Clinical Protocol No. NAB-BC-3781-3102

A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Oral Lefamulin (BC-3781) Versus Oral Moxifloxacin in Adults With Community-Acquired Bacterial Pneumonia

US IND 125546 (Oral)

EudraCT Number 2015-004782-92

Protocol Status	Version	Date
Original	1.0	21-Dec-2015
Amendment 1	2.0	17-Feb-2016
Amendment 2	3.0	17-Mar-2016

SPONSOR RELATED CONTACT DETAILS

A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Oral Lefamulin (BC-3781) Versus Oral Moxifloxacin in Adults With Community-Acquired Bacterial Pneumonia
(Protocol NAB-BC-3781-3102 with Amendments 1 and 2)

Sponsor:	Nabriva Therapeutics AG Leberstraße 20 1110 Vienna Austria
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PROTOCOL REVIEW AND APPROVAL FORM

SUBMISSION OF PROTOCOL NAB-BC-3781-3102 WITH AMENDMENTS 1 AND 2

Title: **A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Oral Lefamulin (BC-3781) Versus Oral Moxifloxacin in Adults With Community-Acquired Bacterial Pneumonia**

17 March 2016

NAME	TITLE	SIGNATURE	DATE
[redacted]	Senior Director, Clinical Development and Medical Affairs		

INVESTIGATOR SIGNATURE PAGE

A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Oral Lefamulin (BC-3781) Versus Oral Moxifloxacin in Adults With Community-Acquired Bacterial Pneumonia
(Protocol NAB-BC-3781-3102 with Amendments 1 and 2)

In conducting this clinical study, I agree to be responsible for:

- Ensuring that the clinical investigation is conducted according to the World Medical Association Declaration of Helsinki in its revised edition (Fortaleza, Brazil, October 2013), the guidelines of International Conference on Harmonization (ICH) Good Clinical Practice (GCP) (CPMP/ICH/135/95), the signed Form Food and Drug Administration (FDA) 1572 Statement of Investigator (applies to all studies conducted under a United States Investigational New Drug Application) and other applicable local and national laws and requirements.
- Protecting the rights, safety, and welfare of subjects under my care.
- Maintaining control of the drugs under investigation.

I also agree to conduct the study as detailed in the protocol and in accordance with Nabriva Therapeutics AG guidelines and all applicable government regulations. These guidelines and regulations include, but are not limited to:

- Permission to allow Nabriva Therapeutics AG and regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, which ensures subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify Nabriva Therapeutics AG as soon as possible thereafter (no later than 1 week).
- Submission of the proposed clinical investigation, including the protocol, the informed consent documents, and any other subject materials required for study conduct, to a duly constituted Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for approval, and acquisition of written approval for each, prior to the use of the study drug.
- Obtaining written informed consent only after ensuring that the subject, or his/her legal representative, is competent to make the decision, understands what is contained in the informed consent document, and is consenting voluntarily. Written informed consent will be obtained prior to administration of study drug or any non-routine study-related procedures; the document contains all the essential elements of consent and has been previously approved by the sponsor and IEC/IRB. Reference of written informed consent will be provided in source documentation.
- Submission of any protocol amendment to the IEC/IRB. If the protocol amendment change(s) increase risk to the study population, full IEC/IRB written approval must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, prior IEC/IRB approval may be obtained by expedited review.

- Adherence to the study protocol. Documentation and explanation of individual post-enrollment protocol deviations will be recorded in the source documentation at the site and be provided to Nabriva Therapeutics AG.
- Notification to Nabriva Therapeutics AG of all serious adverse events, regardless of relationship to study drug, as specified in the protocol. Notification to the IEC/IRB of serious adverse events as specified in the protocol and per additional guidelines as provided by the IEC/IRB.
- Notification to IEC/IRB of all unanticipated problems within the timeframe provided by the IEC/IRB. For the purposes of this study, unanticipated problems are defined as any incident, experience, or subject outcome that meets **all** of the following criteria: (1) unexpected; (2) related or possibly related to participation in the study; (3) and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known.
- Provision of adequate study oversight by personally conducting or supervising the investigation, including, but not limited to: allotting sufficient time to properly conduct and complete the study within the agreed upon time period; having available an adequate number of qualified staff and adequate facilities for the expected duration of the study and to conduct the study properly and safely; and ensuring that all persons assisting with the study are adequately informed about the protocol and the investigational product(s) and are capable of performing their study-related duties and functions. Qualifications of individuals assigned responsibility for the administration of the investigational product will be compliant with state and local law or national regulations, as applicable.
- Submission of timely progress reports to the IEC/IRB and Nabriva Therapeutics AG at appropriate intervals not to exceed 1 year and submission of a final report to the IEC/IRB within the timeframe set by the IEC/IRB, but not later than 3 months after the completion or termination of the clinical investigation.
- Maintenance of accurate source records from which case report forms are completed as well as drug accountability records that show the receipt and disposition (on an overall and per subject basis) of all study drug(s) shipped to the investigator by Nabriva Therapeutics AG.

In addition, I agree to provide all the information requested in the eCRF presented to me by Nabriva Therapeutics AG by carefully following the completion guidelines provided as part of the eCRF.

If I opt to terminate my participation in the study, the foregoing shall equally apply.

_____
Investigator's Name (Please Print)

_____ _____
Investigator's Signature Date

AMENDMENT 2: 17-MAR-2016

Amendment 2 addresses an inconsistency within the protocol. In accordance with Appendix 4 to the protocol, the use of strong P-glycoprotein inhibitors during study participation is prohibited. Thus, progesterone-containing products (such as oral contraceptives) are prohibited. In addition to revising the inclusion criterion associated with use of oral contraceptives, wording was added to the prohibited medications section for emphasis. These changes were made to the study synopsis, as applicable. Added text is **bolded**; deleted text is ~~struck through~~.

Section 4.1 − Inclusion Criteria

#8 If female, meets the following criteria:

- Surgically sterile or ≥2 years postmenopausal, or if of childbearing potential (including being <2 years postmenopausal), has a negative pregnancy test, and if participating in sexual activity that may lead to pregnancy, agrees to use an effective dual method of contraception (e.g., condom plus diaphragm, condom plus spermicide, intrauterine device plus spermicide~~, oral contraceptive plus condom~~) during the study and for ≥28 days after the last dose of study drug. If a male partner has been surgically sterile for ≥1 year, a single contraception method may be used. **NOTE: The use of contraceptives containing progesterone is not permitted.**

Section 6.9 – Prohibited Medications

Bullet #6

- Strong p-glycoprotein inhibitors (see Appendix 4**) [NOTE: The use of contraceptives containing progesterone is not permitted.]**

AMENDMENT 1: 17-FEB-2016

Amendment 1 addresses revisions to the protocol requested by the US Food and Drug Administration (FDA) at the Type C Meeting held on 27-Jan-2016 with respect to the non-inferiority (NI) margin. The change in NI margin resulted in the change of other statistical parameters including the randomization ratio and sample size.

In addition, FDA requested (1) an increase in the number of subjects with a PORT Risk Class of III or IV; (2) methicillin-resistant *Staphylococcus aureus* (MRSA) be added to the list of pathogens that would exclude study eligibility; and (3) an increase in the number of pharmacokinetic sampling time points (i.e., the 8-9 h PK time point, which was previously optional for all subjects, is now required for inpatients and optional for outpatients). An increase in the number of subjects with PORT Risk Class III or IV resulted in a change of the outcome rates used for determination of the sample size.

These revisions were made to the protocol sections noted below as well as to the study synopsis and the Schedule of Assessments and Procedures (Table 1). Added text is **bolded**; deleted text is ~~struck through~~.

Section 3 – STUDY DESIGN

Paragraph 1, Sentences 2 & 3: The planned enrollment is ~~573~~ **738** subjects (~~382~~ **369** subjects in the lefamulin group and ~~191~~ **369** subjects in the moxifloxacin group) with PORT Risk Class II, III, or IV. Eligible subjects will be randomized ~~2~~ **1**:1 to lefamulin or moxifloxacin, using an interactive response technology (IRT).

Section 4.2 – Exclusion Criteria

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

Section 5.3 – Randomization

Paragraph 1, Sentence 1: Qualified subjects will be randomized to receive lefamulin or moxifloxacin in a ~~2~~ **1**:1 allocation ratio.

