0°C (96.8 to 102.2°F) measured rectally **or 34.5 to 37.5°C (94.1 to 99.5°F) by axillary measurement**

Section 6.2.5 28-Day All-Cause Mortality

Subjects **with an LFU visit on Study Day 27 will be considered alive on Study Day 28 unless known to have died on Study Day 28. Other subjects** who are not known to be alive or deceased ~~on~~ **as of Study** Day 28 will be defined as deceased and included in the numerator and denominator for the calculation of the ACM rate. The 28-day ACM rate is defined by the following formula:

$$\frac{\text{Number of subjects deceased } \sout{\text{on or before Day 28}}}{\text{Number of subjects alive at Day 28} + \text{Number of subjects deceased } \sout{\text{on or before Day 28}}}$$

Section 7.2 Visit Windows

Unless otherwise stated ~~in this SAP~~ **below**, baseline is defined as the last measurement prior to the first dose of study drug.

- **For microbiological pathogen determination, baseline is defined as the 24-hour period prior to the administration of the first dose of study drug and the 24 hours after the first dose of study drug. A pathogen identified from a respiratory (pleural fluid, bronchoalveolar lavage (BAL), sputum), blood for culture, urine, nasopharyngeal or oropharyngeal specimen collected at baseline is considered a baseline pathogen. An atypical pathogen identified by serology is considered a baseline pathogen if the baseline sample is collected in the 24-hour period prior to or the 24 hours after the administration of the first dose of study drug.**
- **For vital signs, baseline is defined as the last assessment prior to Day 1.**
- **For ECGs, baseline is defined as the mean of the triplicates from the last assessment prior to the first dose of study drug.**
- **If no study drug is received, baseline is defined as the measurement taken at the Screening Visit**

The visit window for ECR is defined in Section 6.1. Clinical efficacy and safety analyses ~~at Day 7 (safety only), EOT, TOC and LFU~~ will utilize the data obtained on the scheduled visit (ie, nominal visit will be utilized). **Safety labs (chemistry, hematology and urinalysis) are collected for all subjects at Screening, Day 4, EOT and TOC. Subjects receiving 10 days of study drug also have safety labs collected at Day 7. Safety labs are completed at LFU only if the subject had an abnormal result at TOC.** For Day 4 safety **lab** assessments, the window is Day 4 ± 1 day. **For Day 7 safety lab assessments, the window is Day 7 +1 day. Vital signs are collected daily while the subject is seen in person and at EOT and TOC. ECGs are collected at Screening, Day 1 and Day 3, prior to the first infusion of study drug on that day and within 15 minutes after the end of the first infusion on that day. See Appendix A for a complete description on the timing of the safety assessments.**

If no scheduled visit was done, but an unscheduled safety assessment was done in the window of the scheduled assessment (for the specific safety parameter), the unscheduled assessment should be used. If more than 1 measurement is taken during the visit window **(a scheduled visit and an unscheduled visit)**, the value taken on the scheduled visit will be utilized ~~or if no scheduled visit was done the measurement closest to but after the scheduled visit will be used~~. **If more than one unscheduled assessment is completed in the visit window of the scheduled assessment (and no scheduled assessment), the earliest assessment should be used.** For overall worst post-baseline analyses, all assessments including those obtained on unscheduled and scheduled visits will be included.

Section 8.1 Subject Disposition and Protocol Deviations

A significant protocol deviation is one that **has the potential to** affects ~~the primary~~ efficacy assessment**s**, **placement into analysis populations**, the safety or ~~mental integrity~~ **ability to monitor the safety** of a subject, or the scientific value of the trial.

Section 8.2 Demographics and Baseline Characteristics

Creatinine clearance based on **the** central lab **determination will be used**. **In those cases where creatinine clearance is not available from the central lab, it will be calculated using the local lab** serum creatinine **based on** ~~will be calculated from~~ the Cockcroft-Gault equation:

A table will provide the frequency counts and percentages by treatment group and overall for PORT Risk Class (both as per IRT [III, IV/V] as well as calculated from components reported in the eCRF [III, IV, V]), subjects meeting the modified American Thoracic Society (ATS) severity criteria, subjects meeting the Systemic Inflammatory Response Syndrome (SIRS), **CURB-65 category**, and subjects with bacteremia for the ITT, mITT and CE-TOC Analysis Sets.

Baseline assessments of clinical signs and symptoms of CABP, including fever (defined as body temperature >38.0°C (100.4°F) oral, tympanic >38.5°C (101.3°F), rectal/core >39.0°C (102.2°F), **or axillary >37.5°C (99.5°F)**), hypothermia (defined as body temperature <35.0°C (95.0°F) oral, tympanic <35.5°C (95.9°F), or rectal/core <36.0°C (96.8°F)), hypotension (systolic blood pressure <90 mmHg), tachycardia (heart rate >100 beats/min), tachypnea (respiratory rate >20 breaths/min), dyspnea, cough, production of purulent sputum and chest pain will be summarized by treatment group and overall for the ITT, mITT and CE-TOC Analysis Sets.

Table 8. Definitions of Pathogen Susceptibility Profile

Pathogen	Susceptibility Profile	Definition
Staphylococcus aureus	MSSA	Susceptible to ~~oxacillin~~ **cefoxitin**
	MRSA	Resistant to ~~oxacillin~~ **cefoxitin**
Streptococcus pneumoniae	PSSP	Susceptible to penicillin
	PISP	Intermediate susceptibility to penicillin
	PRSP	Resistant to penicillin
	Macrolide resistant	Resistant to azithromycin or erythromycin
	Quinolone resistant	Resistant to moxifloxacin
	Multidrug resistant	Resistant to 2 or more of the following classes of drugs: • Penicillins – **oral** penicillin • Fluoroquinolones – moxifloxacin • Cephalosporins – ~~cefuroxime or~~ ceftriaxone • Lincosamides – clindamycin • Macrolides – azithromycin or erythromycin • Tetracyclines – ~~tetracycline~~ **doxycycline** • Folate Pathway Inhibitors – trimethoprim/sulfamethoxazole

Section 8.3 Baseline Microbiological Assessments

In addition, summaries of PMNs and SECs and bacterial morphology for all Gram-stained respiratory specimens will be provided. **Baseline for Gram stains is defined as the 24-hour period prior to first dose of study drug and the 24-hour period after the first dose of study drug.**

Baseline pathogens are considered susceptible (S), intermediate (I), or resistant (R) to moxifloxacin and **S or non-susceptible (NS)** to lefamulin according to the criteria in Table 9 and Table 10.

Table 10. Proposed Tentative Susceptibility Interpretive Criteria for Lefamulin for CABP Pathogens Based on *In Vitro* Data Determined According to CLSI Guidelines

	Lefamulin MIC breakpoint [a] [µg/mL]			**Lefamulin Disk Diffusion Zone Diameter [a] [mm]**		
Pathogen	**S**	~~**I**~~**NS**	~~**R**~~	**S**	~~**I**~~**NS**	~~**R**~~
Streptococcus pneumoniae	≤ 1	**>1**	-	≥ 19	**<19**	-
Staphylococcus spp.	≤ 1	**>1**	~~≥ 2~~	≥ 20	**<20**	~~≤ 19~~
Haemophilus influenzae	≤ 2	**>2**	-	≥ 20	**<20**	-
Moraxella catarrhalis	≤ 1	**>1**	-	≥ 20	**<20**	-
Legionella pneumophila	≤ 1	**>1**	-	- [b]	- [b]	~~-~~ [b]
Mycoplasma pneumoniae	≤ 1	**>1**	-	- [b]	- [b]	~~-~~ [b]

S=susceptible, ~~I=intermediate, R=resistant~~ **NS=non-susceptible**

[a] The current absence of data on resistant isolates except for *S. aureus* precludes defining any category other than "susceptible." ~~If an isolate yields an MIC result other than susceptible it should be retested being sure that the test is performed correctly. If the results are other than susceptible on re-test, the isolate will be subject to additional testing including investigation of the molecular resistance mechanism (including check for presence of *cfr*, *vga*(A), *vga*(B) and *vga*(C) and sequencing of 23S rDNA, *rplC* and *rplD*).~~

[b] No disk diffusion zone diameter criteria have been established for *M. pneumoniae* and *L. pneumophila*.

8.5.2 Additional Analyses of the Primary Efficacy Outcome

- Subjects who are non-responders and receive less than 48 hours **total duration** of study drug will be reclassified as indeterminates and the number and percentage of subjects in each treatment group in each response category will be reported. **Subjects who died prior to receipt of at least 48 hours total duration of study drug will remain classified as a non-responder.** An unadjusted 95% CI will be computed using a continuity corrected Z-test for the difference in the ECR responder rates between lefamulin and moxifloxacin.

Section 8.5.4.1 Clinical Outcome Measures

A summary of subjects who met the criteria for ECR responder (ie, alive, improvement in at least 2 of the 3 or 4 cardinal symptoms of CABP the subject presented with at baseline, no worsening of any of the 4 cardinal symptoms of CABP and did not receive a concomitant antibiotic (other than adjunctive linezolid) for the treatment of CABP through the assessment of the cardinal symptoms of CABP) will be provided by study visit. ~~Analyses of signs and symptoms will only be assessed in subjects with non-missing assessments of all baseline signs and symptoms at the specified visit~~ **For each study visit, ECR will be determined for (ie, the denominator will consist of) those subjects who have died up through the relevant assessment, those subjects who have received an antibiotic for the treatment of CABP up through the relevant visit and those subjects with non-missing assessments of all baseline cardinal CABP symptoms at the relevant visit. If the EOT Visit and the last day of study drug are on the same day and only 1 assessment is performed, the assessment will be summarized both at the study day and the EOT Visit.**

Section 8.7 Safety Analyses

For each safety parameter with the exception of ECGs which are measured in triplicate at each time point **and vital signs which uses the last assessment prior to Day 1**, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses.

Section 8.7.2 Clinical Laboratory Evaluations

Central laboratory data will be utilized for all analyses. ~~Local laboratory data will be analyzed for liver function tests~~ **For the purposes of summarizing post-baseline maximum** alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), **and** total bilirubin and ~~gamma-glutamyl-transferase) if central data are not available~~ **for the purposes of identifying cases of potential Hy's law, both central and local laboratory data will be used. In addition, local laboratory data will be utilized in the assessment of any Potentially Clinically Significant (PCS) labs as defined in Appendix B. Local laboratory data are collected on the eCRF: 1) if the subject did not meet the laboratory inclusion/exclusion criteria based on the central laboratory results, 2) potential Hy's law is reported based on local laboratory results, and 3) the Principal Investigator chooses to report local laboratory results obtained in the clinical management of the patient.**

Section 8.7.3 ECG Parameters

The number and percentage of subjects with a post-baseline QTcF of >~~450~~ **480** msec or >500 msec will also be summarized by treatment group. The number and percentage of subjects with a post-baseline increase in QTcF of >30 msec resulting in a post-baseline QTcF of >~~450~~**480** msec or >500 msec **as well as QTcF of >60 msec resulting in a post-baseline QTcF of >480 msec or >500 msec** will also be summarized by treatment group.

~~The number and percentage of subjects with any treatment-emergent ECG abnormality and a summary of treatment-emergent ECG abnormalities will also be summarized by treatment group. A treatment-emergent ECG abnormality is defined as an ECG abnormality that starts at or during the time of or after the first study drug administration.~~ **A listing will be provided of findings identified on the ECG.**

Section 8.7.4 Vital Signs

Descriptive statistics for **temperature, respiratory rate,** heart rate, diastolic blood pressure, systolic blood pressure, and the change from baseline at each post-baseline visit will be summarized by treatment group for all subjects in the Safety Analysis Set. Change from baseline will be calculated for each subject at the specified visit as the value at the specified visit minus the baseline value. The change from baseline to the minimum and maximum post-baseline values will also be summarized by treatment group. Change from baseline will be calculated for each subject as the minimum or maximum post-baseline value minus the baseline value. Baseline is defined as the last assessment prior to ~~the first dose of study drug~~ **Day 1**.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACM	All-cause mortality
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BUN	Blood urea nitrogen
C	Celsius
CABP	Community-acquired bacterial pneumonia
CE	Clinically evaluable
CE-EOT	Clinically Evaluable at End of Treatment
CE-LFU	Clinically Evaluable at Late Follow Up
CE-TOC	Clinically Evaluable at Test-of-Cure
CI	Confidence interval
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECR	Early Clinical Response
eCRF	Electronic case report form
EMA	European Medicines Agency
emicroITT	Expanded Microbiological Intent-to-Treat
EOT	End of Treatment
EU	European Union
F	Fahrenheit
FDA	US Food and Drug Administration
GGT	Gamma-glutamyl-transferase
IAC	Interim Analysis Committee
IACR	Investigator's Assessment of Clinical Response
IRT	Interactive response technology
ITT	Intent-to-Treat
IV	Intravenous
LFU	Late follow-up
LLN	Lower limit of normal
LPF	Low power field
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
ME-EOT	Microbiologically Evaluable at End of Treatment

ME-LFU	Microbiologically Evaluable at Late Follow Up
ME-TOC	Microbiologically Evaluable at Test-of-Cure
mg	Milligram
MIC	Minimum inhibitory concentration
microITT	Microbiological Intent-to-Treat
microITT-2	Microbiological Intent-to-Treat-2
mITT	Modified Intent-to-Treat
mmHg	Millimeter of mercury
MRSA	Methicillin resistant *Staphylococcus aureus*
MSSA	Methicillin susceptible *Staphylococcus aureus*
NA	Not applicable
NI	Non-inferiority
PCS	Potentially clinically significant
PISP	Penicillin intermediate S*treptococcus pneumoniae*
PMNs	Polymorphonuclear neutrophils
PO	By mouth (oral)
PORT	Pneumonia Outcomes Research Team
PRO	Patient reported outcome
PRSP	Penicillin resistant *Streptococcus pneumoniae*
PSSP	Penicillin susceptible *Streptococcus pneumoniae*
PVL	Panton-Valentine Leukocidin
q12h	Every 12 hours
q24h	Every 24 hours
QTcF	QT interval corrected by the Fridericia formula
RQ-PCR	Real-time quantitative Polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SEC	Squamous epithelial cells
SIRS	Systemic Inflammatory Response Syndrome
Spp	Species
TEAE	Treatment-emergent adverse event
TOC	Test of Cure
UAT	Urinary antigen test
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

1.0 INTRODUCTION

This statistical analysis plan (SAP) provides the framework for the summarization and analysis of the clinical data from the study, "A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Lefamulin (BC-3781) Versus Moxifloxacin (With or Without Adjunctive Linezolid) in Adults With Community-Acquired Bacterial Pneumonia." Changes made to this SAP after it has been signed but prior to database lock will be documented in an amendment. Any important changes made to the analysis after database lock will be described in the clinical study report. Pharmacokinetic analyses (except for the description of plasma concentrations) and health utilization and patient-reported outcome analyses will not be included in this SAP, but will be addressed in separate analysis plans.

Study NAB-BC-3781-3101 has been designed to address both the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory requirements. While the EMA supports the assessment of clinical response by the Investigator at a Test of Cure (TOC) Visit (which is scheduled to occur 5-10 days after the last dose of study drug) as the primary endpoint, the FDA is using an earlier primary endpoint (3-5 days after the first dose of study drug) based on improvement in pneumonia symptoms.

This SAP addresses the primary efficacy outcome and analyses for the FDA. A SAP Addendum will be developed to address the different primary efficacy outcome and analyses for the EMA.

2.0 STUDY DESIGN

This is a Phase 3, multicenter, multinational, randomized, double-blind, double-dummy comparative efficacy and safety study of lefamulin (150 mg intravenous (IV) over 60 minutes every 12 hours (q12h) with an optional switch to oral 600 mg q12h) and moxifloxacin (400 mg IV over 60 minutes every 24 hours (q24h) with an optional switch to oral 400 mg q24h) in the treatment of adult subjects with community-acquired bacterial pneumonia (CABP). If the Investigator determines at baseline based on pre-specified criteria that methicillin-resistant *Staphylococcus aureus* (MRSA) could be the etiological agent of the current CABP episode, then adjunctive linezolid therapy must be added to the moxifloxacin treatment arm with placebo linezolid added to the lefamulin treatment arm. Subjects will be permitted to switch from IV to oral study drug (ie, lefamulin or moxifloxacin ± linezolid) after at least 6 doses of IV therapy and if clinically appropriate (ie, there has been improvement in at least 2 of the 3 or 4 cardinal symptoms of pneumonia [dyspnea, cough, sputum production, chest pain] and subjects are hemodynamically stable, have a normalizing temperature curve with a maximum temperature in the previous 24 hours of <38.0°C (<100.4°F), and are able to swallow and absorb oral medications [ie, have a normally functioning gastrointestinal tract]).

A total of 550 subjects with CABP will be randomized 1:1 to study treatment (275 to each treatment arm) using interactive response technology (IRT). However, if based upon regulatory requirements additional subjects exposed to lefamulin are needed, up to 626 subjects may be enrolled and randomized. Randomization will be stratified by geographic region (US vs. ex-US), prior single dose treatment with a short acting antibiotic vs. none, and by Pneumonia Outcomes Research Team (PORT) risk class (PORT III vs. IV/V). Enrollment of subjects receiving prior

antibiotic therapy will be capped at 25% and enrollment of subjects with a PORT risk class of III will be capped at 75%. An independent Interim Analysis Committee (IAC) will perform a blinded sample size reassessment when approximately 60% of subjects randomized have been followed through the FDA time point (96 ± 24 hours) for the assessment of the primary efficacy outcome.