Paragraph 2, Sentence 3: A minimum of ~~25~~ **50**% of the total number of subjects randomized will have a PORT Risk Class of III or IV.

Section 6.14 – Sample Collection for Pharmacokinetic Analysis

Footnote "c" has been added to Table 5 (Sample Collection Time Points for the Determination of Lefamulin Plasma Concentrations following Oral Administration) in reference to the 8-9 h PK collection time point after the first dose of study drug, as follows:

c: The 8-9h sample is required for inpatients. The 8-9 h sample is optional for outpatients; however, should be obtained if logistically feasible.

Section 9.2 – Sample Size Determination

A total of ~~573~~ **738** subjects will be randomized in a ratio of ~~2~~**1**:1 (lefamulin:moxifloxacin) resulting in ~~382~~ **369** subjects in the lefamulin arm and ~~191~~ **369** in the moxifloxacin arm in this study. 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 as well as 2 recent clinical trials in CABP indicate the point estimates for an ECR responder at Days 3-5 range from 72% to 81% (FDA, 2011; ~~Cempra, 2015a~~ **Barrera et al., 2016**; Cempra, 2015~~b~~; Oldach et al., 2015**)**. Thus, it is reasonable to assume that in a prospective study of subjects with CABP, the proportion of subjects who are responders for ECR at 96 ± 24 hours post first dose of study drug will be approximately ~~77~~ **79%**.

The primary efficacy analysis variables used for NI analyses for the Marketing Authorization Application (MAA) to the EMA will be the proportion 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% to 93% (Cempra, 2015~~b~~) and in the ITT Analysis Set ranged from 85% to 89% depending on the antibiotics under study and the severity of the CABP. Based on these data, an ~~87~~ **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 ~~77~~ **79%** in the ITT Analysis Set, a ~~2~~ **1**:1 randomization ratio, a two-sided alpha of 0.025, and a continuity corrected Z-test with unpooled variance, a sample size of ~~573~~ **738** subjects (~~382~~ **369** subjects in the lefamulin group and ~~191~~ **369** in the moxifloxacin group) provides 90% power to establish the NI of lefamulin to moxifloxacin for ECR using a NI margin of ~~12.5~~ **10.0**% at the ECA. Assuming an IACR success of ~~82~~ **80**% and ~~87~~ **85**% in the mITT and CE-TOC Analysis Sets, respectively, and a clinical evaluability rate of 80%, there is ~~80~~ **91**% power for demonstration of NI for IACR at the TOC Visit using a 10% NI margin.

The calculated power in each analysis set for the primary and secondary outcomes is provided in Table 6 below.

Table 6. Power Calculations for the Primary and Secondary Efficacy Outcomes

	Primary Outcome (FDA) (ECR 96 ± 24 hours After the First Dose of Study Drug)	**Secondary Outcome (Investigator's Assessment of Clinical Response at TOC- Primary for EMA)**	
Analysis Set	ITT	mITT	CE-TOC
NI Margin	~~12.5~~ **10%**	10%	10%
N	~~573~~ **738** (~~382:191~~ **369:369**)	~~573~~ **738**	~~459~~ **590**
Outcome Rate	~~77~~ **79**%	~~82~~ **80%**	~~87~~ **85%**
Evaluability Rate	NA	NA	80%
Power	90%	~~80~~ **91 %**	~~81~~ **91**%

CE = clinically evaluable; ITT = intent to treat; mITT = modified ITT; TOC = test of cure

Section 9.4.4 – Pharmacokinetic Analysis Variables

Paragraph 1, Sentence 3: Individual AUC values from Day 1 and Day 4 [i.e., 96 ± 24 hours post first dose] (collected pre-dose, 1-2 h post dose and 3-4 h post dose, and ~~an optional time point~~ at 8-9 h post dose **[8-9 h post dose is required for inpatients; optional for outpatients])** will be used for the PK/PD analysis.

Section 9.6.1 – Primary Efficacy Analysis

Paragraph 3, Sentence 4: If the lower limit of the 95 % CI for the difference in responder rates in the ITT Analysis Set is greater than ~~-12.5%~~ **-10.0 %,** the null hypothesis will be rejected and the NI of lefamulin to moxifloxacin will be concluded.

In addition, the Sponsor has made the following revisions to the original protocol to provide clarity and to align this protocol with the Phase 3 IV/Oral Protocol (NAB-BC-3781-3101) for the treatment of CABP. These changes will assist in statistical analysis at the time of submission for marketing approval. These revisions were made to the protocol sections noted below as well as to the study synopsis and the Schedule of Assessments and Procedures (Table 1). Added text is **bolded;** deleted text is ~~struck through~~. None of these changes are expected to affect subject safety or the interpretation of study results.

Section 6.5 – Vital Signs and Oxygen Saturation

[Rationale: Collection of supplemental oxygen therapy data has been added to the protocol and eCRF.]

New paragraph (Paragraph 2) was added:

In addition, if the subject is receiving supplemental oxygen therapy, the amount given will be recorded in the eCRF.

Section 6.7 – Arterial Blood Gases

[Rationale: FiO2 is not being collected on the eCRF as part of the results of arterial blood gases.]

Study sites are not required to measure arterial blood gases (PaO_2, $PaCO_2$) ~~(and FiO_2)~~ or pH. However, if these data are available, they should be recorded in the eCRF.

Section 6.15.8 – Nasopharyngeal Specimen

[Rationale: All S. pneumoniae will be tested. H. influenzae testing will depend on validation of procedures using samples collected early in the trial. It is possible that only some subjects will have testing for H. influenzae performed.]

Paragraph 1, Sentences 1 and 2: A nasopharyngeal specimen (1 swab) will be obtained at Screening and sent to the central laboratory/specialty laboratory for *S. pneumoniae* ~~and *H. influenzae* ~~culture, susceptibility testing, as well as identification by PCR**. Culture, susceptibility testing, as well as identification by PCR, may also be performed for *H. influenzae.***

Section 7.5 – Other Reportable Events

[Rationale: All subjects who meet the criteria for potential Hy's Law, regardless of whether it is an SAE, will complete the Hy's Law eCRF.]

- Potential Hy's Law (PHL) [Sentences 1 and 2]

The investigator is responsible for prompt reporting of any patients who has had both (1) AST or ALT > 3 x ULN and (2) total bilirubin > 2 x ULN at any point in the study (i.e., meets criteria for Potential Hy's Law)~~, unless the event is already reported as an SAE~~. **The investigator must complete the Hy's Law eCRF.**

Section 9.4.4 – Pharmacokinetic Analysis Variables

[Rationale: PK analysis will include lefamulin's main metabolite, BC-8041; also edits made to popPK anlaysis.]

Paragraph 1, Sentence 2: Calculated PK will enable descriptive statistical analysis of PK variables such as the maximum observed drug concentration (C_{max}) and area under the concentration-time curve (AUC) for lefamulin **and its main metabolite, BC-8041**.

Paragraph 1, Sentence 4: The **population** PK analysis ~~based on population PK~~ as well as a PK/PD analysis will be reported separately.

Section 9.4.5 – Other Variables

[Rationale: A description of the disk inhibition zone diameter which would qualify as development of decreasing susceptibility is provided.]

- **Development of Decreasing Susceptibility:** Increase in MIC (≥ 4x) **or 6 mm decrease from baseline in disk inhibition zone diameter to the study drug received** for a pathogen isolated at baseline and subsequently isolated from a blood or lower respiratory tract specimen.

Section 9.7 – Safety Analyses

[Rationale: Across the lefamulin clinical development program, corrected QT interval will be summarized using the Frederica formula only.]

Paragraph 5, Sentence 1: Change from baseline to each scheduled evaluation and the overall worst post-baseline for RR interval, PR interval, QRS interval, QT interval, ~~QT interval corrected with Bazzett,~~ and QT interval corrected with Fridericia from the ECG will be summarized for each treatment group with the mean, standard deviation, minimum value, and maximum value.

Section 19 - List of References

Zeitlinger et al, 2014 (poster presentation) has been published in *J Antimicrob Chemother*. Reference and citations throughout the protocol have been updated to Zeitlinger et al, 2016.

Cempra, 2015a (press release) has been published in *Lancet*. Reference and citations throughout protocol have been updated to Barrera et al., 2016. [Cempra, 2015b is now referenced and cited as Cempra, 2015.]

In addition, the Sponsor has made correction of typographical errors (e.g., definition of ELF), updated information (e.g., increase in number of clinical isolates tested [Section 1.3, Paragraph 3, Sentence 1: >13,400 vs. 13,600]), and consistency in formatting.

SYNOPSIS

Study Title: A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Oral Lefamulin (BC-3781) Versus Oral Moxifloxacin in Adults With Community-Acquired Bacterial Pneumonia (Protocol NAB-BC-3781-3102 with Amendments 1 and 2).

Study Objectives:

Primary Objectives

- 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 **(FDA endpoint).**
- Demonstrate the NI of lefamulin versus comparator with respect to the Investigator's Assessment of Clinical Response at Test of Cure (TOC) (i.e., 5-10 days after the last dose of study drug) in the modified-ITT (mITT) and Clinically Evaluable at TOC (CE-TOC) Analysis Sets **(EMA endpoint)**.

Secondary Objectives

- Evaluate the Early Clinical Response in the Microbiological Intent-to-Treat (microITT) Analysis Set.
- Evaluate the Investigator's Assessment of Clinical Response at TOC in the microITT and Microbiologically Evaluable at TOC (ME-TOC) Analysis Sets.
- Evaluate 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 Objectives

- Evaluate the Early Clinical Response by baseline pathogen in the microITT Analysis Set.
- Evaluate the Investigator's Assessment of Clinical Response at the End of Treatment (EOT) (i.e., within 2 days after the last dose of study drug) and at LFU in the mITT and 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 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 Early Clinical Response PLUS improvement in vital signs in the ITT Analysis Set.

- Evaluate the plasma pharmacokinetics (PK) of lefamulin and its main metabolite, BC-8041, in the PK Analysis Set.
- Explore a variety of health utilization variables and an investigational patient reported outcome (PRO) measure in subjects receiving lefamulin compared with subjects receiving comparator.

Study Population:

Inclusion Criteria

Each subject must:

1. Be male or female ≥ 18 years of age.
2. Provide written informed consent and be willing and able to adhere to the study-specified procedures and restrictions. NOTE: Consent may be provided by the subject's legally authorized representative in accordance with local regulations.
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.
4. Have at least 2 of the following vital sign abnormalities:
   - Fever (body temperature > 38.0 °C (100.4 °F) measured orally or equivalent temperature from an alternate body site) or hypothermia (body temperature < 35.0 °C (95.0 °F) 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).
5. Have at least 1 other clinical sign or laboratory finding of CABP:
   - Hypoxemia (i.e., 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 (e.g., crackles, egophony, dullness).
   - White blood cell (WBC) count > 10 000 cells/mm^3 or < 4 500 cells/mm^3 or > 15 % immature neutrophils (bands) regardless of total WBC count.
6. Have radiographically-documented pneumonia within 48 hours before enrollment (i.e., infiltrates in a lobar or multilobar distribution or diffuse opacities on chest x-ray consistent with acute bacterial pneumonia). NOTE: if a chest computed tomography scan

has been performed within 48 hours of enrollment and demonstrates findings consistent with pneumonia, it can be used in place of a chest x-ray.

7. Have a Pneumonia Outcomes Research Team (PORT) Risk Class of II, III, or IV and be an appropriate candidate for oral antibiotic therapy as treatment for the current episode of CABP.
8. If female, meets the following criteria:
   - Surgically sterile or ≥ 2 years postmenopausal, or if of childbearing potential (including being < 2 years postmenopausal), has a negative pregnancy test, and if participating in sexual activity that may lead to pregnancy, agrees to use an effective dual method of contraception (e.g., condom plus diaphragm, condom plus spermicide, intrauterine device plus spermicide) during the study and for ≥ 28 days after the last dose of study drug. If a male partner has been surgically sterile for ≥ 1 year, a single contraception method may be used. NOTE: The use of contraceptives containing progesterone is not permitted.
   - Agrees not to breastfeed during the study and through ≥ 28 days after the last dose of study drug.
9. If male, meets the following criteria:
   - If not surgically sterile and if participating in sexual activity that may lead to pregnancy, agrees to use an effective dual method of contraception (e.g., condom plus diaphragm, condom plus spermicide, intrauterine device plus spermicide, oral contraceptive plus condom) during the study and through ≥ 28 days after the last dose of study drug. If surgically sterile for ≥ 1 year, a single contraception method may be used.

Exclusion Criteria

Each subject must NOT:

1. Have received more than a single dose of a short-acting oral or IV antibacterial for CABP within 72 hours before randomization (See Appendix 2).
   - 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 (i.e., 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 is to fluoroquinolones.
2. Require concomitant systemic antibacterial therapy potentially effective against CABP pathogens (See Section 6.9).
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.
4. Have confirmed or suspected CABP caused by a pathogen known to be resistant to any of the study drugs (e.g., MRSA, *Pseudomonas aeruginosa*, any pathogen of the *Enterobacteriaceae* Family) or attributable to etiologies other than community-acquired

bacterial pathogens (e.g., ventilator-associated pneumonia, hospital-acquired bacterial pneumonia, bacterial aspiration pneumonia, *Pneumocystis jiroveci* pneumonia or other fungal pneumonia, viral or mycobacterial infection of the lung).

5. Have a noninfectious cause of pulmonary infiltrates (e.g., pulmonary embolism, chemical pneumonitis from aspiration, hypersensitivity pneumonia, congestive heart failure, bronchial obstruction, lung cancer, cystic fibrosis).
6. Have confirmed or suspected pleural empyema (does not include sterile parapneumonic effusions).
7. Have or be at risk for major cardiac events or dysfunction including, but not limited to, the following:
    - Known prolonged QT interval or family history of long QT syndrome
    - Clinically significant hypokalemia which has not been treated prior to randomization
    - Clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling pacemaker
    - Complete left bundle branch block
    - Receipt within 7 days before enrollment of Class IA or Class III anti-arrhythmic medication or, in the opinion of the Investigator, subject may require such medication during the study. (Class 1A: Quinidine, Procainamide, Disopyramide; Class III: Amiodarone, Dofetilide, Ibutilide, Sotalol)
    - Receipt within 7 days before enrollment of medication that has the potential of prolonging the QT interval or, in the opinion of the Investigator, subject may require such medication during the study (see Appendix 5).
8. Be receiving a strong p-glycoprotein inhibitor or a strong CYP3A inducer or inhibitor (see Appendix 4).
9. Have a history of tendon disease/disorder, myasthenia gravis, or known or suspected central nervous system (CNS) disorders (severe cerebrovascular arteriosclerosis, epilepsy, or other risk factors that may predispose to seizures).
10. Have a history of any hypersensitivity or allergic reaction to any fluoroquinolone, or any drug in the pleuromutilin class (i.e., retapamulin).
11. Have severely impaired renal function, defined as estimated creatinine clearance (CrCl) ≤ 30 mL/min as calculated by the Cockcroft-Gault formula.
12. Have evidence of significant hepatic, hematologic, or immunologic disease including any of the following:
    - Known acute hepatitis, including acute viral hepatitis.
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 5 times the upper limit of normal (ULN),
    - Total bilirubin > 3 times the ULN (unless known Gilbert's disease).

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 3 times the upper limit of normal (ULN) and total bilirubin > 2 times the ULN.
- History of cirrhosis of the liver.
- Manifestation of end-stage liver disease, such as ascites or hepatic encephalopathy.
- Current or anticipated neutropenia (< 500 neutrophils/mm^3).
- Thrombocytopenia (< 50 000 platelets/mm^3).
- Known infection with human immunodeficiency virus and a CD4 count < 200/mm^3.

13. Have known severe immunosuppression, including but not limited to receipt of corticosteroid therapy (≥20 mg of prednisone/day or equivalent for >4 weeks) within the previous 8 weeks; solid organ or bone marrow transplantation within the previous 12 months; or currently receiving cytotoxic chemotherapy.
14. Have a life expectancy of ≤ 3 months because of any disease other than the current episode of CABP (e.g., current or impending respiratory failure, acute heart failure, shock, acute coronary syndrome, unstable arrhythmia, hypertensive emergency, clinically relevant gastrointestinal bleeding, profound metabolic abnormality, or acute cerebrovascular event).
15. Have participated in any study involving administration of an investigational agent or device within 30 days or ≤ 5 terminal elimination half-lives of the previous investigational medicinal product, whichever is longer, before enrollment.
16. Have been previously treated with lefamulin or previously enrolled in this study.
17. Have any condition that, in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data.