After informed consent is obtained, all potential study participants undergo screening evaluations, which includes a medical history, clinical assessments, and laboratory assessments. It is estimated that the duration of study drug administration for the majority of subjects (approximately 90%) will be 7 days of active treatment. Subjects with CABP due to MRSA will receive 10 days of active treatment. Other treatment scenarios are detailed in the original and Amendment 1 protocols. An assessment of Early Clinical Response (ECR) will occur 96 ± 24 hours after the first dose of study drug. An Investigator's Assessment of Clinical Response (IACR) will be evaluated at the End of Treatment (EOT) Visit (within 1 day after the last dose of study drug or if not logistically feasible [eg, visit would need to be conducted over a weekend], then conducting the visit within 2 days is acceptable), at the TOC Visit (5 to 10 days after the last dose of study drug), and at a Late Follow-up (LFU) Visit conducted between Study Day 27 and 34 (inclusive).

The schedule of assessments and procedures is provided in Appendix A.

3.0 STUDY OBJECTIVES

Primary:

Demonstrate the non-inferiority (NI) of lefamulin versus comparator with respect to the Early Clinical Response (96 ± 24 hours after the first dose of study drug) in the Intent-to-Treat (ITT) Analysis Set.

Secondary:

- Demonstrate the NI of lefamulin versus comparator with respect to the Investigator's Assessment of Clinical Response at TOC (ie, 5-10 days after the last dose of study drug) in the modified-ITT (mITT) and Clinically Evaluable at TOC (CE-TOC) Analysis Sets. **NOTE:** These are the co-primary efficacy endpoints for the EMA.
- Evaluate the Early Clinical Response in the Microbiological Intent-to-Treat (microITT) Analysis Set.
- Evaluate the Early Clinical Response PLUS improvement in vital signs in the ITT Analysis Set.
- Evaluate the Investigator's Assessment of Clinical Response at TOC in the microITT and Microbiologically Evaluable at TOC (ME-TOC) Analysis Sets.
- Evalute the By-Pathogen Microbiologic Response at TOC in the microITT and ME-TOC Analysis Sets.
- Evaluate the safety and tolerability of lefamulin versus comparator in the Safety Analysis Set.
- Evaluate 28 day all-cause mortality in the ITT Analysis Set.

Additional:

- Evaluate the Early Clinical Response by baseline pathogen in the microITT Analysis Set.
- Evaluate the Investigator's Assessment of Clinical Response at EOT (ie, within 2 days after the last dose of study drug) and at LFU in the mITT and Clinically Evaluable (CE) Analysis Sets (CE-EOT for IACR at EOT and CE-LFU for IACR at LFU).
- Evaluate the Investigator's Assessment of Clinical Response by baseline pathogen at TOC and LFU in the microITT and Microbiologically Evaluable (ME) Analysis Sets (ME-TOC for IACR at TOC and ME-LFU for IACR at LFU).
- Evaluate the By-Subject Microbiologic Response at TOC in the microITT and ME-TOC Analysis Sets.
- Evaluate the plasma pharmacokinetics of lefamulin in the Pharmacokinetic Analysis Set.
- Explore a variety of health utilization variables and an investigational patient reported outcome measure (SF-12) in subjects receiving lefamulin compared with subjects receiving comparator.

4.0 PATHOGEN IDENTIFICATION

All microbiology data will be reviewed by the Sponsor for pathogen identification. A pathogen is defined as bacteria implicated as causative in a subject's CABP and will be determined separately for each subject. Baseline pathogens and post-baseline pathogens will be identified.

Additional details regarding the pathogen review process and determination are included in the Evaluability Review Plan.

Baseline is defined as the 24-hour period prior to the administration of the first dose of study drug and the 24 hours after the first dose of study drug. A pathogen identified from a respiratory (pleural fluid, bronchoalveolar lavage (BAL), sputum), blood for culture, urine, nasopharyngeal or oropharyngeal specimen collected at baseline is considered a baseline pathogen. An atypical pathogen identified by serology is considered a baseline pathogen if the baseline sample is collected in the 24-hour period prior to or the 24 hours after the administration of the first dose of study drug.

If more than 1 specimen is taken during the baseline period, all specimens will be reviewed for pathogen identification. If the same pathogen (based on genus and species) is identified from more than 1 specimen, the pathogen with the highest minimum inhibitory concentration (MIC) to study drug received will be considered the baseline pathogen. If the pathogens have the same MIC to study drug received, the one with the highest accession number will be considered the baseline pathogen.

Post-baseline is defined as the period starting 24 hours after the first dose of study drug. A pathogen identified from a specimen collected post-baseline is considered a post-baseline pathogen. Only pathogens identified by culture of the sputum, BAL, pleural fluid or blood are considered post-baseline pathogens.

4.1 "Typical" Respiratory Pathogens

Sputum samples will undergo a microscopic examination. Microscopic examination of Gram-stained sputum specimens will be performed by the local/regional laboratory. Gram's stain slides will be sent to the central laboratory for a confirmatory reading. The stained slide read by the local/regional laboratory as well as an unstained slide will be sent to the central laboratory. The best Gram stain reading from the central read of a central laboratory Gram stained respiratory specimen and the central read of the local/regional laboratory Gram stained respiratory specimen will be used to determine the adequacy of the specimen for pathogen determination. If the Gram stain reading from the central read of a central laboratory Gram stained respiratory specimen and the central read of the local/regional laboratory Gram stained respiratory specimen have the same ranking, the central read of a central laboratory Gram stained respiratory specimen will be considered the best Gram stain. The central reads of polymorphonuclear neutrophils (PMNs)/low power field (LPF) and squamous epithelial cells (SECs)/LPF ranked best to worst are as follows:

1. >25 PMNs/LPF and <10 SECs/LPF
2. 10-25 PMNs/LPF and <10 SECs/LPF
3. <10 PMNs/LPF and <10 SECs/LPF
4. >25 PMNs/LPF and 10-25 SECs/LPF
5. 10-25 PMNs/LPF and 10-25 SECs/LPF
6. <10 PMNs/LPF and 10-25 SECs/LPF
7. >25 PMNs/LPF and >25 SECs/LPF
8. 10-25 PMNs/LPF and >25 SECs/LPF
9. <10 PMNs/LPF and >25 SECs/LPF

If neither of the central reads is available, the local/regional read of the local/regional laboratory Gram stained respiratory specimen will be used.

If the genus identification is the same between the local and central microbiology laboratories but the species identification is discrepant, the central laboratory identification will be used. If the local laboratory grows an isolate but the central laboratory is not able to grow the isolate, if isolates were lost during transportation or storage, or there are major discrepancies between the local and central laboratory in the identification of species, the central laboratory will request the local laboratory to resend the isolate. If the central laboratory identification is not available for an isolate, the local laboratory identification will be used. It is possible for subjects to have different isolates from both central and local laboratories as a result. For any remaining major discrepancies in genus and/or species identification between the central and local laboratory, the central laboratory identification will be used as the default identification.

Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and *Moraxella catarrhalis* will always be considered a CABP pathogen in the presence of the following criteria:

Streptococcus pneumoniae

- Positive BAL, pleural fluid or blood culture; or
- Positive sputum culture in the presence of a Gram stain with >25 PMNs/LPF and <10 SECs/LPF (**NOTE:** ≥10 PMNs/LPF and <10 SECs/LPF in the expanded Microbiological ITT (emicroITT) Analysis Set); or
- Positive urinary antigen test; or
- Positive real-time quantitative Polymerase chain reaction (RQ-PCR) of nasopharyngeal swab or sputum (see Table 1 for cutoff values); or
- Positive nasopharyngeal specimen culture

Haemophilus influenzae

- Positive BAL, pleural fluid or blood culture; or
- Positive sputum culture in the presence of a Gram stain with >25 PMNs/LPF and <10 SECs/LPF (**NOTE:** ≥10 PMNs/LPF and <10 SECs/LPF in the emicroITT Analysis Set); or
- Positive RQ-PCR of sputum (see Table 1 for cutoff value)

Staphylococcus aureus

- Positive BAL, pleural fluid or blood culture; or
- Positive sputum culture in the presence of a Gram stain with >25 PMNs/LPF and <10 SECs/LPF (**NOTE:** ≥10 PMNs/LPF and <10 SECs/LPF in the emicroITT Analysis Set); or
- Positive RQ-PCR of sputum (see Table 1 for cutoff value)

Moraxella catarrhalis

- Positive BAL, pleural fluid or blood culture; or
- Positive sputum culture in the presence of a Gram stain with >25 PMNs/LPF and <10 SECs/LPF (**NOTE:** ≥10 PMNs/LPF and <10 SECs/LPF in the emicroITT Analysis Set); or
- Positive RQ-PCR of sputum (see Table 1 for cutoff value)

The following isolates are considered as contaminants from respiratory specimens rather than primary pathogens of CABP: fungi, *Enterococcus* spp., viridans streptococci, coagulase-negative staphylococci, *Micrococcus* spp., *Neisseria* spp. other than *N. meningitidis*, *Corynebacterium* spp. and other coryneforms, *Lactobacillus* spp., *Vibrio* spp., *Capnocytophaga* spp., *Cardiobacterium* spp., *Flavobacterium* spp.

Other isolates identified from culture of blood and respiratory specimens will be reviewed in a blinded manner by the Sponsor on a case-by-case basis for determination of whether the organism is a pathogen for CABP.

4.2 "Atypical" Respiratory Pathogens

Legionella pneumophila, Mycoplasma pneumoniae, and *Chlamydophila pneumoniae* will always be considered a CABP pathogen in the presence of the following criteria:

Legionella pneumophila

- Positive BAL, plueral fluid or blood culture; or
- Positive sputum culture, regardless of Gram stain findings; or
- Positive urinary antigen test; or
- Between baseline and convalescent (LFU Visit) specimens, a 4-fold or greater increase in *L. pneumophila* antibody titer to ≥1:128; or
- Positive RQ-PCR of sputum

Mycoplasma pneumoniae

- Between baseline and convalescent (LFU Visit) specimens, a 4-fold or greater increase in *M. pneumoniae* IgG serum antibody titer to ≥1:160; or
- Positive oropharyngeal specimen culture; or
- Positive BAL, pleural fluid or blood culture; or
- Positive sputum culture in the presence of a Gram stain with >25 PMNs/LPF and <10 SECs/LPF (**NOTE:** ≥10 PMNs/LPF and <10 SECs/LPF in the emicroITT Analysis Set); or
- Positive RQ-PCR of oropharyngeal swab or sputum (see Table 1 for cutoff values)

Chlamydophila pneumoniae

- Between baseline and convalescent (LFU Visit) specimens, a 4-fold or greater increase in *C. pneumoniae* IgG serum antibody titer; or
- Positive RQ-PCR of sputum

4.3 Other Diagnostic Methods

Real-time quantitative Polymerase chain reaction based methods will also be used to determine the etiology of CABP at baseline.

- Frozen sputum samples will be analyzed by RQ-PCR using specific and conserved primers for the target genes based on current published studies (see Table 1). Single-plex RQ-PCR will be set up, validated and sputum samples will be analyzed by a specialized Good Laboratory Practices-certified bioanalytical laboratory (Accelero Bioanalytics GmbH, Germany).
- Oropharyngeal specimens will be analyzed by a specialized laboratory (K. Waites, Diagnostic Mycoplasma Laboratory, UAB, AL, USA) using RQ- PCR for *Mycoplasma pneumoniae* (*repMp1*) and for detection of macrolide-resistance (23S rDNA).

- Nasopharyngeal specimens will be analyzed by a specialized laboratory (J. Vidal, Emory University, GA, USA) using RQ-PCR for detection of *S. pneumoniae* (*lytA*).

Amplified genes and cut-off values for the definition of a pathogen from the oropharyngeal and nasopharyngeal swabs are presented in Table 1.

Table 1. Amplified Genes and Cut-off Values for RQ-PCR

Specimen / Organism	PCR	Proposed Amplified gene [a]	Cut-off values for consideration of the organism as definite etiological significant for CABP	
			Cut-off values	Reference
Sputum				
S. pneumoniae	RQ-PCR	*lytA*	DNA corresponding to $\geq 10^4$ CFU/mL	Albrich et al, 2014
H. influenzae	RQ-PCR	*frdB*	DNA corresponding to $\geq 10^6$ CFU/mL	Johansson et al, 2010; Kais et al, 2006
M. catarrhalis	RQ-PCR	*copB*	DNA corresponding to $\geq 10^6$ CFU/mL	Johansson et al, 2010; Kais et al, 2006
S. aureus	RQ-PCR	*nuc*	DNA corresponding to $\geq 6 \times 10^5$ CFU/mL	Huang et al, 2015
M. pneumoniae	RQ-PCR	CARDS TX gene	positive	Thurman et al, 2011; Waites et al, 2012
L. pneumophila	RQ-PCR	*ssrA*	positive	Thurman et al, 2011
C. pneumoniae	RQ-PCR	*argR*	positive	Thurman et al, 2011
Oropharyngeal swabs				
M. pneumoniae	RQ-PCR	*repMp1*	positive	Thurman et al, 2011; Waites et al, 2012
Nasopharyngeal swabs				
S. pneumoniae	RQ-PCR	*lytA*	$\geq 1 \times 10^3$ CFU/mL	Chochua et al, 2015

[a] RQ-PCR will amplify the proposed genes provided that the validation is successful. If the RQ-PCR for the proposed target gene cannot be validated, another gene target will be used.

5.0 ANALYSIS SETS

5.1 Intent-to-Treat (ITT) Analysis Set

The ITT Analysis Set will consist of all randomized subjects regardless of whether or not the subject received study drug. A subject is considered randomized when an IRT-generated randomization number has been assigned.

5.2 Modified Intent-to-Treat (mITT) Analysis Set

The mITT Analysis Set will consist of all randomized subjects who receive any amount of study drug. Subjects are analyzed based on the randomized (ie, assigned) treatment group.

5.3 Safety Analysis Set

The Safety Analysis Set will consist of all randomized subjects who receive any amount of study drug. Subjects are analyzed based on the study drug actually received. All safety analyses will be conducted in this population.

5.4 Microbiological ITT (microITT) Analysis Set

The microITT Analysis Set will consist of all subjects in the ITT Analysis Set who have at least 1 baseline bacterial pathogen known to cause CABP as defined in Sections 4.1 and 4.2. Additional isolates not a priori defined as pathogens in this SAP will be evaluated on a case by case basis by the Evaluability Review Team.

5.5 Microbiological ITT-2 (microITT-2) Analysis Set

The microITT-2 Analysis Set will consist of all subjects in the ITT Analysis Set who have at least 1 baseline bacterial pathogen known to cause CABP as defined in Sections 4.1 and 4.2 from a diagnostic method other than PCR. Thus, the following will *not* be considered pathogens for inclusion of subjects in the microITT-2 Analysis Set:

- *Streptococcus pneumoniae* from RQ-PCR of nasopharyngeal swab
- *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus,* or *Moraxella catarrhalis* from RQ-PCR of sputum
- *Legionella pneumophila, Mycoplasma pneumoniae*, or *Chlamydophila pneumoniae* from RQ-PCR of sputum
- *Mycoplasma pneumoniae* from RQ-PCR of oropharyngeal swab

5.6 Clinically Evaluable (CE) Analysis Sets

Three CE Analysis Sets will be defined, the CE-EOT, CE-TOC and CE-LFU Analysis Sets. The CE Analysis Sets will consist of all subjects in the ITT Analysis Set who also meet the criteria listed below. These criteria will be programmed from the electronic case report form (CRF) data and/or reviewed manually by the Sponsor in a blinded manner prior to database lock to confirm each subject's inclusion in or exclusion from the CE Analysis Sets. Details regarding the programming and review of eCRF data are included in the Evaluability Review Plan.

1. Subjects must meet all of the inclusion criteria below to be included in the CE-EOT, CE-TOC and CE-LFU Analysis Sets.

   Inclusion criterion 3: Have an acute illness (≤7 days duration) with at least 3 of the following symptoms consistent with a lower respiratory tract infection (new or worsening):

   - Dyspnea
   - New or increased cough
   - Purulent sputum production
   - Chest pain due to pneumonia

Inclusion criterion 4: Have at least 2 of the following vital sign abnormalities:

- Fever (body temperature >38.0ºC [100.4ºF] measured orally or equivalent temperature from alternate body site) or hypothermia (body temperature <35.0ºC [95.0ºF] measured orally or equivalent temperature from an alternate body site)
- Hypotension (systolic blood pressure <90 mmHg)
- Tachycardia (heart rate >100 beats/min)
- Tachypnea (respiratory rate >20 breaths/min)

Inclusion criterion 5: Have at least 1 other clinical sign or laboratory finding of CABP:

- Hypoxemia (ie, O_2 saturation <90% on room air or while receiving supplemental oxygen at subject's baseline requirement or PaO_2 <60 mmHg)
- Auscultatory and/or percussion findings consistent with pneumonia (eg, crackles, egophony, dullness)
- White blood cell (WBC) count >10,000 cells/mm^3 or <4500 cells/mm^3 or >15% immature neutrophils (bands) regardless of total WBC count

Inclusion criterion 6: Have radiographically-documented pneumonia within 48 hours before enrollment (ie, infiltrates in a lobar or multilobar distribution or diffuse opacities on chest x-ray or chest computed tomography scan consistent with acute bacterial pneumonia). **NOTE:** If the imaging study is done more than 48 hours before enrollment but in the timeframe consistent with onset of the subject's symptoms, the subject will be included in the CE Analysis Sets as long as the imaging study shows an infiltrate or diffuse opacities consistent with CABP.

Inclusion criterion 7: Have a PORT Risk Class ≥III and require IV antibiotic therapy as initial treatment for the current episode of CABP.

2. Completed the visit within the protocol mandated window:
   - For the CE-EOT Analysis Set:
     - Completed the EOT Visit on the day of last dose of study drug or within 2 days after the last dose of study drug.
   - For the CE-TOC Analysis Set:
     - Completed the TOC Visit 5-10 days after the last dose of study drug, unless the subject was considered a failure at the EOT Visit based on the IACR.
   - For the CE-LFU Analysis Set:
     - Completed the LFU Visit between Study Day 27 and 34 (inclusive) unless the subject was considered a failure at either the EOT or TOC Visit based on the IACR.
3. Must not have had a clinical response of indeterminate based on the IACR at EOT (CE-EOT Analysis Set), TOC (CE-TOC Analysis Set) or LFU (CE-LFU Analysis Set).
4. Duration of study drug was at least 48 hours, unless the subject died prior to 48 hours.