Duration of Study: Each subject will participate for approximately 4-5 weeks.

Drug Products: Drug products will be supplied as follows:

Drug Product	Route	Dosage Form/Strength
Lefamulin	PO	600 mg of lefamulin as a yellow oval film coated immediate-release tablet
Moxifloxacin	PO	400 mg of moxifloxacin as an over-encapsulated film-coated tablet

Study Drug Assignment: Subjects will be randomized in a 1:1 ratio to either lefamulin or moxifloxacin.

Study Drug Administration: The duration of blinded study drug administration will be 7 days. Subjects randomized to lefamulin will receive oral lefamulin 600 mg q12h for 5 days (10 doses) and oral moxifloxacin placebo q24h for 7 days (7 doses). Subjects randomized to moxifloxacin will receive oral moxifloxacin 400 mg q24h for 7 days (7 doses) and oral lefamulin placebo q12h for 5 days (10 doses).

On Day 1, study personnel will administer the first dose of study drug at the study site to all subjects as soon as possible after the diagnosis of CABP and completion of all required

Day 1 procedures as outlined in Table 1. While subjects are hospitalized, all doses of study drug will be administered by hospital staff or study personnel.

For Outpatients, or in the event a subject is discharged from the hospital during the study drug administration period, an adequate supply of study drug will be dispensed for self-administration at home. Subjects will be provided instructions regarding the dosing schedule. Subjects may self-administer oral study drug at home with the following exception: Study personnel will advise subjects who are Outpatients that they must return to the study site to assess CABP signs and symptoms at 96 ± 24 hours after the first dose of study drug. Study personnel will inform Outpatients as to the timing of this required study site visit. Subjects will be advised not to take their first dose of study drug at home that day, rather to bring their blister packs (used and unused) to the study site, where they will take their dose while supervised so that specific assessments can be performed both prior to and after taking the dose (i.e., ECGs and PK).

On Study Day 1, if q12h dosing is not feasible, the 1st and 2nd doses may be administered as close as 8 hours apart, in order to allow 2 doses to be given on Day 1. In this circumstance, the subject's dosing schedule should be adjusted on Day 2 to a regular q12h morning and evening schedule. Subsequently, every effort should be made to maintain a q12h dosing schedule. When this is not possible, it is acceptable to administer doses within 4 hours of the scheduled dosing time (i.e., a minimum of 8 hours between doses).

Study drug should be administered at least 1 hour before a meal or 2 hours after a meal. However, in the event that a subject has taken any of the following − antacids containing aluminum, products containing iron, or multivitamins containing zinc − study drug should be administered 2 hours before or 4 hours after consuming any of these medications. Doses should be administered with approximately 240 mL (8 ounces) of water.

Blinding: Study drug will be blinded using a double-dummy technique.

A member(s) of the Sponsor's Clinical Pharmacology group (or designee) will be unblinded to treatment assignment, as appropriate, in order to perform PK/PD assessments. A Data Monitoring Committee (DMC) will review study data by treatment group in accordance with the DMC Charter. In addition, as needed to meet regulatory reporting requirements on a country-by-country basis, designated pharmacovigilance personnel may be unblinded to treatment status of individual subjects. In this circumstance, and if there are no other concerns, neither the Sponsor nor the study personnel will be unblinded to treatment status.

Study Design: This multicenter, multinational, randomized, double-blind, double-dummy, active-controlled efficacy and safety study in subjects with CABP will be conducted at approximately 160 centers. The planned enrollment is 738 subjects (369 subjects in the lefamulin group and 369 subjects in the moxifloxacin group) with PORT Risk Class II, III, or IV. Eligible subjects will be randomized 1:1 to lefamulin or moxifloxacin, using an interactive response technology (IRT). Subject randomization will be stratified according to PORT Risk Class (Risk Class II vs. III/IV), geographic region (US vs. ex-US), and prior (single dose) short-acting antibiotic therapy for CABP vs. none.

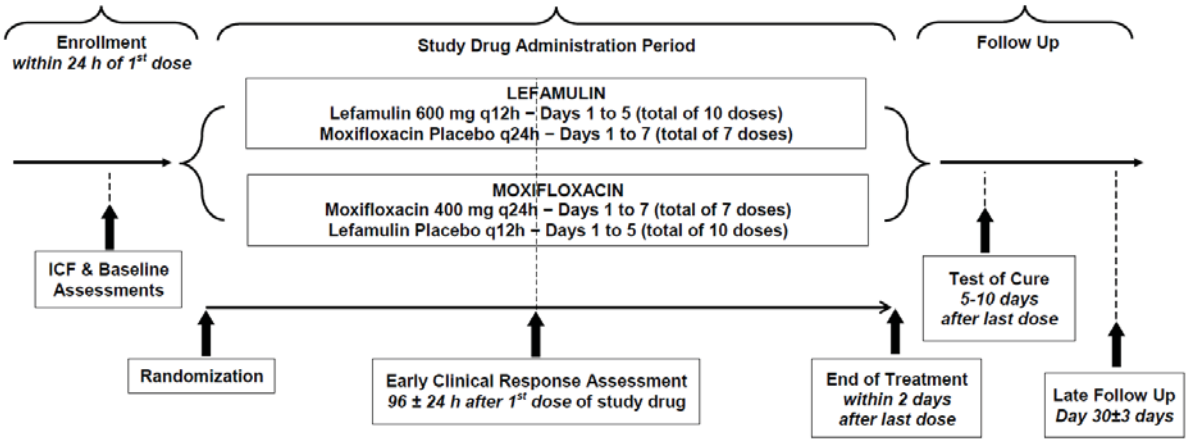
Subjects will be consented for the study prior to study assessments being performed and confirmation of eligibility. Screening assessments will be performed within 24 hours before first dose of study drug.

Subjects will be assessed for response at the following time points during the study:

- Early Clinical Assessment (ECA): 96 ± 24 hours after the first dose of study drug.
- End of Treatment (EOT): within 2 days after the last dose of study drug (NOTE: every attempt should be made to conduct the EOT visit within 1 day after the last dose of study drug. However, if this is not logistically feasible [e.g., visit would need to be conducted over a weekend], then conducting the visit within 2 days is acceptable.).
- Test of Cure (TOC): 5-10 days after the last dose of study drug.
- Late Follow Up (LFU): Day 30 (± 3 days).

An overview of the study design is provided in Figure 1 below.

Figure 1. Study Design Overview



Assessment of the 4 cardinal symptoms of CABP (dyspnea, cough, purulent sputum production, and chest pain) will be conducted daily; an assessment at 96 ± 24 hours after the first dose of study drug will determine Early Clinical Response (ECR) (as defined in the Primary Objective - FDA). NOTE: ECR will be determined programmatically based upon the Investigator's assessment of the 4 cardinal symptoms of CABP; the decision to maintain the subject on study drug therapy will be made by the Investigator, based on all available data and his or her best clinical judgment. In addition, the Investigator's Assessment of Clinical Response (IACR) will be performed at the EOT, TOC and LFU visits (Success, Failure and Indeterminate at EOT and TOC; Sustained Success, Relapse and Indeterminate at LFU).

Microbiological assessments will be performed at Screening, and then subsequently throughout the study as clinically indicated. Samples will be taken for Gram's staining, for diagnostic tests (serology, urine antigen tests, molecular tests), and for culture and antimicrobial susceptibility testing. Subjects who have confirmed *S. aureus* bacteremia must be withdrawn from the study.

Safety will be assessed by monitoring vital signs, ECG measurements, safety laboratory parameters, and recording of adverse events (AEs). A Data Monitoring Committee (DMC) will review the safety data throughout the study.

Blood samples for PK analyses will be collected from all subjects.

Exploratory evaluation of a variety of health utilization variables (e.g., length of hospital stay, duration of antibiotic therapy, discharge status, discharge destination) as well as a PRO instrument (SF-12) will be administered. The schedule of study procedures is provided immediately following the synopsis (Table 1: Schedule of Assessments and Procedures).

Statistical Considerations:
Sample Size: Utilizing an anticipated ECR responder rate of 79% in the ITT Analysis Set, 1:1 randomization ratio (lefamulin:moxifloxacin) and a two-sided alpha of 0.025, a sample size of 738 subjects (369 subjects in the lefamulin group and 369 in the moxifloxacin group) provides 90% power to establish the non-inferiority (NI) of lefamulin to moxifloxacin for ECR using a NI margin of 10.0 % at the ECA. Assuming an IACR success rate of 80% and 85% in the mITT and CE-TOC Analysis Sets, respectively, and a clinical evaluability rate of 80%, there is 91% power for demonstration of NI for IACR at the TOC Visit using a 10% NI margin.

Treatment Comparison of Interest: All comparisons will be for lefamulin vs. comparator therapy (moxifloxacin).

Analysis Populations:

- *Intent-to-treat (ITT) Analysis Set*: 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.
- *Modified ITT (mITT) Analysis Set*: All randomized subjects who receive any amount of study drug. Subjects are analyzed based on the randomized (i.e., assigned) treatment group.
- *Microbiological ITT (microITT) Analysis Set*: All subjects in the ITT Analysis Set who have at least 1 baseline "typical" bacterial pathogen known to cause CABP, *Legionella pneumophila* from an appropriate microbiological specimen, or who have CABP caused by *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae*.
- *Clinically Evaluable (CE) Analysis Sets (CE-EOT, CE-TOC, and CE-LFU):* A subset of the ITT Analysis Set that will include subjects who meet the criteria for CABP described in Inclusion criteria Nos. 3 - 7, and who received at least the pre-specified minimal amount of the intended dose of study drug and duration of treatment, do not have an

indeterminate response based on the IACR (at EOT for the CE-EOT Analysis Set, at TOC for the CE-TOC Analysis Set. and at LFU for the CE-LFU Analysis Set), did not receive concomitant antibacterial therapy that is potentially effective against CABP pathogens (except in the case of clinical failure) from the first dose of study drug through the EOT Visit (CE-EOT Analysis Set), through the TOC Visit (CE-TOC Analysis Set) and through the LFU Visit (CE-LFU Analysis Set), and for whom there are no other confounding factors that interfere with the assessment of the outcome.

- *Microbiologically Evaluable (ME) Analysis Sets (ME-EOT, ME-TOC, and ME-LFU):* Subjects who meet the criteria for both the microITT and the CE-EOT (ME-EOT) Analysis Sets, the CE-TOC (ME-TOC) Analysis Set or CE-LFU (ME-LFU) Analysis Set.
- *Safety Analysis Set:* 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.
- *Pharmacokinetic Analysis Set*: All subjects who receive any amount of study drug will be included in the formal analysis of PK parameters providing they have at least 1 evaluable PK sample.

Variables for Analysis

Primary Efficacy Analysis Variable

- Proportion of Responders for ECR at 96 ± 24 hours following the first dose of study drug in the ITT Analysis Set (**FDA**)
  - Subjects will be programmatically defined as a **Responder** if the following 4 criteria are met:
    - Alive
    - Improvement in at least 2 of the 4 cardinal symptoms of CABP (see Section 6.11) 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 from Baseline by at least 1 level of severity of any symptom.
    - Did not receive a concomitant antibiotic for the treatment of CABP.
  - Subjects will be programmatically defined as a **Non-Responder** if any of the following criteria are met:
    - Did not show an improvement in at least 2 of the 4 cardinal symptoms of CABP the subject presented with at Baseline. Improvement is defined as a decrease by at least 1 level in severity; or
    - Worsening of any of the 4 cardinal symptoms of CABP. Worsening is defined as an increase from Baseline by at least 1 level in severity for any symptom; or
    - Received a concomitant antibiotic for the treatment of CABP; or
    - Died from any cause.

- Subjects will be programmatically defined as **Indeterminate** if the following criterion is met:
    - The symptom data are missing such that a response or non-response cannot be determined.

- Proportion of subjects with an IACR of Success at TOC in the mITT and CE-TOC Analysis Sets (IACR definitions are provided below) (**Primary for EMA and secondary for FDA**)
    - **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 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.

Secondary Efficacy Analysis Variables

Efficacy will be assessed by ECR, IACR and by Microbiological Response.

Microbiological Assessment

The By-Pathogen Microbiological Response will be assessed using the categories for outcome in the microITT and ME analysis sets as follows:

- **Success** includes**:**
    - Eradication: the baseline causative pathogen was absent from repeat culture(s).
    - Presumed Eradication: the IACR was Success, and culture was not repeated.
- **Failure** includes**:**
    - Persistence: the baseline causative pathogen was isolated in repeat culture(s).
    - Presumed Persistence: the IACR was Failure and a culture was not repeated.

- **Indeterminate:**
  - The IACR was Indeterminate and a culture was not repeated.

Safety Analysis Variables

Safety will be assessed by monitoring vital signs, ECG measurements, clinical laboratory parameters, and AEs.

Pharmacokinetic Analysis Variables

Population PK modeling will be performed to determine the model-predicted plasma concentration time curves of lefamulin for each subject. Calculated PK parameters will enable descriptive statistical analysis of PK variables such as the maximum observed drug concentration (C_{max}) and area under the concentration-time curve (AUC) for lefamulin.

Individual AUC values from Day 1 [all subjects] and Day 4 [Inpatients] or 96 ± 24 hours post first dose [Outpatients] (collected pre-dose, 1-2 h post dose and 3-4 h post dose, and a 8-9 h post dose (the 8-9 h sample is required for inpatients and optional for outpatients) will be used for the PK/PD analysis. The PK analysis based on population PK as well as a PK/PD analysis will be reported separately.

Other Variables

Exploratory evaluation of a variety of health utilization variables (e.g., length of hospital stay, duration of antibiotic therapy, discharge status, discharge destination) as well as a PRO instrument will be performed.

Statistical Methods:

A 2-sided unstratified 95 % confidence interval (CI) for the observed difference between treatment groups (lefamulin minus moxifloxacin) in ECR responder rates at 96 ± 24 hours post first dose will be calculated using a continuity corrected Z-statistic. Non-inferiority for the primary efficacy analysis variable (FDA) will be concluded if the lower limit of the 2-sided 95% CI is greater than –10.0% in the ITT Analysis Set.

For the efficacy outcome measure of IACR of Success at TOC in the mITT and CE-TOC Analysis Sets, unstratified 95% CIs will be calculated using a continuity corrected Z-statistic (FDA secondary efficacy outcome). For the primary analysis for the EMA, a stratified (for the randomization stratification factors) 2-sided 95% CIs will be calculated using the method of Miettinen and Nurminen. Non-inferiority for the primary efficacy analysis variable (EMA) will be concluded if the lower limit of the 2-sided stratified 95% CI is greater than -10% for both the mITT and CE-TOC Analysis Sets.

The number and percentage of subjects with an ECR of Responder at 96 ± 24 hours will also be presented for the microITT Analysis Set, and a 2-sided unstratified 95% CI for the difference in responder rate will be calculated using a continuity-corrected Z-statistic. However, the formal test of NI will be conducted in the weighted (based on the inverse variance of each effect size) pooled population from this study and a second study in CABP.

The incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), deaths, and discontinuations of study drug due to an AE or SAE will be summarized by System Organ Class (SOC) and Preferred Term according to the Medical Dictionary for Regulatory Activities (MedDRA), by relationship to study drug, and by severity. The incidence of potentially clinically significant laboratory results, vital signs, and ECGs will be summarized.