5. Did not receive another systemic antibacterial (other than adjunctive linezolid for subjects randomized to the moxifloxacin treatment group) from the first dose of study drug through EOT (CE-EOT), through TOC (CE-TOC) or through LFU (CE-LFU) Visits with likely or documented activity against confirmed or potential CABP pathogens, unless the antibacterial was administered due to clinical failure (or relapse at LFU) or the subject had been classified as clinical failure by the Investigator prior to receipt of the antibacterial. Subjects who do not have a pathogen isolated at baseline and receive a concomitant antibiotic with activity against any potential CABP pathogen will be excluded from the relevant CE-EOT, CE-TOC and CE-LFU Analysis Set(s), unless the antibacterial was administered due to clinical failure (or relapse at LFU) or the subject had been classified as clinical failure by the Investigator prior to receipt of the antibacterial.
6. Received the correct study drug, based on randomization assignment, for all active doses taken.
7. Study personnel involved in the assessment of efficacy, or monitoring of the efficacy data, remained blinded to the subject treatment assignment through EOT (CE-EOT), TOC (CE-TOC) or LFU (CE-LFU) Visits. Subjects whose treatment assignments were unblinded to study personnel due to an adverse event (AE) will be included in the CE Analysis Sets.
8. Subjects who meet any of the following exclusion criteria at baseline as indicated on the Inclusion Exclusion eCRF will be *excluded* from the CE Analysis Sets:

   Exclusion criterion 1: Have received more than a single dose of a short-acting oral or IV antibacterial for CABP within 72 hours before randomization. **EXCEPTION:** Subjects who have received >48 hours of prior systemic antibacterial therapy for the current episode of CABP with unequivocal clinical evidence of treatment failure (ie, worsening signs and symptoms) and isolation of an organism from blood or respiratory tract that is resistant to the prior systemic antibacterial therapy provided the organism is not resistant to fluoroquinolones and, in the case of MRSA, oxazolidinones.

   Exclusion criterion 3: Have been hospitalized for 2 or more days within 90 days prior to the onset of symptoms or have resided in a nursing home or long-term healthcare facility within 30 days prior to the onset of symptoms. **NOTE:** Residence in an independent living facility is permitted.

   Exclusion criterion 4: Have confirmed or suspected CABP caused by a pathogen known to be resistant to any of the study drugs (eg, *Pseudomonas aeruginosa*, any pathogen of the *Enterobacteriaceae* Family) or attributable to etiologies other than community-acquired bacterial pathogens (eg, ventilator-associated pneumonia, hospital-acquired bacterial pneumonia, bacterial aspiration pneumonia, *Pneumocystis jiroveci* pneumonia or other fungal pneumonia, viral or mycobacterial infection of the lung).

   Exclusion criterion 5: Have a noninfectious cause of pulmonary infiltrates (eg, pulmonary embolism, chemical pneumonitis from aspiration, hypersensitivity pneumonia, congestive heart failure, bronchial obstruction, lung cancer, cystic fibrosis).

   Exclusion criterion 6: Have confirmed or suspected pleural empyema (does not include sterile parapneumonic effusions).

Exclusion criterion 7: Require mechanical ventilation.

Exclusion criterion 17: Have been previously treated with lefamulin or previously enrolled in this study.

9. Subjects who have pneumonia attributable to etiologies other than community-acquired pneumonia, a noninfectious cause of pulmonary infiltrates or confirmed pleural empyema at Screening but discovered post-baseline will be excluded from the CE Analysis Sets.
10. Any additional factor that may confound the assessment of efficacy as determined by the Sponsor during blinded review for evaluability. If a subject is excluded from the CE Analysis Sets due to an additional factor, the reason for exclusion will be documented in the appropriate analysis database and the Evaluability Review Plan.

5.7 Microbiologically Evaluable (ME) Analysis Sets

The ME Analysis Sets (ME-EOT, ME-TOC and ME-LFU) will consist of all subjects who meet criteria for inclusion in both the microITT and the CE-EOT (ME-EOT) Analysis Set, the CE-TOC (ME-TOC) Analysis Set or the CE-LFU (ME-LFU) Analysis Set. Subjects who have CABP caused *only* by a pathogen(s) resistant to moxifloxacin or lefamulin will be excluded from the ME Analysis Sets. Resistance is defined as: 1) a pathogen resistant to moxifloxacin or non-susceptible to lefamulin based on susceptibility results from the central laboratory, or 2) a pathogen in the *Enterobacteriaceae* family or a non-fermenting Gram-negative pathogen (with the exception of *Legionella pneumophila* and *Moraxella catarrhalis*), unless susceptibility data from the central laboratory is available and indicates the pathogen is susceptible to both moxifloxacin (Table 9) and lefamulin (Table 10).

5.8 Expanded Microbiological ITT (emicroITT) Analysis Set

The emicroITT Analysis Set will consist of all subjects in the ITT Analysis Set who have at least 1 baseline bacterial pathogen known to cause CABP as defined in Sections 4.1 and 4.2, except a baseline pathogen from a sputum culture is defined using the presence of a Gram stain with ≥10 PMNs/LPF and <10 SECs/LPF rather than >25 PMNs/LPF and <10 SECs/LPF.

5.9 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set will consist of all subjects in the mITT Analysis Set who have at least one pharmacokinetic sample analyzed.

6.0 DEFINITIONS OF OUTCOME MEASURES

Efficacy will be assessed, either programmatically or by the Investigator (as outlined below), at the following time points:

- 96 ± 24 hours after the first dose of study drug (ECR only).
- EOT – within 2 days after the last dose of study drug.

- TOC – 5 to 10 days after last dose of study drug.
- LFU – between Study Day 27 and 34 (inclusive). **NOTE:** To address an inconsistency in the study protocol regarding the timing of the LFU Visit (ie, 30 ± 3 days after the first dose of study drug vs. Day 30 ± 3 days), the LFU Visit window comprises the cumulative range of possible study days.

For the EOT, TOC and LFU assessments, subjects will be assigned an IACR (success, failure, or indeterminate at EOT and TOC, sustained success, relapse, prior failure or indeterminate at LFU). Early Clinical Response will be determined programmatically based on recorded symptom assessments that compare the assessments at Baseline and at 96 ± 24 hours after the first dose of study drug. The Investigator will not make a determination of Early Clinical Response and will make treatment decisions based on the subject's overall response to therapy. Microbiologic responses will be determined programmatically at EOT, TOC and LFU.

6.1 Primary Efficacy Outcome: Early Clinical Response

The primary efficacy outcome is the percentage of subjects with an ECR of responder at 96 ± 24 hours after the first dose of study drug in the ITT Analysis Set. Symptom definitions for the assessment are shown in Table 2. Subjects will be programmatically defined as a **responder** if the following 4 criteria are met:

- Alive;
- Improvement in at least 2 of the 3 or 4 cardinal symptoms of CABP the subject presented with at baseline. Improvement is defined as a decrease by at least 1 level of severity;
- No worsening of any of the 4 cardinal symptoms of CABP. Worsening is defined as an increase by at least 1 level of severity for any symptom;
- Did not receive a concomitant antibiotic (other than adjunctive linezolid for subjects randomized to the moxifloxacin treatment group) for the treatment of CABP up through the assessment of the cardinal symptoms of CABP.

Table 2. Symptom Assessment for Early Clinical Response Assessment

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

Subjects will be programmatically defined as a **non-responder** if any of the following are met:

- Did not show an improvement in at least 2 of the 3 or 4 cardinal symptoms of CABP the subject presented with at baseline. Improvement is defined as a decrease by at least 1 level of severity; or
- Worsening of any of the 4 cardinal symptoms of CABP. Worsening is defined as an increase by at least 1 level of severity for any symptom; or
- Received a concomitant antibiotic (other than adjunctive linezolid for subjects randomized to the moxifloxacin treatment group) for the treatment of CABP up through the assessment of the cardinal symptoms of CABP, or if no assessment was completed, up to 120 hours after the first dose of study drug (or randomization if the subject did not receive study drug); or
- Died from any cause up through the assessment of the cardinal symptoms of CABP, or if no assessment was completed, up through Study Day 5.

If more than 1 assessment of symptoms is obtained in the 96 ± 24 hour window, the following rules apply:

- Use the latest assessment of symptoms conducted in person occurring in the 96 ± 24 hour window
- If no assessment was conducted in person, use the latest assessment of symptoms conducted via a telephone call occurring in the 96 ± 24 hour window

If no assessment of symptoms (either in person or by telephone) was conducted in the 96 ± 24 hour window, the following rules apply:

- Use the latest assessment of symptoms conducted in person occurring 60 to <72 hours after the first dose of study drug
- If no assessment was conducted in person in the 60 to <72 hour window, use the latest assessment of symptoms conducted via a telephone call occurring 60 to <72 hours after the first dose of study drug

Subjects with missing data such that a response cannot be determined will be considered an indeterminate response. Subjects who did not have at least 2 symptoms of CABP at baseline will also be considered to have an indeterminate response. Since the analysis of the primary outcome is based on the ITT Analysis Set, subjects with an indeterminate response are essentially considered non-responders. For the ITT Analysis Set, the percentage of ITT subjects considered responders for ECR is defined using the following formula (where the denominator is comprised of the total number of subjects in the ITT Analysis Set):

$$\frac{\text{Number of subjects who are a responder}}{\text{(Number of subjects who are a responder + Number of subjects who are a non-responder + Number of indeterminate subjects)}} \times 100\%$$

6.2 Secondary Efficacy Outcomes

Secondary efficacy outcomes include:

- Percentage of subjects with IACR of success at the TOC Visit in the mITT and CE-TOC Analysis Sets
- Percentage of subjects with ECR of responder in the microITT Analysis Set
- Percentage of subjects with ECR of responder PLUS improvement in vital signs in the ITT Analysis Set
- Percentage of subjects with IACR of success at the TOC Visit in the microITT and ME-TOC Analysis Sets
- Proportion of subjects with a by-pathogen microbiologic response of success at the TOC Visit in the microITT and ME-TOC Analysis Sets
- All-cause mortality (ACM) through Day 28 in the ITT Analysis Set

6.2.1 Investigator's Assessment of Clinical Response

Clinical response will be assessed by the Investigator at the EOT, TOC and LFU Visits. The IACR at EOT and TOC will be classified as success, failure, or indeterminate according to the definitions in Table 3. Subjects who are deemed to have an IACR of failure at the EOT Visit will not have an IACR performed at the TOC Visit and will be considered to have an IACR of failure at the TOC Visit.

Table 3. Investigator's Assessment of Clinical Response at EOT and TOC

Outcome	EOT and TOC
Success	The subject's clinical signs and symptoms have resolved or improved such that no additional antibacterial therapy is administered for the treatment of the current episode of CABP.
Failure	A subject is a treatment failure if any of the following is met: • Signs and symptoms of CABP have not resolved, not improved or have worsened such that non-study antibacterial therapy is administered for the treatment of the current episode of CABP. • Measures of inflammation such as temperature or elevated WBC have worsened or failed to improve such that non-study antibacterial therapy is administered for the treatment of the current episode of CABP. • Bacteremia has worsened or failed to improve resulting in administration of non-study antibacterial therapy. • The occurrence of an AE requiring discontinuation of study drug and institution of non-study antibacterial therapy for the treatment of the current episode of CABP. • Death from any cause.
Indeterminate	Insufficient information is available to determine success or failure, specifically lost to follow-up.

For subjects who do not have an IACR of failure at the TOC Visit, a determination of clinical response (sustained success, relapse, prior failure or indeterminate) will be made at the LFU Visit as outlined in Table 4. Subjects who are deemed to have an IACR of failure at the TOC Visit will not have an IACR performed at the LFU Visit and will be considered to have an IACR of prior failure at the LFU Visit.

Table 4. Investigator's Assessment of Clinical Response at LFU

Outcome	LFU
Sustained Success	The subject's clinical signs and symptoms remain resolved or further improved such that no additional antibacterial therapy has been administered for the treatment of the current episode of CABP.
Relapse	The subject was a clinical success at TOC, however, any of the following are met: • Clinical signs and symptoms of CABP have recurred such that additional non-study antibacterial therapy is administered for the treatment of the current episode of CABP. • Measures of inflammation such as temperature or elevated WBC have recurred such that additional non-study antibacterial therapy is administered for the treatment of the current episode of CABP. • Recurrent bacteremia resulting in administration of non-study antibacterial therapy. • Death from any cause.
Prior Failure	The subject had an IACR of failure at the TOC Visit.
Indeterminate	Insufficient information is available to determine sustained success or relapse, specifically lost to follow-up.

The secondary efficacy analysis of IACR at the TOC Visit will be conducted in the mITT, CE-TOC, microITT, and ME-TOC Analysis Sets. An additional analysis will be conducted in the microITT-2 and emicroITT Analysis Sets (see Section 6.3). Analyses of IACR at the EOT Visit will be conducted in the mITT, microITT, CE-EOT and ME-EOT Analysis Sets, and analyses at the LFU Visit will be conducted in the mITT, microITT, CE-LFU and ME-LFU Analysis Sets (see Section 6.3). For the analysis of IACR at the EOT and TOC Visits in the mITT, microITT, microITT-2 and emicroITT Analysis Sets, the success rate will be calculated as follows:

$$\frac{\text{Number of subjects who are a success}}{\text{(Number of subjects who are a success + Number of subjects who are a failure + Number of subjects with an indeterminate IACR)}} \times 100\%$$

For the analysis of IACR at the LFU Visit in the mITT and microITT Analysis Sets, the sustained success rate will be calculated as follows:

$$\frac{\text{Number of subjects who are a sustained success}}{\text{(Number of subjects who are a sustained success + Number of subjects who are a relapse + Number of subjects who are a prior failure (carried forward from TOC) + Number of subjects with an indeterminate IACR)}} \times 100\%$$

Subjects with an indeterminate IACR at the EOT, TOC and LFU Visits will be excluded from the analysis of IACR at the EOT, TOC and LFU Visits, respectively, in the CE and ME Analysis Sets. For the analysis of IACR at the EOT and TOC Visits in the CE and ME Analysis Sets, the success rate will be calculated as follows:

$$\frac{\text{Number of subjects who are a success}}{\text{(Number of subjects who are a success + Number of subjects who are a failure)}} \times 100\%$$

For the analysis of IACR at the LFU Visit in the CE-LFU and ME-LFU Analysis Sets, the sustained success rate will be calculated as follows:

$$\frac{\text{Number of subjects who are a sustained success}}{\text{(Number of subjects who are a sustained success + Number of subjects who are a relapse + Number of subjects who are a prior failure (carried forward from TOC))}} \times 100\%$$

6.2.2 Early Clinical Response in the microITT Analysis Set

The secondary efficacy analysis of ECR will be conducted in the microITT Analysis Set. An additional analysis will be conducted in microITT-2 and emicroITT Analysis Sets (see Section 6.3). For the microITT and microITT-2 Analysis Sets, the percentage of subjects considered responders for ECR is defined using the following formula (where the denominator is comprised of the total number of subjects in the microITT and microITT-2 Analysis Sets):

$$\frac{\text{Number of subjects who are a responder}}{\text{(Number of subjects who are a responder + Number of subjects who are a non-responder + Number of indeterminate subjects)}} \times 100\%$$

6.2.3 Early Clinical Response Plus Improvement in Vital Signs

Subjects will be programmatically defined as a **responder** if the following 5 criteria are met:

- Alive;
- Improvement in at least 2 of the 3 or 4 cardinal symptoms of CABP the subject presented with at baseline. Improvement is defined as a decrease by at least 1 level of severity;
- No worsening of any of the 4 cardinal symptoms of CABP. Worsening is defined as an increase by at least 1 level of severity for any symptom;
- Improvement in vital signs (ie, body temperature, blood pressure, heart rate, respiratory rate), if abnormal at baseline. Improvement is defined as returning to normal. If vital signs are normal at baseline (ie, not abnormal as per the definitions below), none can have worsened. Abnormal vital signs are defined as:
    - Fever: defined as body temperature >38.0°C (100.4°F) measured orally, >38.5°C (101.3°F) measured tympanically, >39.0°C (102.2°F) measured rectally or >37.5°C (99.5°F) by axillary measurement

  - Hypothermia: defined as body temperature <35.0°C (95.0°F) measured orally, <35.5°C (95.9°F) measured tympanically, or <36.0°C (96.8°F) measured rectally
  - Hypotension: defined as systolic blood pressure <90 mmHg
  - Tachycardia: defined as heart rate >100 beats/min
  - Tachypnea: defined as respiratory rate >20 breaths/min
- Did not receive a concomitant antibiotic (other than adjunctive linezolid for subjects randomized to the moxifloxacin arm) for the treatment of CABP up through the assessment of the cardinal symptoms of CABP.

Subjects will be programmatically defined as a **non-responder** if any of the following are met:

- Did not show an improvement in at least 2 of the 3 or 4 cardinal symptoms of CABP the subject presented with at baseline. Improvement is defined as a decrease by at least 1 level of severity; or
- Worsening of any of the 4 cardinal symptoms of CABP. Worsening is defined as an increase by at least 1 level of severity for any symptom; or
- Did not show an improvement in vital signs. Improvement is defined as the following:
  - Body temperature 35.0 to 38.0°C (95.0 to 100.4°F) measured orally, 35.5 to 38.5°C (95.9 to 101.3°F) measured tympanically, 36.0 to 39.0°C (96.8 to 102.2°F) measured rectally or 34.5 to 37.5°C (94.1 to 99.5°F) by axillary measurement
  - Systolic blood pressure ≥90 mmHg
  - Heart rate >50 to ≤100 beats/min
  - Respiratory rate ≤20 breaths/min; or
- Received a concomitant antibiotic (other than adjunctive linezolid for subjects randomized to the moxifloxacin treatment group) for the treatment of CABP up through the assessment of the cardinal symptoms of CABP, or if no assessment was completed, up to 120 hours after the first dose of study drug (or randomization if the subject did not receive study drug); or
- Died from any cause up through the assessment of the cardinal symptoms of CABP, or if no assessment was completed, up through Study Day 5.

Section 6.1 describes rules for determining the outcome if more than 1 assessment of symptoms is obtained in the 96 ± 24 hour window or if no assessment of symptoms is obtained in the 96 ± 24 hour window. Subjects with missing data such that a response cannot be determined will be considered to have an indeterminate response. Subjects who did not have at least 2 symptoms of CABP at baseline or who did not have an assessment of vital signs at baseline will also be considered to have an indeterminate response. Since the analysis of ECR plus improvement in vital signs is based on the ITT Analysis Set, subjects with an indeterminate response are essentially considered non-responders. For the ITT Analysis Set, the percentage of ITT subjects determined to be responders for ECR plus improvement in vital signs is defined using the following formula (where the denominator is comprised of the total number of subjects in the ITT Analysis Set):

$$\frac{\text{Number of subjects who are a responder}}{\text{(Number of subjects who are a responder + Number of subjects who are a non-responder + Number of indeterminate subjects)}} \times 100\%$$

6.2.4 By-Pathogen Microbiological Response

By-pathogen microbiological responses are eradication, presumed eradication, persistence, presumed persistence and indeterminate, as defined in Table 5. Microbiological responses of eradication and persistence are based on comparing the baseline pathogen(s) to post-baseline pathogens, where post-baseline organisms are identified from post-baseline cultures and considered pathogens based on the criteria in Section 4.0. If a pathogen is persistent at the EOT Visit, the persistence is carried forward to the TOC and LFU Visits. If a pathogen is presumed persistent at the EOT Visit, the presumed persistence is carried forward to the TOC and LFU Visits, unless a repeat culture is obtained between the EOT and TOC or EOT and LFU Visits, respectively, which shows persistence. Baseline pathogens identified by a modality other than culture of a blood or respiratory sample (ie, pathogen from serology, urine antigen or PCR) can only have a presumed or indeterminate microbiological response.

Table 5. By-Pathogen Microbiological Response at EOT, TOC and LFU

Outcome		EOT	TOC and LFU
Success	Eradication	The baseline causative pathogen was absent from repeat culture(s) obtained at EOT (ie, the post-baseline culture showed no growth or the post-baseline culture did not grow the same pathogen as isolated at baseline, or the same organism(s) was present but did not meet the definition of pathogen as defined in Section 4.0).	The baseline causative pathogen was absent from repeat culture(s) obtained between EOT and TOC or EOT and LFU, respectively (ie, the post-baseline culture showed no growth or the post-baseline culture did not grow the same pathogen as isolated at baseline, or the same organism(s) was present but did not meet the definition of pathogen as defined in Section 4.0).
	Presumed eradication	The IACR was success and culture was not repeated at EOT.	The IACR was success (TOC) or sustained success (LFU) and culture was not repeated (at TOC and LFU, respectively).
Failure	Persistence	The baseline causative pathogen was isolated in repeat culture(s) obtained at EOT.	Persistence at EOT is carried forward or a culture obtained after EOT and up to and including TOC grew the same pathogen identified at baseline (TOC). Persistence at TOC is carried forward or a culture obtained after TOC and up to an including LFU grew the same pathogen identified at baseline (LFU).
	Presumed persistence	The IACR was failure and culture was not repeated at EOT.	The IACR was failure (TOC) or prior failure/relapse (LFU) and culture was not repeated (at TOC and LFU, respectively) and no cultures demonstrated persistence (between EOT and TOC and EOT and LFU, respectively).
Indeterminate		The IACR was indeterminate and culture was not repeated at EOT.	The IACR was indeterminate and culture was not repeated (at TOC and LFU, respectively) and no cultures demonstrated persistence (between EOT and TOC and EOT and LFU, respectively).

The by-pathogen microbiological response success rate at the EOT, TOC and LFU Visits in the microITT and microITT-2 (TOC Visit only; see Section 6.3) Analysis Sets is calculated as follows:

$$\frac{\text{Number of subjects who are a success for the specific pathogen}}{\text{(Number of subjects who are a success for the specific pathogen + Number of subjects who are a failure for the specific pathogen + Number of subjects who are indeterminate for the specific pathogen)}}$$

Subjects with an indeterminate microbiological response at the EOT, TOC and LFU Visits will be excluded from the ME Analysis Sets. Thus, the by–pathogen microbiological response success rate is calculated as follows:

$$\frac{\text{Number of subjects who are a success for the specific pathogen}}{\text{(Number of subjects who are a success for the specific pathogen + Number of subjects who are a failure for the specific pathogen)}}$$

Subjects who have the same pathogen isolated at baseline from more than 1 specimen type are counted only once in the determination of by-pathogen microbiological response. If a subject has the same baseline pathogen identified by culture of blood or respiratory sample and another modality and a repeat culture is obtained, microbiological response is based on the post-baseline culture results. If a subject has the same baseline pathogen identified from culture of blood and a respiratory sample, eradication requires the baseline pathogen to be absent from respiratory sample culture without evidence of ongoing bacteremia. Persistence requires the baseline pathogen to be present from either the blood or respiratory sample culture.

6.2.5 28-Day All-Cause Mortality

The outcome measure of all-cause mortality (ACM) is defined as deceased on or before Study Day 28.

Subjects with an LFU visit on Study Day 27 will be considered alive on Study Day 28 unless known to have died on Study Day 28. Other subjects who are not known to be alive or deceased as of Study Day 28 will be defined as deceased and included in the numerator and denominator for the calculation of the ACM rate. The 28-day ACM rate is defined by the following formula:

$$\frac{\text{Number of subjects deceased}}{\text{(Number of subjects alive at Day 28 + Number of subjects deceased)}} \times 100\%$$

6.3 Additional Efficacy Outcomes

Additional efficacy outcomes specified in the protocol include:

- Proportion of subjects with an ECR of responder by baseline pathogen in the microITT Analysis Set
- Percentage of subjects with an IACR of success at the EOT Visit in the mITT and CE-EOT Analysis Sets, and at the LFU Visit (sustained success) in the mITT and CE-LFU Analysis Sets
- Proportion of subjects with an IACR of success by baseline pathogen at the TOC Visit in the microITT and ME-TOC Analysis Sets, and at the LFU Visit (sustained success) in the microITT and ME-LFU Analysis Sets
- Number and percentage of subjects with a by-subject microbiologic response of success at the TOC Visit in the microITT and ME-TOC Analysis Sets

Other additional efficacy outcomes specified in this SAP include:

- Percentage of subjects with an ECR of responder in the microITT-2 and emicroITT Analysis Sets
- Proportion of subjects with an ECR of responder by baseline pathogen in the microITT-2 Analysis Set
- Proportion of subjects with an ECR of responder by baseline pathogen and MIC to study drug received in the microITT Analysis Set
- Proportion of subjects with an ECR of responder by baseline pathogen and disk diffusion zone diameter to study drug received in the microITT Analysis Set
- Proportion of subjects with an ECR of responder by baseline pathogens identified from blood specimens in the microITT Analysis Set
- Percentage of subjects with an IACR of success at the TOC Visit in the microITT-2 and emicroITT Analysis Sets, at the EOT Visit in the microITT and ME-EOT Analysis Sets, and at the LFU Visit (sustained success) in the microITT and ME-LFU Analysis Sets
- Proportion of subjects with an IACR of success by baseline pathogen at the TOC Visit in the microITT-2 Analysis Set, and at the EOT Visit in the microITT and ME-EOT Analysis Sets
- Proportion of subjects with an IACR of success at the TOC Visit by baseline pathogen and MIC to study drug received in the microITT and ME-TOC Analysis Sets
- Proportion of subjects with an IACR of success at the TOC Visit by baseline pathogen and disk diffusion zone diameter to study drug received in the microITT and ME-TOC Analysis Sets
- Proportion of subjects with an IACR of success at the TOC Visit by baseline pathogens identified from blood specimens in the microITT Analysis Set

- Proportion of subjects with a by-pathogen microbiologic response of success at the TOC Visit in the microITT-2 Analysis Set, at the EOT Visit in the microITT and ME-EOT Analysis Sets, and at the LFU Visit in the microITT and ME-LFU Analysis Sets
- Proportion of subjects with a by-pathogen microbiologic response of success at the TOC Visit by baseline pathogen and MIC to study drug received in the microITT and ME-TOC Analysis Sets
- Proportion of subjects with a by-pathogen microbiologic response of success at the TOC Visit by baseline pathogen and disk diffusion zone diameter to study drug received in the microITT and ME-TOC Analysis Sets
- Number and percentage of subjects with a by-subject microbiologic response of success at the TOC Visit in the microITT-2 Analysis Set, at the EOT Visit in the microITT and ME-EOT Analysis Sets, and at the LFU Visit in the microITT and ME-LFU Analysis Sets

6.3.1 By-Subject Microbiological Response at the EOT, TOC and LFU Visits

By-subject microbiological response is determined from the by-pathogen microbiological responses as defined in Table 6.

Table 6. By-Subject Microbiological Response at EOT, TOC and LFU

Outcome		Definition
Success	Eradication or Presumed eradication	All baseline pathogens have a by-pathogen microbiological response of eradication or presumed eradication at the specified visit.
Failure	Persistence or Presumed persistence	At least 1 baseline pathogen has a by-pathogen microbiological response of persistence or presumed persistence at the specified visit.
Indeterminate		At least 1 baseline pathogen has a by-pathogen microbiological response of indeterminate and none have a by-pathogen microbiological response of persistence or presumed persistence.

The by-subject microbiological response success rate at the EOT, TOC and LFU Visits in the microITT and microITT-2 (TOC Visit only) Analysis Sets is calculated as follows:

$$\frac{\text{Number of subjects who are a success}}{\text{(Number of subjects who are a success + Number of subjects who are a failure + Number of subjects who are indeterminate)}} \times 100\%$$

Subjects with an indeterminate microbiological response at the EOT, TOC and LFU Visits will be excluded from the ME Analysis Sets. Thus, the by–subject microbiological response success rate is calculated as follows:

$$\frac{\text{Number of subjects who are a success}}{\text{(Number of subjects who are a success + Number of subjects who are a failure)}} \times 100\%$$

6.4 Other Microbiological Outcomes

Superinfections are defined as new pathogens (ie, pathogen(s) not present at baseline) identified in post-baseline cultures through the TOC Visit with persistent signs and symptoms of CABP (ie, IACR of failure at the TOC Visit), such that additional antibacterial therapy is necessary for current episode of CABP.

Colonization is defined as new pathogens (ie, pathogen(s) not present at baseline) identified in at least 2 post-baseline cultures through the TOC Visit but signs and symptoms of CABP have resolved (ie, IACR of success at the TOC Visit), such that no additional antibacterial therapy is necessary for the current episode of CABP.

Development of decreasing susceptibility is defined as a ≥4x increase from baseline in MIC to the study drug received or a ≥6 mm decrease from baseline in disk inhibition zone diameter to the study drug received for a baseline pathogen subsequently isolated from culture of a post-baseline blood or respiratory sample (ie, for a post-baseline pathogen).

6.5 Pharmacokinetic Outcomes

Measured plasma concentrations of BC-3781 and BC-8041 will be summarized.

6.6 Safety Outcomes

Safety will be assessed by analysis of AEs and changes in laboratory parameters (chemistry and hematology), electrocardiogram (ECG) parameters, and vital signs. Laboratory abnormalities are not considered AEs unless they are associated with clinical signs and symptoms or require medical intervention. Clinically significant abnormal clinical laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

6.7 Additional Exploratory Outcomes

Exploratory evaluation of a variety of health utilization variables (eg, length of hospital stay, discharge status and discharge destination) and a patient-reported outcome instrument (SF-12) will be performed. Details of this exploratory analysis will be presented in a separate SAP and results will be presented in a separate report.

7.0 STATISTICAL METHODS

7.1 Sample Size

A total of 550 subjects will be randomized in this study (275 subjects in each treatment group). However, if based upon regulatory requirements additional subjects exposed to lefamulin are needed, up to 626 subjects may be enrolled. The total number of subjects included in this study is sufficient to achieve the primary and secondary study objectives based on statistical considerations.

Retrospective analyses of clinical study data for patients with CABP of varying severity indicate the point estimates for an ECR responder at Days 3-5 range from 72%-81% (FDA, 2011). Thus, it is reasonable to assume that in a prospective study of subjects with CABP, the percentage of subjects who are responders for ECR at 96 ± 24 hours post first dose of study drug will be approximately 79%.

The primary efficacy analysis variables used for NI analyses for the Marketing Authorization Application to the EMA will be the percentage of subjects with an IACR of Success at TOC in the mITT and CE-TOC Analysis Sets. In recent clinical studies, IACR success rates at the TOC Visit in the CE Analysis Set ranged from 77%-87% depending on the antibiotics under study and the severity of the CABP. The IACR success rate for subjects receiving moxifloxacin is 86% as reported in the prescribing information (AVELOX® [moxifloxacin] PI, 2013). Based on these data, an 85% IACR success rate in the CE-TOC Analysis Set was chosen for determination of the sample size. The success rate is expected to be about 5% lower in the mITT Analysis Set. It is expected that <1% of subjects will be excluded from the mITT Analysis Set and thus, the sample size determination assumes the same number of subjects in the ITT and mITT Analysis Sets.

Utilizing an anticipated ECR responder rate of 79% in the ITT Analysis Set, and a 1-sided alpha of 0.025, a sample size of 550 subjects (275 in each treatment group) provides >90% power to establish the NI of lefamulin to moxifloxacin for ECR using a NI margin of 12.5%. Assuming an IACR success of 80% and 85% in the mITT and CE-TOC Analysis Sets, respectively, and a clinical evaluability rate of 80%, there is 80% power for demonstration of NI for IACR at the TOC Visit using a 10% NI margin. If the sample size is increased to 626 subjects, it will provide >95% power for demonstration of NI for ECR and 85% power for demonstration of NI for IACR at the TOC Visit.

The calculated power for the primary and secondary outcome measures is provided in Table 7.

Table 7. Power Calculations for the Primary and Secondary Outcome Measures

	Primary Outcome (Early Clinical Response)	Secondary Outcome (Primary for EMA) (Investigator's Assessment of Clinical Response - TOC)	
Analysis Set	ITT	mITT	CE-TOC
NI Margin	12.5%	10%	10%
Evaluability Rate	NA	NA	80%
Outcome Rate	79%	80%	85%
N	550	550	440
Power	93.8%	80.6%	80%

7.2 Visit Windows

Unless otherwise stated below, baseline is defined as the last measurement prior to the first dose of study drug.

- For microbiological pathogen determination, baseline is defined as the 24-hour period prior to the administration of the first dose of study drug and the 24 hours after the first

dose of study drug. A pathogen identified from a respiratory (pleural fluid, bronchoalveolar lavage (BAL), sputum), blood for culture, urine, nasopharyngeal or oropharyngeal specimen collected at baseline is considered a baseline pathogen. An atypical pathogen identified by serology is considered a baseline pathogen if the baseline sample is collected in the 24-hour period prior to or the 24 hours after the administration of the first dose of study drug.

- For vital signs, baseline is defined as the last assessment prior to Day 1.
- For ECGs, baseline is defined as the mean of the triplicates from the last assessment prior to the first dose of study drug.
- If no study drug is received, baseline is defined as the measurement taken at the Screening Visit

Study Day 1 is defined as the first calendar day of study drug administration. The calendar day prior to the first dose of study drug is Study Day -1; there is no Study Day 0.

For all clinical assessments and procedures performed prior to the date of the first study drug administration, study day will be calculated as the date of the assessment minus the date of the first dose of study drug. For all clinical assessments and procedures performed on or after the date of the first dose of study drug, study day will be calculated as the date of the assessment minus the date of the first dose of study drug, plus 1.

The visit window for ECR is defined in Section 6.1. Clinical efficacy and safety analyses will utilize the data obtained on the scheduled visit (ie, nominal visit will be utilized). Safety labs (chemistry, hematology and urinalysis) are collected for all subjects at Screening, Day 4, EOT and TOC. Subjects receiving 10 days of study drug also have safety labs collected at Day 7. Safety labs are completed at LFU only if the subject had an abnormal result at TOC. For Day 4 safety lab assessments, the window is Day 4 ± 1 day. For Day 7 safety lab assessments, the window is Day 7 +1 day. Vital signs are collected daily while the subject is seen in person and at EOT and TOC. ECGs are collected at Screening, Day 1 and Day 3, prior to the first infusion of study drug on that day and within 15 minutes after the end of the first infusion on that day. See Appendix A for a complete description on the timing of the safety assessments.

If no scheduled visit was done, but an unscheduled safety assessment was done in the window of the scheduled assessment (for the specific safety parameter), the unscheduled assessment should be used. If more than 1 measurement is taken during the visit window (a scheduled visit and an unscheduled visit), the value taken on the scheduled visit will be utilized. If more than one unscheduled assessment is completed in the visit window of the scheduled assessment (and no scheduled assessment), the earliest assessment should be used. For overall worst post-baseline analyses, all assessments including those obtained on unscheduled and scheduled visits will be included.

7.3 Randomization

Subjects will be assigned to receive lefamulin or moxifloxacin in a 1:1 ratio with stratification by geographic region (US vs. ex-US), receipt of prior single dose short-acting antibiotic therapy for CABP vs. none, and PORT risk class (III vs. IV/V) using blocked randomization via the IRT.

The randomization schedule will be generated by the Sponsor (or designee). 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.