Table 1. Schedule of Assessments and Procedures

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

NOTE: Hospitalization is not a requirement for this study. However, all subjects, including Outpatients, must be evaluated at the investigational site by study personnel at the following time points/visits: Screening/Baseline; Day 1; Day 4 / 96 ± 24 hours after the first dose of study drug; EOT; TOC; and LFU.

a: Perform Screening/Baseline assessments within 24 hours before the first dose of study drug. Administration of study drug should begin as soon as possible after the diagnosis of CABP. ***See Footnote x.*** Assessments performed as part of routine standard of care prior to consent (e.g., 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. Assessments/ procedures on Day 1 should be performed prior to first dose.

c: INPATIENTS will be assessed daily while hospitalized; thus, data required for ECR Assessment (96 ± 24 hours after the first dose of study drug) will be collected.
OUTPATIENTS **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 during the course of daily telephone contact. In addition to the assessment of CABP signs/symptoms, subjects will also have the following procedures/assessments performed at that study site visit: ECGs, physical examination, AE monitoring, review of concomitant medications, vital signs, oxygen saturation, and blood sampling for PK analysis and safety laboratory evaluations. Importantly, study personnel will advise OUTPATIENTS not to take their first dose of study drug at home that day, rather to bring their blister packs (used and unused) to the study site where they will take their dose while supervised; thus, specific assessments can be performed both prior to and after taking the dose (i.e., ECGs and PK). ***See Footnotes i, k, l, m, o, p, and y below for details***.

d: Perform End of Treatment (EOT) assessments at the study site within 1 day (up to 2 days permitted) 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.

e: Perform Test of Cure (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.

f: Perform Late Follow Up (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.

g: Obtain informed consent before initiating any study-specific assessments or procedures.

h: Assessment or procedure may occur at either Screening OR prior to the first dose of study drug on Day 1 once eligibility has been determined.

i: All subjects will have vital signs and O_2 saturation evaluated at Screening/Baseline and Day 1. If screening/baseline and Day 1 occur on the same calendar day, vital signs and O_2 saturation do not need to be repeated. All subjects will also have assessments at EOT and TOC; at LFU, vital signs should be performed if medically indicated. 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 (i.e., as part of the EOT assessment). Record the vital signs associated with the highest temperature after the first dose of study drug.
INPATIENTS: Vital signs, O_2 saturation, and supplemental O_2 usage will be measured daily. If multiple vital signs are taken on a study day, the highest temperature and the vital signs associated with that high temperature will be recorded.
OUTPATIENTS: In addition to the above time points, vital signs, O_2 saturation and, if applicable, supplemental O_2 usage will be measured at the study visit scheduled 96 ± 24 hours after the first dose of study drug.

j: Study personnel will evaluate signs and symptoms of CABP at Baseline, daily while on study therapy, and at EOT, TOC, and LFU Visits. *NOTE*: 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 (i.e., as part of the EOT assessment). Signs and symptoms are not obtained at TOC or LFU if the subject was previously deemed to have an IACR of Failure.
OUTPATIENTS: Study personnel will contact subjects daily by telephone to track signs and symptoms of CABP; **however, subjects must report to the study site for the assessment of CABP signs/symptoms 96 ± 24 hours after the first dose of study drug**. ***See Footnote c***.

k: 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. In addition, study personnel will monitor AEs for OUTPATIENTS in conjunction with daily telephone contacts for CABP signs/symptoms and at the study site visit 96 ± 24 hours after the first dose of study drug. ***See Footnote c.***

l: **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. If Screening and Day 1 are on the same day, the Screening ECG can serve as the Day 1 ECG prior to the first dose of study drug; an additional ECG must be performed 1-3 hours after administration of first dose. ***See Footnote m.***

m: INPATIENTS: The Day 4 ECG in triplicate is required prior to the first dose of study drug and again within 1-3 hours after the first dose of study drug.
OUTPATIENTS: The Day 4 ECG can be performed at the required study site visit 96 ± 24 hours after the first dose. ***See Footnote c.*** The Day 4 ECG in triplicate is required prior to the first dose of study drug and again within 1-3 hours after the first dose of study drug.

n: A complete physical examination is performed at Baseline and directed physical examinations are performed thereafter.

o: INPATIENTS: On Day 4, a directed physical examination will be performed..
OUTPATIENTS: A directed physical examination will be performed at the study site visit scheduled 96 ± 24 hours after the first dose. ***See Footnote c.***

p: 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. Collect blood and/or urine at LFU only if subject had an abnormal (high/low flag) result at TOC.

q: INPATIENTS: On Day 4, blood and urine samples will be collected for safety laboratory evaluations.
OUTPATIENTS: Blood and urine samples will be collected for safety laboratory evaluations at the study site visit scheduled 96 ± 24 hours after the first dose. ***See Footnote c.***

r: A urine pregnancy test will be performed at the site on all females unless surgically sterile or at least 2 years post-menopausal. A negative urine pregnancy test is required prior to randomization. Serum must be collected on Day 1 prior to 1st dose and sent to the central lab for confirmatory testing.

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

t: Collect blood samples (2 sets via peripheral venipuncture) for microbiologic culture and susceptibility testing at the local/regional lab at Baseline 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.

u: All lower respiratory tract and expectorated sputum samples should be sent to the local/regional laboratory for Gram's stain, culture and susceptibility testing. A sputum sample will be taken at Screening for Gram's staining, culture and susceptibility testing at the local/regional laboratory. 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 Baseline sputum samples must be frozen until sent to the central laboratory for quantitative PCR. Subjects with a urinary antigen positive for *Legionella* spp. will also have a portion of their sputum sample sent frozen to the central laboratory for isolation of *L. pneumophila.*

v: 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.

w: An oropharyngeal specimen (2 swabs) and a nasopharyngeal specimen (1 swab) 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. The nasopharyngeal specimen will be used for culture and identification by PCR of *S. pneumoniae,* and potentially, *H. influenzae.*

x: Study personnel will administer the first dose of study drug at the study site, as soon as possible after the diagnosis of CABP and completion of all required pre-dose Day 1 procedures. On Day 1, if q12h dosing is not feasible, the 1st and 2nd doses may be administered as close as 8 hours apart, in order to allow 2 doses to be given on Day 1. In this circumstance, the subject's dosing schedule should be adjusted on Day 2 to a regular q12h morning and evening schedule. Subsequently, every effort should be made to maintain a q12h dosing schedule. When this is not possible, it is acceptable to administer doses within 4 hours of the scheduled dosing time (i.e., a minimum of 8 hours between doses). For Outpatients, or in the event a subject is discharged from the hospital during the study drug administration period, an adequate supply of study drug will be dispensed for self-administration at home. Subjects will be provided instructions regarding the dosing schedule. Subjects may self-administer oral study drug at home with the following exception: Study personnel will advise subjects who are Outpatients that they must return to the study site to assess CABP signs and symptoms at 96 ± 24 hours after the first dose of study drug. **See Footnote c.** Administration of study drug may occur on the same calendar day as EOT, and if so will be completed before EOT assessments begin.

y: Collect blood samples for PK analysis relative to the first dose of study drug. Blood will be collected within 1 h pre-dose, 1-2 h post dose, and 3-4 h post dose, and 8-9 h post dose. INPATIENTS: PK sampling should occur on Day 4 but, if not feasible, it can be done relative to the first dose on Day 5; the 8-9 h post dose is required. OUTPATIENTS: PK sampling will be done during the 96 ± 24 hours post 1st dose visit. The 8-9 h post dose sample is optional; however, it should be obtained if logistically feasible.

z: Investigator to determine IACR - Success, Failure or Indeterminate (i.e., 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
24 h AUC/MIC	24 h AUC over the MIC
24 h AUC_{ELF}/MIC ratio	AUC at site of infection over the MIC
ABPI	Association of British Pharmaceutical Industry
ABSSSI	Acute bacterial skin and skin structure infection
ADME	Absorption, Distribution, Metabolism, and Elimination
AE	Adverse event
AGP	α1-acid glycoprotein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the drug concentration–time curve
BAL	Bronchoalveolar Lavage
BP	Blood pressure
C	Celsius
CABP	Community-acquired bacterial pneumonia
CA-MRSA	Community-acquired MRSA
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
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
CFR	Code of Federal Regulation
CFU	Colony Forming Unit
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
CNS	Central Nervous System
CrCl	Creatinine clearance
CS	Clinically significant
CT	Computerized tomography
CXR	Chest x-ray
CV [%]	Coefficient of variation [%]
CYP3A4	Cytochrome P450 3A4
DMC	Data Monitoring Committee
DSS	Drug Safety Services
ECA	Early Clinical Assessment