The Sponsor designee (ie, IRT vendor) will maintain the randomization codes in accordance with standard operating procedures to ensure the blind is properly maintained, and that only Sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in maintaining the clinical supplies or SAE reporting). After the database is locked and the SAP is final, the study blind codes will be broken.

7.4 Interim Analysis

In order to ensure that the point estimate of the ECR responder rate used in the estimate of the sample size is valid for this study, an interim analysis for sample size re-estimation will be performed when ECR data at 96 ± 24 hours post first dose are available for approximately 60% of the randomized subjects. The FDA Guidance "Non-inferiority Clinical Trials to Establish Effectiveness" notes that such a sample size re-estimation if based on the blinded overall response rate is not only acceptable but is advisable (FDA, 2016). The interim analysis will involve a sample re-estimation to either confirm that the initial sample size estimate is adequate or increase the sample size (number of randomized subjects) to ensure the study has adequate power for determining whether lefamulin is NI to moxifloxacin for the primary outcome measure. The sample size re-estimation will be based on the blinded overall (not by treatment group) ECR responder rate and will be conducted by an independent, blinded statistician. An Independent Interim Analysis Committee (IAC) will be provided the results of the interim analysis by the independent, blinded statistician and will make a recommendation regarding any increase to the sample size. A detailed IAC charter will be developed which outlines the analyses to be completed, statistical rules, the potential increase to the sample size, and the recommendations that can be made to the Sponsor. The members of the IAC will not participate in the ongoing assessment of the important aspects of study conduct, including the assessment of safety data.

In addition, an independent Data Monitoring Committee (DMC) will be constituted for this study to monitor important aspects of study conduct, including safety results on an ongoing basis. The DMC will receive masked data (treatment "A" vs. treatment "B") at pre-specified time points for their review of safety data throughout the conduct of the trial. DMC meeting frequency and conduct will be outlined in a separate DMC Charter. An independent, unblinded statistician will provide the committee with masked data for review, but will not be a member of the committee. In addition, a clinical representative from the Sponsor will be available during an open session of each meeting to help answer questions or relay additional information to the DMC as needed, but this individual will not be a voting member of the committee. All members of the DMC will treat study data, reports, meeting discussions, and conclusions as confidential. The members of the DMC will not participate in the interim analysis and re-assessment of the sample size for this trial.

7.5 Comments on the Statistical Analyses

- All clinical data will be provided in by-subject listings.
- Continuous variables will be summarized using number (N), mean, standard deviation (SD), median, minimum, and maximum.
- Frequency counts and percentages will be reported for all categorical data.
- If a laboratory result (other than an MIC value) is reported relative to a lower/upper range of detection for an assay, for example, "<10", the numeric portion of the result (10) will be used for statistical analyses and the full result, including any symbols, will be provided in the subject listings.
- For AEs with onset on or after the first dose of study drug, onset day will be calculated as the date of onset of the AE minus the date of the first dose of study drug, plus 1. For AEs with onset prior to the first dose of study drug, onset day will be calculated as the date of onset of the AE minus the date of the first dose of study drug.
- For prior medications, start day will be calculated as the start date of the medication minus the date of the first dose of study drug. For concomitant medications and prior medications taken on the same day as the first dose of study drug, start day will be calculated as the start date of the medication minus the date of the first dose of study drug, plus 1.
- Version 9.2 (or higher) of SAS statistical software package will be used to provide all summaries, listings, figures and statistical analyses.

7.6 Handling of Missing Data

For ECR, missing data will be handled as follows:

- If any component of ECR is missing in the time frame detailed in Section 6.1 (unless the subject dies or is deemed a failure prior to this time point), or if the subject does not have at least 2 symptoms of CABP at baseline, ECR will be defined as an indeterminate.
- If the time of an assessment of CABP symptoms obtained in the window for determination of ECR is missing but the date of the ECR assessment is known, the time will be imputed to noon on the date of the CABP symptom assessment.
- Missing start and stop times of antibiotics will be set to 00:00 on the start and stop date of the antibiotic.
- For the analysis of ECR in the ITT Analysis Set, where ECR may be missing (indeterminate), all subjects in the ITT Analysis Set will be included in the denominator. Thus, subjects with an indeterminate response are essentially considered as a failure.

For IACR, missing data will be handled as follows:

- A missing IACR at the EOT Visit will be considered indeterminate at the EOT Visit.
- A missing IACR at the TOC Visit will be considered indeterminate unless the IACR at the EOT Visit is failure. An IACR of failure at the EOT Visit will be carried forward to the TOC Visit.
- A missing IACR at the LFU Visit will be considered indeterminate unless the IACR at the TOC Visit is failure. An IACR of failure at the TOC Visit will be carried forward to the LFU Visit.
- For the analysis of IACR at the EOT, TOC and LFU Visits in the mITT, microITT, microITT-2 and emicroITT Analysis Sets, where Clinical Response may be missing (indeterminate), all subjects who meet the analysis set criteria will be included in the denominator.
- For the analysis of IACR at the EOT, TOC and LFU Visits in the CE and ME Analysis Sets, subjects with a missing (indeterminate) IACR will not be included in the analyses, since by definition, subjects in the CE or ME Analysis Sets cannot have a missing IACR.

For microbiological response, missing data will be handled as follows:

- A missing microbiological response at the EOT Visit will be presumed from the IACR at the EOT Visit.
- A by-pathogen microbiological response of persistence and a by-subject microbiological response of failure at the EOT Visit will be carried forward to the TOC Visit. A missing microbiological response at the TOC Visit will be presumed from the IACR at the TOC Visit. If the IACR at the TOC Visit is missing, the microbiological response at the TOC Visit will be indeterminate.
- A by-pathogen microbiological response of persistence and a by-subject microbiological response of failure at the TOC Visit will be carried forward to the LFU Visit. A missing microbiological response at the LFU Visit will be presumed from the IACR at the LFU Visit. If the IACR at the LFU Visit is missing, the microbiological response at the LFU Visit will be indeterminate.
- For the analysis of microbiological response at the EOT, TOC and LFU Visits in the microITT and microITT-2 Analysis Sets, where microbiological response may be missing (indeterminate), all subjects who meet the analysis set criteria will be included in the denominator.
- For the analysis of microbiological response at the EOT, TOC and LFU Visits in the ME Analysis Sets, subjects with a missing (indeterminate) microbiological response will not be included in the analysis, since by definition, subjects in the ME Analysis Sets cannot have a missing microbiological response.

For all other outcome measures, missing data are handled as follows:

- Missing values for individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.
- When individual data points are missing, categorical data will be summarized based on reduced denominators (ie, only subjects with available data will be included in the denominators).

8.0 STATISTICAL ANALYSES

8.1 Subject Disposition and Protocol Deviations

The number of subjects randomized by region, country and center will be presented by treatment group in the ITT Analysis Set. The number of subjects included in each of the study analysis sets (ITT, mITT, Safety, emicroITT, microITT, microITT-2, CE-EOT, CE-TOC, CE-LFU, ME-EOT, ME-TOC and ME-LFU) will be summarized overall and by geographic region, for each treatment group and across treatment groups. Regions are defined as follows: North America (United States), Latin America (Argentina, Brazil, Peru), Eastern Europe (Bosnia and Herzegovina, Bulgaria, Georgia, Latvia, Romania, Russian Federation, Serbia, Ukraine), Western Europe (Hungary, Poland and Netherlands) and Rest of World (Philippines, Thailand, South Africa). The reasons for exclusion from the mITT, Safety, emicroITT, microITT, microITT-2, CE and ME Analysis Sets will be tabulated. A by-subject listing will be provided that will include the reason(s) for exclusion from each of the study analysis sets.

A listing will provide the date of informed consent for all randomized subjects, whether or not the subject met all inclusion/exclusion criteria and if not, which criteria were not met. The number of subjects completing the study (ie, completing the LFU Visit), prematurely withdrawing from the study, completing study drug, prematurely discontinuing study drug, and the reasons for premature withdrawal and premature discontinuation will be summarized by treatment group and overall for all subjects in the ITT Analysis Set. The percentages of subjects discontinued from study drug and prematurely withdrawn from the study will be compared between treatment groups using Fisher's exact test. A listing of study completion/premature withdrawal and study drug completion/premature discontinuation for all subjects will be provided and will display subject ID, treatment, the primary reason for premature withdrawal or discontinuation, date and study day of last study visit, and vital status at Day 28.

The number and percentage of subjects in the ITT Analysis Set with at least 1 significant protocol deviation will be summarized by treatment group and overall. A significant protocol deviation is one that has the potential to affect efficacy assessments, placement into analysis populations, the safety or ability to monitor the safety of a subject, or the scientific value of the trial. The number and percentage of subjects with at least 1 significant deviation that excludes a subject from the CE Analysis Sets and the number and percentage of subjects with at least 1 other significant deviation will also be summarized by treatment group and overall, and by deviation subtype.

A by-subject listing of all significant protocol deviations will also be provided.

8.2 Demographics and Baseline Characteristics

Descriptive statistics for continuous variables (age, height, weight, and body mass index), and frequency counts and percentages for categorical variables (age group, race, ethnicity, gender and renal status [severe impairment [<30 mL/min], moderate impairment [30-<60 mL/min], mild impairment [60-<90 mL/min] and normal function [≥90 mL/min]) will be summarized by treatment group and overall for the ITT, mITT and CE-TOC Analysis Sets. Body mass index will be calculated by dividing weight (kg) by height (m^2). Creatinine clearance based on the central lab determination will be used. In those cases where creatinine clearance is not available from the central lab, it will be calculated using the local lab serum creatinine based on the Cockcroft-Gault equation:

$$\frac{(140\text{-age[yrs]}) * \text{weight [kg]} * (Z)}{\text{Cr [mg/dL]} * 72} \qquad \begin{array}{l} Z = 1.0, \text{ if Male} \\ Z = 0.85, \text{ if Female} \end{array}$$

A table will provide the frequency counts and percentages by treatment group and overall for PORT Risk Class (both as per IRT [III, IV/V] as well as calculated from components reported in the eCRF [III, IV, V]), subjects meeting the modified American Thoracic Society (ATS) severity criteria, subjects meeting the Systemic Inflammatory Response Syndrome (SIRS), CURB-65 category, and subjects with bacteremia for the ITT, mITT and CE-TOC Analysis Sets. PORT score and CURB-65 Score will also be summarized as a continuous variable. CURB-65 is derived from the eCRF data and ranges from 0-5 where 1 point is given for each of the following at baseline: confusion, blood urea nitrogen (BUN) >19 mg/dL (>6.8 mmol/L), respiratory rate ≥30 breaths/min, systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg, and age ≥65 years. Confusion is defined as altered mental status as recorded on the PORT Risk Assessment eCRF. Modified ATS severity and SIRS criteria are derived from the eCRF data and baseline PMNs reported in the central laboratory data. Modified ATS severity criteria is defined as presence of ≥3 of the following 9 criteria at baseline: respiratory rate ≥30 breaths/min, O_2 saturation <90% or PaO_2 <60 mmHg, BUN ≥20 mg/dL, WBC <4000 cells/mm^3, confusion, multilobar infiltrates, platelets <100,000 cells/mm^3, temperature <36°C, and systolic blood pressure <90 mmHg. SIRS criteria is defined as ≥2 of the following 4 symptoms at baseline: temperature <36°C or >38°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, WBC <4000 cells/mm^3 or WBC >12,000 cells/mm^3, or immature PMNs >10%.

Baseline assessments of clinical signs and symptoms of CABP, including fever (defined as body temperature >38.0°C (100.4°F) oral, tympanic >38.5°C (101.3°F), rectal/core >39.0°C (102.2°F), or axillary >37.5°C (99.5°F)), hypothermia (defined as body temperature <35.0°C (95.0°F) oral, tympanic <35.5°C (95.9°F), or rectal/core <36.0°C (96.8°F)), hypotension (systolic blood pressure <90 mmHg), tachycardia (heart rate >100 beats/min), tachypnea (respiratory rate >20 breaths/min), dyspnea, cough, production of purulent sputum and chest pain will be summarized by treatment group and overall for the ITT, mITT and CE-TOC Analysis Sets.

Medical history (including diseases/conditions and surgical procedures) will be summarized by treatment group and overall for subjects in the ITT Analysis Set. For the summary of medical history, subjects with more than 1 abnormality within the same preferred term will be counted only once for that preferred term. Subjects are counted only once in a system organ class.

CABP risk factors, including tobacco history (current and previous use of cigarettes, cigars, chewing tobacco and other), history of pneumococcal vaccination, evidence of influenza during the current illness and history of influenza vaccination, will be summarized by treatment group and overall for subjects in the ITT, mITT and CE-TOC Analysis Sets.

Readings of baseline chest radiographs by the radiologist, including the type of assessment (chest X-ray or CT scan), radiographic evidence of CABP (ie, a pulmonary infiltrate or diffuse opacity), presence of pleural effusion, whether the pleural effusion is unilateral or bilateral, presence of pulmonary infiltrate, whether the pulmonary infiltrate was uni- or multi-lobar, the location of the pulmonary infiltrate(s), presence of diffuse opacities and the location of the diffuse opacities will be summarized by treatment group and overall for all subjects in the ITT, mITT and CE-TOC Analysis Sets.

Descriptive statistics of baseline procalcitonin and number and percentage of subjects in the categories <0.1 mcg/L, 0.1 mcg/L to 0.25 mcg/L and >0.25 mcg/L will be presented by treatment group and overall for the ITT, mITT and CE-TOC Analysis Sets.

8.3 Baseline Microbiological Assessments

Baseline pathogens will be summarized by genus and species, treatment group and overall for the microITT, microITT-2, emicroITT, and ME-TOC Analysis Sets. Selected pathogens will also be summarized by phenotypic susceptibility profile. In addition, for *Staphylococcus aureus* isolated at baseline, the PVL and MecA status (positive or negative) will be summarized. Table 8 provides the definition for each pathogen susceptibility profile.

Table 8. Definitions for Pathogen Susceptibility Profile

Pathogen	Susceptibility Profile	Definition
Staphylococcus aureus	MSSA	Susceptible to cefoxitin
	MRSA	Resistant to cefoxitin
Streptococcus pneumoniae	PSSP	Susceptible to penicillin
	PISP	Intermediate susceptibility to penicillin
	PRSP	Resistant to penicillin
	Macrolide resistant	Resistant to azithromycin or erythromycin
	Quinolone resistant	Resistant to moxifloxacin
	Multidrug resistant	Resistant to 2 or more of the following classes of drugs: • Penicillins – oral penicillin • Fluoroquinolones – moxifloxacin • Cephalosporins –ceftriaxone • Lincosamides – clindamycin • Macrolides – azithromycin or erythromycin • Tetracyclines – doxycycline • Folate Pathway Inhibitors – trimethoprim/sulfamethoxazole
Haemophilus influenzae	B-lactamase positive	Zone diameter for ampicillin ≤18 mm
	B-lactamase negative	Zone diameter for ampicillin >18
Mycoplasma pneumoniae	Macrolide susceptible	Susceptible to azithromycin and erythromycin
	Macrolide resistant	Resistant to azithromycin or erythromycin
	Quinolone resistant	Resistant to moxifloxacin

Findings from baseline Gram-stained respiratory specimens (ie, the best Gram stain reading from the central read of a central laboratory Gram stained respiratory specimen and the central read of the local/regional laboratory Gram stained respiratory specimen, or if neither central read is available, the local/regional read of the local/regional laboratory Gram stained respiratory specimen as detailed in Section 4.1) will be tabulated by treatment group and overall for subjects in the microITT, microITT-2, emicroITT and ME-TOC Analysis Sets. The number and percentage of subjects with a Gram-stained respiratory specimen that shows >25 PMNs and <10 SECs per LPF and >10 PMNs and <10 SECs per LPF will be presented. In addition, summaries of PMNs and SECs and bacterial morphology for all Gram-stained respiratory specimens will be provided. Baseline for Gram stains is defined as the 24-hour period prior to first dose of study drug and the 24-hour period after the first dose of study drug.

Baseline pathogens will be summarized by treatment group and overall, by genus and species, and diagnostic modality for the microITT, microITT-2, and ME-TOC Analysis Sets. The number and percentage of subjects with specimens tested, by testing modality, and the number and percentage of subjects with specimens positive for a pathogen and the specific pathogen (genus and species) will be presented. The number and percentage of subjects with monomicrobial or polymicrobial gram-positive or gram-negative pathogen infections, only atypical pathogens, a mixture of gram-positive and gram-negative pathogens, a mixture of gram-positive and atypical pathogens, a mixture of gram-negative and atypical pathogens or a

mixture of gram-positive, gram-negative and atypical pathogens will be summarized by treatment group and overall for the microITT, microITT-2 and ME-TOC Analysis Sets.

The MIC distribution detailing the number and percentage of pathogens at the respective MIC values and the cumulative distribution will be presented for lefamulin and moxifloxacin by baseline pathogen, phenotype and study drug for both treatment groups combined and by treatment group for subjects in the microITT and ME-TOC Analysis Sets. Disk diffusion zone diameters for lefamulin and moxifloxacin will be summarized by baseline pathogen, phenotype, and study drug for both treatment groups combined and by treatment group for subjects in the microITT and ME-TOC Analysis Sets. Scatter plots of the MIC to lefamulin versus the disk diffusion zone diameter will be provided for *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Moraxella catarrhalis*, as long as there are at least 10 pathogens in the lefamulin group.

The minimum inhibitory concentration 50 (MIC50), 90 (MIC90), and range of lefamulin and moxifloxacin for baseline pathogens and susceptibility (susceptible and resistant, based on MIC and zone diameter) of pathogens to lefamulin and moxifloxacin will be summarized by baseline pathogen for both treatment groups combined and by treatment group for subjects in the microITT and ME-TOC Analysis Sets. MIC50 and MIC90 will be provided only where there are at least 10 pathogens of a particular species; range will be provided for all pathogens. If at least 10 MRSA pathogens are isolated in 1 of the treatment groups, the MIC50, MIC90, MIC range and susceptibility to linezolid will be summarized for MRSA for both treatment groups combined and by treatment group.

Baseline pathogens are considered susceptible (S), intermediate (I), or resistant (R) to moxifloxacin and S or non-susceptible (NS) to lefamulin according to the criteria in Table 9 and Table 10.

Table 9. Interpretive Criteria for Moxifloxacin for CABP Pathogens According to CLSI Guidelines

	Moxifloxacin MIC breakpoint [a] [µg/mL]			Moxifloxacin Disk Diffusion Zone Diameter [a] [mm]		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Streptococcus pneumoniae	≤ 1	2	≥ 4	≥ 18	15-17	≤ 14
Staphylococcus spp.	≤ 0.5	1	≥ 2	≥ 24	21-23	≤ 20
Haemophilus influenzae	≤ 1	-	-	≥ 18	-	-
Moraxella catarrhalis	-	-	-	-	-	-
Legionella pneumophila	-	-	-	-	-	-
Mycoplasma pneumoniae [b]	≤ 0.25	-	≥ 0.5	-	-	-

S=susceptible, I=intermediate, R=resistant
[a] According to CLSI M100-S25 (2015)
[b] Breakpoints according to CLSI M43-A (2011)

Table 10. Proposed Tentative Susceptibility Interpretive Criteria for Lefamulin for CABP Pathogens Based on *In Vitro* Data Determined According to CLSI Guidelines

	Lefamulin MIC breakpoint [a] [µg/mL]			Lefamulin Disk Diffusion Zone Diameter [a] [mm]		
Pathogen	**S**	**NS**		**S**	**NS**	
Streptococcus pneumoniae	≤ 1	> 1		≥ 19	< 19	
Staphylococcus spp.	≤ 1	> 1		≥ 20	< 20	
Haemophilus influenzae	≤ 2	> 2		≥ 20	< 20	
Moraxella catarrhalis	≤ 1	> 1		≥ 20	< 20	
Legionella pneumophila	≤ 1	> 1		- [b]	- [b]	
Mycoplasma pneumoniae	≤ 1	> 1		- [b]	- [b]	

S=susceptible, NS=non-susceptible

[a] The current absence of data on resistant isolates except for *S. aureus* precludes defining any category other than "susceptible."

[b] No disk diffusion zone diameter criteria have been established for *M. pneumoniae* and *L. pneumophila*.

For linezolid, *Staphylococcus* spp. with an MIC ≤4 µg/mL are considered susceptible.

By-subject listings of pathogen MICs, susceptibilities, and disk diffusion zone diameters will also be provided.

8.4 Extent of Exposure and Study Drug Treatment Compliance

8.4.1 Duration of Study Drug Therapy

Duration of study drug treatment (IV and oral) will be summarized by treatment group for the Safety, mITT and CE-TOC Analysis Sets. Duration of study drug treatment is defined as the date of last dose – the date of first dose + 1. The number and percentage of subjects who received study drug for <3 days, 3-5 days, 6-7 days, 8-10 days and >10 days as well as descriptive statistics of the duration of study drug treatment (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group. Duration of study drug will also be summarized separately for IV drug only (<3 days, 3 days, 4-5 days, 6-7 days, 8-10 days and >10 days) and oral drug only (<3 days, 3-4 days, 5-7 days, and >7 days). The number and percentage of subjects who switched to oral study drug will be presented for the Safety, mITT and CE-TOC Analysis Sets. Descriptive statistics for duration of IV drug and duration of oral drug will be presented by treatment group.

The number and percentage of subjects who received linezolid/linezolid placebo (IV and oral) as well as descriptive statistics of the number of days on linezolid/linezolid placebo will be provided by treatment group. The proportion of subjects who discontinued moxifloxacin or the linezolid placebo and who discontinued the linezolid or matching placebo will be provided. The number and percentage of subjects who received study treatment for <3 days, 3-5 days, 6-7 days, 8-10 days and >10 days as well as descriptive statistics for the duration of treatment will be summarized separately for those subjects whose microbiological results confirm MRSA as a causative pathogen, and for those subjects with *Legionella pneumophila* or *Streptococcus*

pneumoniae bacteremia (prior to protocol Amendment 2) at baseline. The number and percentage of subjects who received study treatment for <3 days, 3-4 days, 5-7 days, and >7 days as well as descriptive statistics for the duration of treatment will be summarized separately for those subjects with *Legionella pneumophila* or *Streptococcus pneumoniae* bacteremia (protocol Amendment 2 or later) at baseline, and for those subjects with an other baseline pathogen or no pathogen identified at baseline.

8.4.2 Prior and Concomitant Medications

The World Health Organization (WHO) drug dictionary will be used to classify prior and concomitant medications, including antibacterial medications, by therapeutic class. A prior medication is defined as any medication taken prior to the date and time of the first dose of study drug. For non-antibacterials (for which only start and stop dates [not times] are collected), any medication taken on or after the date of first dose of study drug will be considered concomitant; medications stop dates occurring prior to the date of first dose of study drug will be considered prior medications. A concomitant medication is defined as any medication taken on or after the date and time of the first dose of study drug. If the start date of a medication is missing, the medication will be assumed to be both prior and concomitant, unless the end date of the medication clearly indicates the medication was stopped prior to the first dose of study drug. If the start date is a partial date such that it cannot be determined if the medication is prior or concomitant, the medication will be assumed to be both prior and concomitant, unless the end date of the medication clearly indicates the medication stopped prior to the first dose of study drug.

For antibacterials, missing start and stop times will be set to 00:00 on the start and stop date of the antibiotic.

Prior systemic antibacterial medications and concomitant systemic antibacterial medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 4 and preferred term separately by treatment group for the ITT, mITT and CE-TOC Analysis Sets. Subjects receiving the same medication more than once will be counted only once for a particular ATC level and preferred term. Prior systemic antibacterial medications will be summarized based on receipt within 72 hours prior to randomization and receipt more than 72 hours prior to randomization.

Additional tables (ITT and CE-TOC Analysis Sets) will summarize the percent of subjects receiving any prior systemic antibacterial medication, the percent of subjects receiving an antibacterial medication in the 72 hours prior to randomization, the percent receiving the antibacterial for the current episode of CABP, the percent receiving a single dose of a short-acting oral or IV antibacterial for CABP (per the eCRF), the percent receiving more than 1 dose of a short-acting antibacterial for CABP or ≥1 dose of a long-acting antibacterial for CABP, the percentage of subjects receiving >48 hours of prior systemic antibacterial therapy for the current episode of CABP enrolled as a treatment failure (ie, the exception to exclusion criterion 1), the percentage of subjects receiving a prior systemic antibacterial for an infection not related to CABP and the percentage of subjects receiving a prior systemic antibacterial for an “other” reason.

Prior and concomitant non-antibacterial medications will be presented in a by-subject listing and concomitant non-antibacterial medications will be summarized by ATC level 4, preferred term and treatment group for the ITT Analysis Set. Subjects receiving the same medication more than once will be counted only once for a particular ATC level and preferred term.

The reasons for receipt of concomitant systemic antibacterial medications will be summarized by treatment group for the ITT, mITT and CE-TOC Analysis Sets. For concomitant systemic antibacterial medications, the number and percentage of subjects excluded from the CE Analysis Sets due to receipt of an antibacterial and not excluded from the CE Analysis Sets will be summarized. The reasons for receipt of the antibacterial will be provided for each category (excluded and not excluded from the CE Analysis Sets) and include current CABP prior to randomization, infection prior to randomization not related to CABP, concomitant infection unrelated to CABP, insufficient therapeutic effect of study drug (only for not excluded from the CE Analysis Sets), treatment-limiting AE resulting in study drug discontinuation (only for not excluded from the CE Analysis Sets), and "other."

8.4.3 Study Drug Treatment Compliance

Each subject's compliance with study drug treatment will be calculated based on the number of doses the subject would have been expected to receive based on the baseline pathogen(s) identified and the version of the protocol a subject was enrolled under. Treatment compliance is defined as the number of doses actually received divided by the number of doses expected for the time period × 100. Compliance includes active drug plus placebo with or without linezolid/linezolid placebo. Descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) of compliance for IV and oral, and for IV and oral separately will be presented for the mITT and CE-TOC Analysis Sets.

8.5 Efficacy Analyses

For all efficacy analyses, subjects will be analyzed in the group to which they were randomized. By definition, subjects who receive the wrong study drug are not included in the CE and ME Analysis Sets. Unless otherwise stated, subjects who are randomized to the wrong geographic region, prior antibiotic, or PORT risk class stratum will be analyzed in the stratum to which they were randomized.

8.5.1 Primary Efficacy Analysis

The primary efficacy outcome is the percentage of subjects with an ECR of responder at 96 ± 24 hours after the first dose of study drug in the ITT Analysis Set. Each subject will be programmatically categorized as a responder, non-responder, or indeterminate based on data on the eCRF. Subjects with missing data or who are lost to follow up are defined as indeterminate for the primary analysis and are included in the denominator for the calculation of the response rate. Thus, subjects with an indeterminate outcome are considered non-responders for the primary analysis. The number and percentage of subjects in each treatment group in each response category (and combined non-responder/indeterminate) will be reported.

The null and alternative hypotheses are:

H_0: P_1-$P_2 \leq -\Delta$
H_1: P_1-$P_2 > -\Delta$
Where P_1 = the primary efficacy outcome rate in the lefamulin group
P_2 = the primary efficacy outcome rate in the moxifloxacin group
Δ = the non-inferiority margin

The NI hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. This is based on the lower limit of the 2-sided 95% confidence interval (CI) for the observed difference in the early clinical response rate (lefamulin group minus the moxifloxacin group). The CI will be calculated using an unadjusted continuity corrected Z-test. If the lower limit of the 95% CI for the difference in responder rates in the ITT Analysis Set is greater than -12.5%, the null hypothesis will be rejected and the NI of lefamulin to moxifloxacin will be concluded.

The reasons for an ECR of non-responder and indeterminate will be summarized by treatment group for all subjects who are a non-responder or indeterminate at 96 ± 24 hours after the first dose of study drug. Reasons for non-responder are: did not show improvement in at least 2 of the cardinal symptoms of CABP, worsening of at least 1 symptom of CABP, received a concomitant antibacterial and died from any cause. Reasons for indeterminate are: no assessment of symptoms and did not have at least 2 cardinal symptoms at baseline.

8.5.2 Additional Analyses of the Primary Efficacy Outcome

Early Clinical Response will be assessed separately across the randomization stratification factors (from the IRT) of geographic regions (US vs. ex-US), prior antibiotic use vs. none, and PORT risk class (III vs. IV/V). For each geographic region, prior antibiotic use, and PORT risk class stratum a 2-sided 95% CI for the observed difference in ECR responder rates will be calculated for the ITT Analysis Set.

Sensitivity analyses of early clinical response include:

- An analysis adjusted for the stratification factors of geographic region, prior antibiotic use and PORT risk class stratum (based on the randomization stratum the subject was actually randomized to). A 95% CI using the method proposed with stratification by Miettinen and Nurminen will be computed for the difference in the ECR responder rates between lefamulin and moxifloxacin. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI.
- An analysis adjusted for the stratification factors of geographic region, prior antibiotic use, and PORT risk class stratum based on the randomization stratum the subject correctly belongs to. A 95% CI using the method proposed with stratification by Miettinen and Nurminen will be computed for the difference in the ECR responder rates between lefamulin and moxifloxacin. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI.

- All subjects with missing data at 96 ± 24 hours after the first dose of study drug or with less than 2 symptoms at baseline (ie, indeterminates) as ECR responders (these subjects are considered ECR non-responders in the primary analysis). An unadjusted 95% CI will be computed using a continuity corrected Z-test for the difference in the ECR responder rates between lefamulin and moxifloxacin.
- Subjects who are non-responders and receive less than 48 hours total duration of study drug will be reclassified as indeterminates and the number and percentage of subjects in each treatment group in each response category will be reported. Subjects who died prior to receipt of at least 48 hours total duration of study drug will remain classified as a non-responder. An unadjusted 95% CI will be computed using a continuity corrected Z-test for the difference in the ECR responder rates between lefamulin and moxifloxacin.

Subgroup analyses of the primary efficacy outcome, including treatment differences and 95% CIs (computed using a continuity corrected Z-test), will also be conducted for descriptive purposes. These include but are not limited to PORT Risk Class per the eCRF (III, IV, V), prior antibiotic use in the 72 hours before randomization per the eCRF (use, no use), SIRS (yes, no), ATS (yes, no), CURB-65, gender, age group (<65, 65-74, ≥75 years), renal impairment category and bacteremic subjects. If at least 20 subjects receive linezolid/linezolid placebo, the percentage of subjects in each treatment group determined to be a responder for ECR will be presented for the ITT Analysis Set in those subjects who received linezolid/linezolid placebo. Exploratory analyses in other subgroups may also be conducted. A Forest plot of the treatment difference in ECR responder rate and CI by the stratification factors and subgroups will also be provided.

The number and percentage of subjects in each treatment group determined to be a responder, non-responder and indeterminate for ECR will be presented for the ITT Analysis Set in those subjects who were enrolled under the original protocol or Amendment 1, and for those subjects who were enrolled under Amendment 2 or later. The treatment difference for the ECR responder rates will be determined and a 95% CI for the treatment difference will be computed using a continuity corrected Z-test.

8.5.3 Secondary Efficacy Analyses

8.5.3.1 Investigator's Assessment of Clinical Response at the TOC Visit in the mITT and CE-TOC Analysis Sets

The number and percentage of subjects in each treatment group determined to have an IACR of success, failure, or indeterminate (and combined failure and indeterminate) at the TOC Visit will be presented for the mITT and CE-TOC Analysis Sets (indeterminates are excluded from the CE-TOC Analysis Set). Two-sided unadjusted 95% CIs for the difference in success rate will be calculated using a continuity corrected Z-test.

The reasons for IACR of failure at the TOC Visit will be summarized by treatment group for all subjects in the mITT and CE-TOC Analysis Sets. The reasons for IACR of indeterminate (subject lost to follow-up, missed visit, withdrew from the study or did not have CABP) will also be summarized by treatment group for all subjects at the TOC Visit for the mITT Analysis Set.

8.5.3.2 Early Clinical Response in the Microbiologic Intent-to-Treat Analysis Sets

The number and percentage of subjects categorized as responder, non-responder and indeterminate (and combined non-responder and indeterminate) for the outcome of ECR will be presented for the microITT, microITT-2 and emicroITT Analysis Sets and a 2-sided unadjusted 95% CI for the difference in responder rate will be calculated using a continuity corrected Z-test.

The reasons for an ECR of non-responder and indeterminate at 96 ± 24 hours after the first dose of study drug will be summarized by treatment group for all subjects in the microITT and microITT-2 Analysis Sets.

8.5.3.3 Early Clinical Response Plus Improvement in Vital Signs in the ITT Analysis Set

The number and percentage of subjects categorized as responder, non-responder and indeterminate (and combined non-responder and indeterminate) for the outcome of ECR plus improvement in vital signs, will be presented for the ITT Analysis Set and a 2-sided unadjusted 95% CI for the difference in responder rate will be calculated using a continuity corrected Z-test. The reasons for an ECR plus improvement in vital signs of non-responder and indeterminate at 96 ± 24 hours after the first dose of study drug will be summarized by treatment group for all subjects in the ITT Analysis Set. Reasons for non-response include those for ECR (Section 8.5.1) as well as did not show an improvement in body temperature, hypotension, tachycardia and tachypnea. Reasons for indeterminate include no assessment of symptoms, did not have at least 2 cardinal symptoms of CABP at baseline and had no assessment of vital signs.

8.5.3.4 Investigator's Assessment of Clinical Response at the TOC Visit in the microITT and ME-TOC Analysis Sets

The number and percentage of subjects in each treatment group determined to have an IACR of success, failure, or indeterminate (and combined failure and indeterminate) at the TOC Visit will be presented for the microITT and ME-TOC Analysis Sets (indeterminates are excluded from the ME-TOC Analysis Set). Two-sided unadjusted 95% CIs for the difference in success rate will be calculated using a continuity corrected Z-test.

The reasons for IACR of failure at the TOC Visit will be summarized by treatment group for all subjects in the microITT and ME-TOC Analysis Sets. The reasons for IACR of indeterminate at the TOC Visit will also be summarized by treatment group for all subjects in the microITT Analysis Set.

8.5.3.5 By-Pathogen Microbiological Response at the TOC Visit in the microITT and ME-TOC Analysis Sets

The proportion of subjects with a microbiological response of success by baseline pathogen (and where relevant, the susceptibility phenotype) at the TOC Visit will be tabulated separately by treatment group for subjects in the microITT and ME-TOC Analysis Sets. Distinct pathogens are based on genus and species and where relevant, the susceptibility phenotype as defined in Table 8.

For all by-pathogen analyses, subjects with a pathogen of the same genus and species with more than 1 phenotype, for example both MRSA and MSSA, will be counted once for each phenotype and once for the overall tabulation of the pathogen, for example, *Staphylococcus aureus*.

8.5.3.6 28-Day All-Cause Mortality in the ITT Analysis Set

All-cause mortality through Study Day 28 will be summarized by treatment group in the ITT Analysis Set. Subjects who are lost to follow-up will be considered deceased for analysis and will be summarized separately on the table. A 2-sided unadjusted 95% CI will be calculated for the treatment difference in survival rates at Study Day 28 using a continuity corrected Z-test.

8.5.4 Additional Efficacy Analyses

Additional efficacy analyses will be conducted to support the efficacy findings for the primary and secondary efficacy outcomes. Confidence intervals for proportions will be determined for descriptive purposes, as indicated below, but no conclusions of NI will be made.