Abbreviation	Definition
ECG	Electrocardiogram
ECR	Early Clinical Response
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELF	Epithelial Lining Fluid
EMA	European Medicines Agency
EOT	End-of-Treatment
ESBL	Extended-spectrum β-lactamase
EU	European Union
F	Fahrenheit
*f*AUC	Area under the concentration-time curve of the unbound fraction of the drug
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
hERG	Human ether a go go related Gene
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
HSA	Human serum albumin
IAC	Interim Analysis Committee
IACR	Investigator's Assessment of Clinical Response
IC_{50}	Half-maximal inhibitory concentration
ICF	Informed Consent
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous
K_3EDTA	Tripotassium ethylene diamine tetraacetic acid
LFU	Late Follow-up
LLQ	Lower limit of quantification
MAA	Marketing Authorization Application
LPF	Low power field
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
ME-EOT	Microbiologically Evaluable at End-of-Treatment

Abbreviation	Definition
ME-LFU	Microbiologically Evaluable at Late Follow Up
ME-TOC	Microbiologically Evaluable at Test-of-Cure
mg	Milligram
MIC	Minimum inhibitory concentration
MIC_{90}	Concentration of drug required to inhibit growth of 90% of pathogens
microITT	Microbiological Intent-to-Treat
mITT	Modified Intent-to-Treat
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of mercury
MRSA	Methicillin-resistant *Staphylococcus aureus*
ms	Millisecond
MSSA	Methicillin-susceptible *Staphylococcus aureus*
n	Group size, number of replicates
NaCl	Sodium chloride
NCS	Not clinically significant
NI	Non-inferiority
NOAEL	No Observed Adverse Effect Level
O_2	Oxygen
Pa O_2	Partial Pressure of Arterial Oxygen
PCR	Polymerase Chain Reaction
PCS	Potentially clinically significant
PD	Pharmacodynamics
p-gp	p-glycoprotein
Ph. Eur.	European Pharmacopoeia
PHL	Potential Hy's Law
PK	Pharmacokinetic
PMN	Polymorphonuclear
PO	By mouth (oral)
PORT	Pneumonia Outcomes Research Team
PRO	Patient-reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
PV	Pharmacovigilance
q12h	Every 12 hours
q24h	Every 24 hours
QA	Quality Assurance
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected according to Fridericia
ΔQTcF	QTcF change from baseline

Abbreviation	Definition
rRNA	Ribosomal ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SENTRY	SENTRY Antimicrobial Surveillance Program
SOC	System organ class
STD	Sexually Transmitted Diseases
SUSAR	Suspected Unexpected Serious Adverse Event
$T_{> MIC}$	Time plasma concentration exceeds the MIC
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TOC	Test-of-Cure
tRNA	Transfer ribonucleic acid
ULN	Upper Limit of Normal
US	United States
USP	United States Pharmacopeia
VRE	Vancomycin-resistant enterococcus
WBC	White Blood Cell Count

NOTE: Table includes a comprehensive list of abbreviations used in lefamulin regulatory documents.

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1 INTRODUCTION

1.1 Background of the Disease and Treatment Options

Community-acquired bacterial pneumonia (CABP) is a commonly occurring serious infection that requires systemic antibiotic therapy and is associated with substantial morbidity, mortality, and considerable healthcare costs. It is the leading cause of death from infectious diseases in the United States (US) and, when combined with influenza, remains the eighth leading cause of death in the US (CDC, 2013). In Europe, there are 44 cases of CABP for every 1 000 patients treated in a single general practice (Lim et al., 2009), while in the US, 5.6 million cases of CABP lead to as many as 1.1 million hospitalizations and > 53 000 deaths annually (CDC, 2013).

Community-acquired bacterial pneumonia is more common in the elderly, with an incidence that is 2- to 4-times greater in those > 60 years of age than in those ≤ 50 years. The mortality rate in the US and Europe is < 1 % for individuals with CABP that do not require hospitalization; however, the average mortality rate is 12 % to 14 % among those hospitalized (Fine et al., 1996; Fine et al., 1997; Lim et al, 2009). Individuals who are admitted to the intensive care unit (ICU), who are bacteremic, or who are admitted from a nursing home, have a mean mortality rate of 30% to 40% (Mandell et al., 2007; Lim et al., 2009).

The most common organisms of CABP identified by culture include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and selected Gram-negative pathogens. The incidence of CABP due to atypical pathogens — *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila* — lies between 20% and 28% depending on the region (Arnold et al., 2007).

The emergence of pathogens resistant to antimicrobials has become an increasingly complicating factor in the selection of empiric therapy for CABP. Antimicrobial susceptibility data for respiratory pathogens in the US reveal high rates of resistance among *S. pneumoniae* and *H. influenzae*. A surveillance program conducted between 2008 and 2010 in the US showed that, of 3 329 *S. pneumoniae* strains, 21.1 % were penicillin non-susceptible or resistant. Increases in an already elevated resistance rate for erythromycin (38.4% to 41.7%) were also observed in the same study (Pfaller et al., 2012). Recent global surveillance studies have revealed increased resistance to fluoroquinolones in all monitored bacterial species with the exception of *S. pneumoniae* and *H. influenzae* (Dalhoff, 2012).

M. pneumoniae is a common pathogen of respiratory tract infection in children and adolescents and can cause serious pneumonia and extra-pulmonary complications (Waites and Talkington, 2004). Current preferred treatment is with a macrolide antibiotic. In recent years, however, many countries have reported the isolation of clinically drug-resistant strains, the main mechanism of resistance being a mutation in the 23S ribosomal ribonucleic acid (rRNA) gene which is the target of macrolide antibiotic action. These resistant isolates remain susceptible to fluoroquinolones or tetracyclines, but use of these antibiotics is limited in children (Liu et al., 2014).

S. aureus, including methicillin-resistant *S. aureus* (MRSA), has emerged as an important pathogen in CABP. In a retrospective analysis that included hospitalized patients with microbiologically-confirmed CABP, approximately 25.5% of these patients were culture-positive for *S. aureus* and, among these patients, 6.3% had MRSA isolated (Kollef et al., 2005). In general, the hospitalized patients with pneumonia due to *S. aureus* in this study had an increased mortality rate. These findings correlate with recent case series of CABP due to community-acquired MRSA (CA-MRSA), which describe severe, necrotizing pneumonia in previously healthy young individuals (Francis et al, 2005; Hidron et al., 2009). Optimal management for these patients is not yet clear, and even the best available treatment may still result in poor outcomes (Gillet et al., 2007). Therefore, there is a need for more treatment options for CABP caused by MRSA.

1.2 Background on Lefamulin and the Pleuromutilins

Lefamulin is a potent, semi-synthetic antibacterial belonging to a novel class known as the pleuromutilins. The oral formulation of lefamulin is under investigation in this study. The first marketed representative of the pleuromutilin class for human use is retapamulin (GlaxoSmithKline), approved in 2007 in the US (Altabax®) for the topical treatment of impetigo and in Europe (Altargo®) for the topical short-term treatment of impetigo and infected small lacerations, abrasions or sutured wounds. Tiamulin (Denagard®) and valnemulin (Econor®), two other semi-synthetic pleuromutilin derivatives, have been used systemically in veterinary medicine for many years.

1.3 Mechanism of Action and Non-Clinical Pharmacology

Lefamulin is a prokaryotic protein synthesis inhibitor. Its novel mode of action is mediated by a unique interaction with the central part of domain V of 23S rRNA, subsequently preventing the correct positioning of the CCA-ends of transfer ribonucleic acid (tRNA) for peptide transfer (Davidovich et al., 2007). The uniqueness of this mechanism implies a very low probability of cross-resistance with other antibacterial classes.

Lefamulin's *in vitro* antibacterial profile covers the most important bacterial pathogens causing community acquired bacterial pneumonia (CABP) acute bacterial skin and skin structure infection (ABSSSI) and sexually transmitted diseases (STD). The antibacterial spectrum comprises *S. aureus* including MRSA and CA-MRSA, ß-haemolytic streptococci including *S. pyogenes* and *S. agalactiae*, *Enterococcus faecium* including vancomycin-resistant enterococci (VRE), *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, the atypical respiratory pathogens *L. pneumophila*, *C. pneumoniae*, and *M. pneumoniae*, and organisms causing STD such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium* among others. Moreover, lefamulin remains active against clinical isolates resistant to the following antimicrobial(s) (classes): macrolides, lincosamides, streptogramin B, oxazolidinones, tetracyclines, ß-lactams, quinolones, trimethoprim-sulfamethoxazole, mupirocin, and vancomycin as demonstrated in cross-resistance studies. The only exceptions are the rarely encountered *Staphylococcus* spp. producing the Cfr-methyltransferase and the Vga(A)-efflux pump, where lefamulin showed reduced activity. Although some linezolid-resistant isolates have a minimum inhibitory concentration (MIC) of >1 µg/mL for lefamulin, no consistent cross-resistance could be observed with linezolid.