8.5.4.1 Clinical Outcome Measures

The proportion of subjects in each treatment group with an ECR of responder at 96 ± 24 hours after the first dose of study drug will be determined by baseline pathogen (and where relevant, the susceptibility phenotype) in the microITT and microITT-2 Analysis Sets.

The number and percentage of subjects in each treatment group determined to have an IACR of success, failure, or indeterminate (and combined failure and indeterminate) at the TOC Visit in the microITT-2 and emicroITT Analysis Sets will be presented. A 2-sided unadjusted 95% CI for the difference in IACR success rate will be calculated using a continuity corrected Z-test.

The number and percentage of subjects in each treatment group determined to have an IACR of success, failure, or indeterminate (and combined failure and indeterminate) at the EOT Visit in the mITT, microITT, CE-EOT and ME-EOT Analysis Sets will be presented. A 2-sided unadjusted 95% CI for the difference in IACR success rates will be calculated using a continuity corrected Z-test.

The number and percentage of subjects in each treatment group determined to have an IACR of sustained success, relapse, prior failure or indeterminate (and combined relapse, prior failure and indeterminate) at the LFU Visit in the mITT, microITT, CE-LFU and ME-LFU Analysis Sets will be presented. Prior failure is defined as a subject who had an IACR of failure at the TOC Visit.

The proportion of subjects with an IACR of success will be presented by baseline pathogen (and where relevant, the susceptibility phenotype) at the TOC Visit in the microITT, microITT-2, and ME-TOC Analysis Sets. The proportion of subjects with an IACR of sustained success will be presented by baseline pathogen (and where relevant, the susceptibility phenotype) at the LFU Visit in the microITT and ME-LFU Analysis Sets. The proportion of subjects with an IACR of success will be presented by baseline pathogen (and where relevant, the susceptibility phenotype) at the EOT Visit in the microITT and ME-EOT Analysis Sets.

The proportion of subjects with an ECR of responder will be presented by baseline pathogens (and where relevant, the susceptibility phenotype) identified from blood specimens in the microITT Analysis Set. The proportion of subjects with an IACR of success will be presented by baseline pathogens (and where relevant, the susceptibility phenotype) identified from blood specimens at the TOC Visit in the microITT Analysis Set.

A summary (number and percentage of subjects) of the assessment of clinical signs and symptoms of CABP at each time point throughout the study will be presented by treatment group as a shift table compared to baseline in the ITT Analysis Set. If the EOT Visit and the last day of study drug are on the same day and only 1 assessment is performed, the assessment will be summarized both at the study day and the EOT Visit. The proportion of subjects with resolution of all baseline signs and symptoms will also be provided by study visit (CAPB signs and symptoms were collected at baseline, daily while on study drug, at EOT, TOC and LFU). Analyses of signs and symptoms will only be assessed in subjects with non-missing assessments of all baseline signs and symptoms at the specified visit.

A summary of subjects who met the criteria for ECR responder (ie, alive, improvement in at least 2 of the 3 or 4 cardinal symptoms of CABP the subject presented with at baseline, no worsening of any of the 4 cardinal symptoms of CABP and did not receive a concomitant antibiotic (other than adjunctive linezolid) for the treatment of CABP through the assessment of the cardinal symptoms of CABP) will be provided by study visit. For each study visit, ECR will be determined for (ie, the denominator will consist of) those subjects who have died up through the relevant assessment, those subjects who have received an antibiotic for the treatment of CABP up through the relevant visit and those subjects with non-missing assessments of all baseline cardinal CABP symptoms at the relevant visit. If the EOT Visit and the last day of study drug are on the same day and only 1 assessment is performed, the assessment will be summarized both at the study day and the EOT Visit.

The proportion of subjects with an ECR of responder at 96 ± 24 hours after the first dose of study drug by baseline pathogen (and where relevant, the susceptibility phenotype) and MIC to study drug received and by baseline pathogen (and where relevant, the susceptibility phenotype) and disk diffusion zone diameter will be determined for each pathogen isolated at baseline in the microITT Analysis Set.

The proportion of subjects with an IACR of success at the TOC Visit by baseline pathogen (and where relevant, the susceptibility phenotype) and MIC to study drug received and by baseline pathogen (and where relevant, the susceptibility phenotype) and disk diffusion zone diameter will be determined for each pathogen isolated at baseline in the microITT and ME-TOC Analysis Sets.

A concordance analysis of ECR and IACR at the TOC Visit by treatment group will be provided in the ITT Analysis Set.

8.5.4.2 Microbiological Response Measures

The number and percentage of subjects determined to have a by-subject microbiological response of success (eradication or presumed eradication), failure (persistence or presumed persistence) or indeterminate at the EOT, TOC and LFU Visits will be tabulated by treatment

group for subjects in the microITT, microITT-2 (TOC Visit only) and ME-EOT (EOT Visit), ME-TOC (TOC Visit) and ME-LFU (LFU Visit) Analysis Sets. A 2-sided unadjusted 95% CI for the difference in by-subject microbiological response success rates between the lefamulin and moxifloxacin treatment groups will be provided.

The proportion of subjects with a microbiological response of success by baseline pathogen (and where relevant, the susceptibility phenotype) at the TOC Visit will be tabulated separately by treatment group for subjects in the microITT-2 Analysis Set. The proportion of subjects with a microbiological response of success by baseline pathogen (and where relevant, the susceptibility phenotype) at the EOT Visit will be tabulated separately by treatment group for subjects in the microITT and ME-EOT Analysis Sets. The proportion of subjects with a microbiological response of sustained success by baseline pathogen (and where relevant, the susceptibility phenotype) at the LFU Visit will be tabulated separately by treatment group for subjects in the microITT and ME-LFU Analysis Sets.

A by-subject listing will present the by-pathogen and by-subject microbiological response at the EOT, TOC and LFU Visits in the ITT Analysis Set. A second by-subject listing will present the by-pathogen and by-subject microbiological response at the EOT, TOC and LFU Visits for non-responders, clinical failures, or subjects with persistence.

The proportion of subjects with a microbiological response of success at the TOC Visit by baseline pathogen (and where relevant, the susceptibility phenotype) and MIC to study drug received and by baseline pathogen (and where relevant, the susceptibility phenotype) and disk diffusion zone diameter will be determined for each pathogen isolated at baseline in the microITT and ME-TOC Analysis Sets.

A by-subject listing of subjects in the ITT Analysis Set with a superinfection or colonization will be provided. The listing will include subject ID, treatment group, baseline and post-baseline pathogen genus and species, study day of post-baseline pathogen, and whether the emergent pathogen is a superinfection or a colonization.

A by-subject listing of subjects in the ITT Analysis Set showing at least 1 pathogen with decreasing susceptibility will be presented in a listing providing the subject ID, treatment group, collection date/time and study day, type of specimen, pathogen (baseline and post-baseline), MIC values, disk diffusion zone diameters, and susceptibility to study drug received.

8.6 Pharmacokinetic Analyses

Measured plasma concentrations of BC-3781 and BC-8041 will be summarized descriptively by treatment group and nominal time point of collection. Summary statistics in the tabulation will include n, mean, standard deviation, CV [%], median, minimum and maximum.

8.7 Safety Analyses

All safety analyses will be conducted in the Safety Analysis Set. Subjects who receive the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received. Subjects who receive the wrong study drug less than the entire course of treatment will be analyzed in the as randomized treatment group.

For each safety parameter with the exception of ECGs which are measured in triplicate at each time point and vital signs which uses the last assessment prior to Day 1, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses.

8.7.1 Adverse Events

Adverse events will be monitored throughout the study from the time a subject is consented through the TOC Visit; SAEs are to be collected from the time of consent through the LFU Visit. Adverse events will be coded using Version 18.0 or higher of MedDRA. A treatment-emergent AE (TEAE) is defined as an AE that starts or worsens at or during the time of or after the first study drug administration. If the AE start date is unknown or is a partial date such that it cannot be determined if the AE started on or after the first study drug administration, it will be categorized as a TEAE.

An overall summary of AEs will include the number and percentage of subjects who experienced at least 1 AE of the following categories: any AE, any TEAE, any serious TEAE, any treatment-related TEAE, any treatment-related serious TEAE, any TEAE leading to premature discontinuation of study drug, any TEAE leading to premature discontinuation from the study, and any TEAE leading to death.

The number and percentage of subjects reporting a TEAE and the number and percentage of subjects reporting a treatment-related TEAE (related defined as possibly, probably or definitely related to study drug) in each treatment group will be tabulated by system organ class, preferred term, and severity (mild, moderate, and severe). A summary of TEAEs and treatment-related TEAEs sorted by decreasing frequency of preferred term in lefamulin subjects will also be provided. Likewise, the number and percentage of subjects reporting a serious TEAE and the number and percentage of subjects reporting a TEAE leading to premature discontinuation of study drug in each treatment group will be tabulated separately by system organ class and preferred term. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to study drug.

A listing of TEAEs leading to discontinuation of study drug will be provided and will include subject ID, subject age, sex and race, onset day of the AE, duration of AE in days, duration of study drug (days), preferred term, verbatim term, severity, relationship to study drug, outcome, therapy given (Y/N) and seriousness (Y/N). A listing of all serious TEAEs will also be provided and will include subject ID, subject age, sex and race, onset day of the AE, duration of AE in days, preferred term, verbatim term, severity, relationship to study drug, outcome, therapy given (Y/N) and drug withdrawn (Y/N). If the outcome of the SAE is death, the date and study day of the death and whether it was prior to EOT or after EOT will be presented.

8.7.2 Clinical Laboratory Evaluations

Central laboratory data will be utilized for all analyses. For the purposes of summarizing post-baseline maximum alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin and for the purposes of identifying cases of potential Hy's law, both central and local laboratory data will be used. In addition, local laboratory data

will be utilized in the assessment of any Potentially Clinically Significant (PCS) labs as defined in Appendix B. Local laboratory data are collected on the eCRF: 1) if the subject did not meet the laboratory inclusion/exclusion criteria based on the central laboratory results, 2) potential Hy's law is reported based on local laboratory results, and 3) the Principal Investigator chooses to report local laboratory results obtained in the clinical management of the patient.

Laboratory values will be defined as potentially clinically significant (PCS) according to the table in Appendix B. To be considered PCS, the laboratory value must meet both the lower limit and the percent decrease from baseline or both the upper limit and the percent increase from baseline. The proportion of subjects in the Safety Analysis Set with at least 1 PCS laboratory value will be summarized by treatment group and PCS laboratory values will be summarized by treatment group, laboratory parameter, visit and for the overall worst post-baseline value (minimum and maximum value, where appropriate defined in Appendix C). Percentages for each laboratory test will be based on the number of subjects with a baseline and post-baseline evaluation at the visit for the specific laboratory test. By-subject listings of all laboratory values for a subject with any PCS post-baseline laboratory value will also be provided.

Shift tables will be presented to show the number and percentage of subjects with a laboratory value below the lower limit of normal (LLN), within normal limits, above the upper limit of normal (ULN) and missing at baseline versus the value at each visit and the worst post-baseline value. Percentages for each laboratory test will be based on the number of subjects in the Safety Analysis Set.

A listing of subjects who have the laboratory criteria for potentially meeting Hy's Law will also be provided. The laboratory criteria for potentially meeting Hy's Law is defined as ALT or AST >3 x ULN, ALP ≤2.0 x ULN and total bilirubin >2 x ULN. The proportion of subjects with any post-baseline AST >3 x ULN, >5 x ULN and >10 x ULN, any post-baseline ALT >3 x ULN, >5 x ULN and >10 x ULN, any post-baseline total bilirubin >1.5 x ULN and >2 x ULN, any post-baseline ALP >2 x ULN, and any post-baseline ALT or AST value >3 x ULN and any post-baseline total bilirubin value >2 x ULN with an ALP ≤2 x ULN and with an ALP >2 x ULN will be presented by treatment group.

Descriptive statistics for chemistry and hematology parameter values and the change from baseline at Day 4 (for subjects receiving a 7 or 10-day course of therapy), Day 7 (for subjects receiving a 10-day course of therapy), EOT, and TOC will be summarized by treatment group for the Safety Analysis Set. Change from baseline will be calculated for each subject at the specified visit as the value at the specified visit minus the baseline value. The change from baseline to the minimum and maximum post-baseline values for chemistry and hematology parameters will also be summarized by treatment group. Change from baseline will be calculated for each subject as the minimum or maximum post-baseline value minus the baseline value. Baseline is defined as the last assessment prior to the first dose of study drug. Box-plots, which provide the median, mean, inter-quartile range, 5^{th} and 95^{th} percentile, and outliers will also be provided for ALP, AST, ALT, BUN, calcium, creatinine, phosphate, sodium, total bilirubin, absolute neutrophil count, hemoglobin, platelets, and WBC by scheduled study visit and treatment group.

Urinalysis data will be provided in a listing.

8.7.3 ECG Parameters

ECG data are being read centrally. The mean of the triplicates (or if triplicates not available, the duplicates or single ECG, whichever is available) will be used for all analyses, even if not performed within a 5-minute interval. Descriptive statistics for heart rate, PR interval, QRS interval, QT interval, and QT interval corrected by the Fridericia formula (QTcF) and the change from baseline at Day 1 (after the first infusion of study drug), Day 3 (prior to the first infusion of study drug) and Day 3 (after the first infusion of study drug) will be summarized by treatment group for subjects in the Safety Analysis Set. Change from baseline will be calculated for each subject at Day 1 (after the first infusion of study drug) and Day 3 (prior to and after the first infusion of study drug) as the value at the specified visit and time point minus the baseline value. The change from baseline to the minimum and maximum post-baseline values will also be summarized by treatment group, where these post-baseline values include unscheduled visits. Change from baseline will be calculated for each subject as the minimum or maximum post-baseline value minus the baseline value. Baseline is defined as the mean of the triplicates from the last assessment prior to the first dose of study drug. ECG parameters for each of the triplicates (including the change in QTcF value from pre-dose to post-dose) and the overall interpretation of the ECG will be presented on a listing.

The number and percentage of subjects with any post-baseline increase in QTcF and any post-baseline increase of >30 msec or >60 msec in QTcF will be summarized by treatment group. The number and percentage of subjects with a post-baseline QTcF of >480 msec or >500 msec will also be summarized by treatment group. The number and percentage of subjects with a post-baseline increase in QTcF of >30 msec resulting in a post-baseline QTcF of >480 msec or >500 msec as well as QTcF of >60 msec resulting in a post-baseline QTcF of >480 msec or >500 msec will also be summarized by treatment group. The distribution of QTcF values (≤450 msec, >450 - ≤480 msec, >480 - ≤500 msec, and >500 msec) at each time point and the distribution of change from baseline in QTcF values at each time point (0 or less (no increase), 1-<30 msec, 30-60 msec, and >60 msec) will be summarized by treatment group for subjects in the Safety Analysis Set. These analyses will also be provided by study visit.

A listing will be provided of findings identified on the ECG.

8.7.4 Vital Signs

Descriptive statistics for temperature, respiratory rate, heart rate, diastolic blood pressure, systolic blood pressure, and the change from baseline at each post-baseline visit will be summarized by treatment group for all subjects in the Safety Analysis Set. Change from baseline will be calculated for each subject at the specified visit as the value at the specified visit minus the baseline value. The change from baseline to the minimum and maximum post-baseline values will also be summarized by treatment group. Change from baseline will be calculated for each subject as the minimum or maximum post-baseline value minus the baseline value. Baseline is defined as the last assessment prior to Day 1.

Post-baseline vital signs will be defined as high or low if the criterion value listed in Table 11 is met. All vital signs will be presented in a listing with a flag for high and low indicating the criterion value was met. PCS is defined as meeting both the criterion value and the change from

baseline criterion listed in Table 11. The number and percentage of subjects with any post-baseline PCS vital sign will be presented by treatment group. The overall post-baseline incidence of PCS values, which includes values from unscheduled post-baseline visits, will be summarized by treatment group for the Safety Analysis Set, and all PCS vital sign values will be listed and flagged in by subject listings.

Table 11. Criteria for Treatment Emergent Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criterion Value	Change from Baseline
Systolic Blood Pressure (mmHg)	High (CH)	≥ 180	Increase of ≥ 20 mmHg
	Low (CL)	<90	Decrease of ≥ 20 mmHg
Diastolic Blood Pressure (mmHg)	High (CH)	≥ 105	Increase of ≥ 15 mmHg
	Low (CL)	≤ 50	Decrease of ≥ 15 mmHg
Heart Rate (beats/min)	High (CH)	≥ 120	Increase of ≥ 15 beats/min
	Low (CL)	≤ 50	Decrease of ≥ 15 beats/min

9.0 CHANGES FROM THE PROTOCOL SPECIFIED ANALYSES

Two additional microbiologic Analysis Sets (microITT-2 and emicroITT) were included. The microITT-2 Analysis Set will consist of all subjects in the ITT Analysis Set who have at least 1 baseline bacterial pathogen known to cause CABP as defined in Sections 4.1 and 4.2 from a diagnostic method other than PCR. The emicroITT Analysis Set will consist of all subjects in the ITT Analysis Set who have at least 1 baseline bacterial pathogen known to cause CABP as defined in Sections 4.1 and 4.2, except a baseline pathogen from a sputum culture is defined using the presence of a Gram stain with ≥10 PMNs/LPF and <10 SECs/LPF rather than >25 PMNs/LPF and <10 SECs/LPF. Additional analyses performed in these Analysis Sets include summaries of the following: ECR (microITT-2 and emicroITT), ECR by baseline pathogen (microITT-2), IACR at TOC (microITT-2 and emicroITT), IACR at TOC by baseline pathogen (microITT-2), by-subject microbiologic response at TOC (microITT-2), and by-pathogen microbiologic response at TOC (microITT-2).

Other additional efficacy analyses specified in this SAP include summaries of the following: ECR by baseline pathogen and MIC or disk diffusion zone diameter to study drug received (microITT), ECR by baseline pathogen identified from blood (microITT), IACR at EOT and LFU (microITT and relevant ME Analysis Sets), IACR at EOT by baseline pathogen (microITT and ME-EOT), IACR at TOC by baseline pathogen and MIC or disk diffusion zone diameter to study drug received (microITT and ME-TOC), IACR at TOC by baseline pathogen identified from blood (microITT), by-subject and by-pathogen microbiologic response at EOT and LFU (microITT and relevant ME Analysis Sets), and by-pathogen microbiologic response at TOC by MIC or disk diffusion zone diameter to study drug received (microITT and ME-TOC).

10.0 REFERENCES

Albrich WC, Madhi SA, Adrian PV, Telles JN, Paranhos-Baccala G, Klugman KP. Genomic load from sputum samples and nasopharyngeal swabs for diagnosis of pneumococcal pneumonia in HIV-infected adults. J Clin Microbiol. 2014; 52(12):4224-9.

AVELOX® (moxifloxacin) Prescribing Information. Manufactured for Bayer HealthCare Pharmaceuticals Inc. Distributed by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. PI revised and approved by FDA on 14-Aug-2013.

Chochua S, Sheets A, Keedy K, et al. Detection of pneumococcal pneumonia in a phase 3 trial comparing oral solithromycin versus oral moxifloxacin for treatment of community-acquired bacterial pneumonia in adults. Poster presented at IDWeek 2015 Oct 7-11; San Diego, CA, USA. 894.

CLSI. Methods for antimicrobial susceptibility testing for human mycoplasmas. Approved Guideline. CLSI document M43-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.

CLSI. Performance standards for antimicrobial susceptibility testing. Twenty-fifth Informational Supplement. CLSI document M-100-S25. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.

FDA Anti-infective Drugs Advisory Committee (03-Nov-2011). Endpoints and clinical trial issues in community-acquired bacterial pneumonia. Recommendations to FDA for interim endpoints for clinical trials in community-acquired bacterial pneumonia (document dated, 26-Aug-2011). Prepared by: Foundation for the National Institutes of Health Biomarkers Consortium Project Team. CABP Docket ID: FDA-2009-D-0136. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm275823.pdf.

FDA Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness. November 2016.

Huang ZG, Zheng XZ, Guan J, Xiao SN, Zhuo C. Direct detection of methicillin-resistant Staphylococcus aureus in sputum specimens from patients with hospital-associated pneumonia using a novel multilocus PCR assay. Pathogens. 2015; 4(2):199-209.

Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis. 2010; 50(2):202-9.

Kais M, Spindler C, Kalin M, Ortqvist A, Giske CG. Quantitative detection of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis in lower respiratory tract samples by real-time PCR. Diagn Microbiol Infect Dis. 2006; 55(3):169-78.

Thurman KA, Warner AK, Cowart KC, Benitez AJ, Winchell JM. Detection of Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella spp. in clinical specimens using a single-tube multiplex real-time PCR assay. Diagn Microbiol Infect Dis. 2011; 70(1):1-9.

Waites KB, Xiao L, Paralanov V, Viscardi RM, Glass JI. Molecular methods for the detection of Mycoplasma and ureaplasma infections in humans: a paper from the 2011 William Beaumont Hospital Symposium on molecular pathology. J Mol Diagn. 2012; 14(5):437-50.

APPENDIX A: SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessment or Procedure	*Screening/ Baseline* [a]	*Study Drug Administration*					*Follow-up*	
		Day 1 [b]	*Day 2*	*Day 3*	*Days 4 to 7* [c] *[Days 4 to 10]* [d]	*EOT* [e]	*TOC* [f]	*LFU* [g]
Informed consent form completed [h]	X							
Verify inclusion/exclusion criteria	X							
Medical and surgical history	X							
Determine PORT Risk Class	X							
Urine sample for *L. pneumophila* and *S. pneumoniae* antigen tests	X							
Height and weight	X							
Randomization [i]	X							
Prior and concomitant medications	X	X	X	X	Daily [c, d]	X	X	X
Vital signs including oxygen saturation and supplemental oxygen [j]	X	X	X	X	Daily [c, d]	X	X	
CABP signs and symptoms [k]	X	X	X	X	Daily [c, d]	X	X	X
AEs and SAEs [l]	X	X	X	X	Daily [c, d]	X	X	X
12-lead ECG [m]	X	X		X				
Physical examination [n]	X				Day 4 [c, d]	X	X	
Hematology, clinical chemistry, urinalysis and procalcitonin [o]	X				Day 4 [c] [Day 4 & 7] [d]	X	X	
Urine and serum pregnancy tests [p]	X							
Blood sample for serologic tests for *M. pneumoniae, C. pneumoniae*, and *L. pneumophila* [q]	X							X
CXR or CT scan	X	if clinically indicated [c, d]						
Arterial blood gases (PaO_2, $PaCO_2$) and pH [r]	if clinically indicated [c, d]							
Calculate CrCl (Cockcroft-Gault formula)	X	if clinically indicated [c, d]						
Blood sample for culture [s]	X	if clinically indicated [c, d]						
Respiratory sample for Gram's stain and culture [t]	X	if clinically indicated [c, d]						
Frozen oropharyngeal sample [u]	X							
Nasopharyngeal sample [v]	X							
Administer PRO instrument (SF-12 questionnaire)	X						X	
Study drug administration [w]		X	X	X	Daily [c, d]			
Blood samples for PK analyses [x]				X	(X) optional [c, d]			
Evaluate feasibility of switch to oral administration of study drug					Daily [c, d]			
Investigator's Assessment of Clinical Response (IACR) [y]						X	X	X
Pleural fluid and/or bronchoalveolar lavage (BAL) sample for Gram's stain and culture [z]	if clinically indicated [c, d]							

NOTE: Hospitalization is not a requirement for this study. However, all subjects, including Outpatients, must be evaluated in person by study personnel at the following time points/visits: Screening/Baseline; Day 1; during each IV administration, 96 ± 24 hours after the first dose of study drug; End of Treatment (EOT); Test of Cure (TOC); and Late Follow-up (LFU).

a: Perform Screening/Baseline assessments within 24 hours before first dose of IV study drug. Administration of study drug should begin as soon as possible after the diagnosis of CABP. Assessments performed as part of routine standard of care prior to consent (eg, chest X-ray, blood culture) may be used to satisfy study screening requirements; however, no study specific procedures may be performed prior to informed consent.

b: Day 1 is the first day of study drug administration; subsequent study days are consecutive calendar days.

c: Days 4 to 7: Subjects receiving 7 days of randomized study drug.

d: [Days 4 to 10: Subjects receiving 10 days of randomized study drug.]

e: Perform EOT assessments at the study site within 2 days (1 day preferred) after the last dose of study drug or at the time of premature discontinuation of study drug or early withdrawal from study. EOT assessments resulting from premature discontinuation of study drug should be done in place of the regular study visit on Days 1 to 7 (or Days 1 to 10, as applicable).

f: Perform TOC assessments at the study site 5–10 days after the last dose of study drug. All subjects will have a TOC Visit irrespective of early clinical failure or receipt of an alternative antibiotic.

g: Perform LFU assessments at the study site on Day 30 ± 3 days. All subjects will have a LFU Visit irrespective of early clinical failure or receipt of an alternative antibiotic.

h: Obtain informed consent before initiating any study assessments or procedures.

i: Randomization may occur at either Screening or on Day 1 prior to receipt of the first dose of study drug.

j: Record vital signs (heart rate, blood pressure, respiratory rate, body temperature), O_2 saturation, and supplemental oxygen usage daily on days the subject is seen in person (ie, at baseline, daily while the subject is hospitalized [record vital signs associated with highest temperature], daily while the subject is on IV therapy, at in-person visits while the subject is taking oral study drug as an outpatient), and at EOT and TOC. Record vital signs, O_2 saturation, and supplemental oxygen usage at LFU if medically indicated. If Screening and Day 1 occur on the same day, vital signs should be obtained as part of the Screening evaluation (prior to administration of any study drug) and repeated as part of the Day 1 assessment (record the vital signs associated with the highest temperature post dosing). If EOT and the last day of study drug are the same day, vital signs do not need to be repeated, they may be recorded once on that day (ie, as part of the EOT assessment).

k: Evaluate signs and symptoms of CABP at baseline, daily while receiving study drug and at EOT, TOC, and LFU. Signs and symptoms are not obtained at TOC or LFU if the subject was previously deemed to have an IACR of Failure. Subjects who are receiving medication at home may be contacted by phone to track signs and symptoms of CABP if an in-person assessment is not required or planned for that day. **EXCEPTION: Subjects must have a visit at the study site that is 96 ± 24 hours after the first dose of study drug to assess CABP signs and symptoms for calculation of ECR.** Study personnel will inform subjects as to the timing of this visit. If Screening and Day 1 are the same day, signs and symptoms of CABP do not need to be repeated on Day 1. If EOT and the last day of study drug are the same day, signs and symptoms of CABP should be done only once on that day (ie, as part of the EOT assessment).

l: Record AEs from the signing of the ICF through TOC and SAEs from signing of the ICF through LFU. Study personnel will follow unresolved AEs and SAEs present at LFU until resolution or stabilization.

m: **At each required time point, ECGs should be recorded in triplicate within a 5-minute interval.** The subject should be stabilized in a supine position for 5 min before recording the ECG. Record ECGs at Screening. On Day 1 and Day 3 record ECGs prior to the first infusion of study drug on that day and within 15 minutes after the end of the first infusion on that day. If Screening and Day 1 are on the same day, the Screening ECG can serve as the Day 1 ECG prior to the first infusion of study drug. Additional ECG's may be performed if clinically indicated. If at any time the subject demonstrates an average QTcF value >500 ms (mean of 3 ECG's at any time point), or an average QTcF value >480ms with a concurrent increase in average QTcF value of > 60 ms (mean of 3 post-dose ECGs compared to mean pre-dose ECG's taken on that day) study drug will be discontinued.

n: A complete physical examination is performed at baseline and directed physical examinations are performed on Day 4 (Day 3 is acceptable for outpatients who are not able to return on Day 4) and at EOT and TOC.

o: For all subjects, collect blood and urine at Screening, Day 4 (Day 3 is acceptable for outpatients who are not able to return on Day 4), EOT, and TOC. In addition, for subjects receiving 10 days of study drug, collect blood and urine on Day 7 (Day 8 is acceptable for outpatients who are not able to return on Day 7). Subjects treated as outpatients must agree to return to the site for blood draws. Collect blood and/or urine at LFU only if subject had an abnormal (high/low flag) result at TOC. Blood samples sent to the local laboratory for the purposes of determining study eligibility must be repeated and sent to the central laboratory following enrollment.

p: A pregnancy test will be performed on all females unless surgically sterile or at least 2 years post-menopausal. A negative urine pregnancy test is required prior to randomization and must be confirmed as soon as possible using a serum pregnancy test.

q: Blood to be collected and sent to central laboratory for serologic tests for *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila* at Screening and LFU.

r: Record arterial blood gas and blood pH data if available. Study sites are not required to measure arterial blood gas or blood pH.

s: Collect blood samples (2 sets via peripheral venipuncture) for microbiologic culture and susceptibility testing at the local/regional lab at Screening and as clinically indicated during the study. Repeat blood cultures after a positive result until sterilization is documented. If possible, subjects who are discontinued from study drug due to confirmed MRSA or MSSA bacteremia should have blood samples collected for microbiologic culture prior to switching to alternate appropriate therapy. All organisms isolated from blood cultures which are not considered contaminants will be sent to the central laboratory for confirmatory identification and susceptibility testing.

t: All lower respiratory tract and expectorated sputum samples (including the Screening sample) should be sent to the local/regional laboratory for Gram's stain, culture and susceptibility testing. If a subject is unable to produce an adequate (> 25 polymorphonuclear [PMN] cells **AND** < 10 squamous epithelial cells per LPF) sputum sample at Screening, a specimen should be obtained, if possible, within 24 hours after the first dose of study drug. Gram's stain and culture results from the local/regional laboratory will be recorded in the eCRF. Slides (stained and unstained) will also be sent to the central laboratory for a confirmatory reading of the Gram's stain. If possible, subjects who are discontinued from study drug due to clinical failure should have repeat cultures collected for microbiologic culture prior to switching to alternate appropriate therapy. All organisms isolated from sputum samples, which are not considered contaminants, will be sent to the central laboratory for confirmatory identification and susceptibility testing. In addition, a portion of all sputum samples must be frozen until sent to the central laboratory for PCR. Subjects with a positive urinary antigen will also have isolation of *L. pneumophila* performed at the central laboratory on the frozen sputum.

u: An oropharyngeal specimen (2 swabs) will be collected and frozen until sent to the central laboratory. The oropharyngeal specimen will be used for culture of *M. pneumoniae* and identification by PCR.

v: A nasopharyngeal specimen will be collected and frozen until sent to the central laboratory. The nasopharyngeal specimen will be used for culture of *S. pneumoniae* and identification by PCR.

w: Study drug should be administered approximately the same time each day. On days when this is not feasible, doses should be given within 4 hours of the scheduled dosing time (ie, a minimum of 8 hours between doses). Subjects who receive only a single dose of study drug on Day 1 will receive their final dose in the morning on either Day 8 (to complete a 7-day course) or on Day 11 (to complete a 10-day course). Administration of study drug may occur on the same calendar day as EOT, and if so will be completed before EOT assessments begin.

x: Collect blood for PK analysis in association with the morning dose of IV study drug on Day 3. Collect blood for PK samples within 1 h before administration of IV study drug, within 10 minutes following completion of the infusion, at 2–4 h after infusion, and at 8–12 h after the infusion. In subjects who agree via written consent, and for whom collection is logistically feasible, blood for PK analysis will be collected in association with the first morning dose of oral study drug. Blood will be collected within 1 h prior to dose, 1–3 h after dose, and 4–8 h after dose. Since blood collection is required both before and after the first morning oral dose, outpatients should be instructed to <u>not</u> take their first morning dose of oral study drug at home, rather to bring all blister packs (used and unused) to the study site. Following collection of the pre-dose blood sample, subjects will take their dose of study drug under supervision of study personnel, and subsequent PK blood samples will be collected.

y: Investigator to determine IACR - Success, Failure or Indeterminate (ie, subject lost to follow up) at EOT and TOC and Sustained Success, Relapse or Indeterminate at LFU**.** The Investigator will not determine Clinical Response at TOC or LFU if the subject was previously deemed to have an IACR of Failure.

z: Collect pleural fluid samples and/or BAL only if medically indicated. Gram's stain samples, culture, and test the isolated pathogens for susceptibility. Pathogens isolated from pleural fluid and/or BAL samples will be sent to the central laboratory for confirmatory identification and susceptibility testing. If possible, pleural fluid samples should be incubated in blood culture bottles for optimal pathogen recovery.

APPENDIX B: CLINICAL LABORATORY POTENTIALLY CLINICALLY SIGNIFICANT VALUES

Parameter	Lower Limit	% Decrease from Baseline	Upper Limit	% Increase from Baseline
HEMATOLOGY				
Hemoglobin	<0.8 x LLN	>20%	>1.3 x ULN	>30%
WBC	<0.65 x LLN	>60%	>1.6 x ULN	>100%
Neutrophils	<0.65 x LLN	>75%	>1.6 x ULN	>100%
Lymphocytes	<0.65 x LLN	>75%	>1.6 x ULN	>100%
Platelets	<0.65 x LLN	>50%	>1.5 x ULN	>100%
CHEMISTRY				
Sodium	<0.85 x LLN	>10%	>1.1x ULN	>10%
Potassium	<0.8 x LLN	>20%	>1.2xULN	>20%
Creatinine	NA	NA	>2.0 x ULN	>100%
Urea nitrogen (BUN)	NA	NA	>3.0 x ULN	>200%
Calcium	<0.7 x LLN	>30%	>1.3 x ULN	>30%
Magnesium	<0.5 x LLN	>50%	NA	NA
Phosphorus	<0.5 x LLN	>50%	>3.0 x ULN	>200%
Alkaline phosphatase	<0.5 x LLN	>80%	>2.0 x ULN	>100%
ALT	NA	NA	>3.0 x ULN	>200%
AST	NA	NA	>3.0 x ULN	>200%
GGT	NA	NA	>3.0 x ULN	>200%
Total bilirubin	NA	NA	>=2.0 x ULN	>150%
Albumin	<0.5 x LLN	>50%	>1.5 x ULN	>50%
Glucose	<0.6 x LLN	>40%	>3.0 x ULN	>200%

APPENDIX C: DIRECTIONALITY OF WORST LABORATORY PARAMETERS

Laboratory Test	Parameter	Worst Value
Hematology	Hematocrit	Lowest value
	Red blood cell count	Lowest value
	Mean cell hemoglobin	Lowest value
	Mean cell hemoglobin concentration	Lowest value
	Hemoglobin	Lowest value
	Mean cell volume	Lowest value
	White blood cell count	Lowest value
	Platelets	Lowest value
	Neutrophils	Lowest value
	Lymphocytes	Lowest value
	Monocytes	Lowest value
	Eosinophils	Highest value
	Basophils	Lowest value
Chemistry	Albumin	Lowest value
	Alkaline phosphatase	Highest value
	Alanine aminotransferase (ALT/SGPT)	Highest value
	Aspartate aminotransferase (AST/SGOT)	Highest value
	Blood urea nitrogen (BUN)	Highest value
	Calcium	Both highest value and lowest value
	Chloride	Both highest value and lowest value
	Creatinine	Highest value
	Creatine kinase (CK)	Highest value
	Direct bilirubin	Highest value
	Gamma-glutamyl transferase (GGT)	Highest value
	Glucose	Both highest value and lowest value
	Magnesium	Both highest value and lowest value
	Phosphorus	Both highest value and lowest value
	Potassium	Both highest value and lowest value
	Sodium	Both highest value and lowest value
	Total bilirubin	Highest value
	Total protein	Lowest value
	Uric acid	Highest value
Other Tests	Procalcitonin	Highest value