Multiple interaction sites with the ribosomal target are the most likely explanation for the observed low mutation frequency of below 10^{-11}. *In vitro* resistance development was a slow and stepwise process with resistant *S. aureus* clones being selected at sub-MIC levels only after 22-42 passages, whereas no stable resistant clones could be selected for *S. pyogenes* and *S. pneumoniae*.

Susceptibility testing of lefamulin was performed with >13,600 contemporary clinical isolates including >7800 staphylococcal strains (including MRSA and methicillin-susceptible *S. aureus* [MSSA] strains) collected from patients world-wide, including the SENTRY Antimicrobial Surveillance Program (SENTRY) in 2010 (Paukner et al, 2013). Lefamulin demonstrated *in vitro* antibacterial activity (MIC_{90}) against the most relevant respiratory pathogens including *S. pneumoniae* (0.25 µg/mL), *H. influenzae* (2 µg/mL), *M. catarrhalis* (0.25 µg/mL), *L. pneumophila* (0.5 µg/mL), *M. pneumoniae* (0.006 µg/mL), and *C. pneumoniae* (0.04 µg/mL). When compared with other antibiotics used to treat bacterial pneumonia such as macrolides, ß-lactams, fluoroquinolones or doxycycline, lefamulin was among the most active compounds *in vitro* irrespective of resistance phenotype present in *S. pneumoniae* or *H. influenzae*. Furthermore, lefamulin showed complete activity (100% susceptibility) against *S. pneumoniae* that are resistant to macrolides (36.2-37.4%; SENTRY 2010) or to levofloxacin (1.0-1.1%; SENTRY 2010) (Sader et al., 2012; Paukner et al., 2013).

Analysis of *in vitro* bacterial-killing properties suggested that lefamulin exhibits bactericidal activity against *S. pneumoniae* and *H. influenzae,* while it is predominantly a bacteriostatic agent against *S. aureus*. *In vivo*, the extent of bacterial killing in neutropenic mice was excellent for most strains of *S. pneumoniae* and moderate for strains of *S. aureus*.

The potential for synergy/antagonism of lefamulin with various currently marketed antibiotics was evaluated using the broth microdilution technique according to CLSI (M7-A9, 2012) for *S. aureus* (*n* = 6), *S. pneumoniae* (*n* = 6), ß-hemolytic *S. pyogenes* (*n* = 3), *S. agalactiae* (*n* = 3), *H. influenzae* (*n* = 6), *Enterobacteriaceae* (*n* = 10) and *P. aeruginosa* (*n* = 2). Lefamulin was largely indifferent/additive when combined with other antibacterial agents and did not exhibit an antagonistic effect with any antibiotic against any bacterial strains tested, including those with important resistance phenotypes (e.g., MRSA and ESBL). No apparent synergy was observed with the exception of a trend towards synergy observed against *S. aureus* isolates when lefamulin was combined with doxycycline (in 5 of 6 tested isolates) and for all *S. pneumoniae* isolates (6 of 6 tested isolates) when lefamulin was combined with aztreonam. Based on studies completed to date, there is no potential concern if lefamulin is used in combination with other antibacterial agents.

Lefamulin accumulated 30- to 50-fold in murine macrophages at clinically relevant concentrations of 1 and 5 µg/mL. The antimicrobial potency of lefamulin was unaffected by lung surfactant.

A number of animal infection models have established the *in vivo* efficacy of lefamulin, including the septicemia, thigh infection, and pneumonia models in mice. Lefamulin has proven to be highly efficacious against *S. aureus* (MSSA and MRSA) and *S. pneumoniae* (penicillin-susceptible and penicillin-resistant *S. pneumoniae*). Evaluation of the

pharmacokinetic/pharmacodynamic (PK/PD) target associated with efficacy was performed using a neutropenic murine thigh and lung infection model. The major parameters driving efficacy for both *S. aureus* and *S. pneumoniae* were the 24 h area under the drug concentration–time curve (AUC) over the MIC (24 h AUC/MIC) followed by the duration of time plasma concentrations exceeded the MIC ($T_{>MIC}$). The activity of the drug was only minimally diminished in immunocompromised mice in comparison to immuno-competent mice. In lung infections caused by *S. pneumoniae* or *S. aureus*, lefamulin showed enhanced activity when compared to the outcome in the murine thigh infection model. Investigations of the exposure levels in the epithelial lining fluid (ELF) in mice were consistent with the observed good efficacy against lung infections. For the PK/PD analyses, the plasma 24 h *f*AUC/MIC ratio, as well as the AUC at site of infection over the MIC (24 h AUC_{ELF}/MIC ratio), were evaluated on the basis of murine lung infections caused by *S. pneumoniae* and *S. aureus*.

1.4 Nonclinical Pharmacokinetics and Safety

Pharmacokinetic studies after oral and IV administration demonstrated a dose proportional systemic exposure of lefamulin in all species tested. Moderate to high plasma protein binding of 73 % to 88 % in humans and 61 % to 81 % in animals was observed. However, lefamulin displayed low binding affinity to the 2 major drug binding human plasma proteins (human serum albumin [HSA] and α1-acid glycoprotein [AGP]) and, despite the observed moderate to high protein binding, its *in vitro* antimicrobial activity was maintained in the presence of serum. This is suggestive of a weak and loose association of the drug with plasma proteins and probably explains the rapid tissue distribution observed across the species, including humans. Quantitative whole body autoradiography in rats after IV bolus administration showed rapid distribution into tissues and organs consistent with the apparent low protein binding affinity observed *in vitro*. The concentrations measured in the majority of the tissues including skin and soft tissues and lungs were higher compared to the amounts measured in blood.

In vitro metabolic stability testing of lefamulin predicted a mild to moderate influence of Phase I reactions by CYP450 enzymes on its overall metabolism, while Phase II metabolism will have only a very limited effect. Using isolated recombinant CYP450 isoenzymes, CYP3A4 and 3A5 were identified as lefamulin metabolizing enzymes. Lefamulin did not inhibit CYP1A, 2B6, 2C9, 2C19, 2D6, 2C8, or 2E1 to a clinically relevant extent. Lefamulin was identified as a p-glycoprotein (p-gp) substrate and a p-gp inhibitor and was capable of saturating its own efflux in Caco-2 cells. This observation is in-line with the observed dose-dependent increase in bioavailability, as seen in the oral single ascending dose study in humans (NAB-BC-3781-1101). Lefamulin did not induce CYP1A2 and CYP3A4 in human hepatocytes. Consequently, it is not expected that lefamulin will induce CYP1A2 and CYP3A4 or p-gp in a clinical setting.

All data obtained so far suggest that the non-renal route of excretion drives the clearance of lefamulin. Fecal excretion in the bile (and/or via the gut mucosa) is likely the most important route of elimination for this compound, as confirmed by a mass balance study in rats, showing 96 % total recovery, mainly in feces (82 %) and urine (14 %). Furthermore, all

intra-organ radioactivities approached the lower limit of quantification (LLQ) within 72 h, indicating a total elimination of the drug and/or its metabolites.

The safety of lefamulin has been investigated in a number of safety pharmacology and toxicology studies conducted *in vitro* and *in vivo* in different rodent and non-rodent animal species. Safety and toxicology studies have been performed to support oral and IV use in human. Studies include acute and repeated dose toxicity, local tolerance and genotoxicity testing, development and reproductive toxicity, safety pharmacology, and PK/toxicokinetic profiling in rodent and non-rodent species. No clear differences between male and female animals were seen in toxicity or absorption, distribution, metabolism, and elimination (ADME) studies.

Lefamulin did not show any effects on the central and autonomic nervous system in rats or on the respiratory system in cynomolgus monkeys. A potential for QT/QTc interval prolongation was noted after a single IV dose of 40 mg/kg. *In vitro* I_{Kr} (hERG) assays and a study using rabbit Purkinje fibers showed a potential for QT/QTc prolongation, but did not demonstrate any pro-arrhythmic potential for lefamulin at clinically relevant concentrations.

Four-week, IV, repeat-dose toxicity studies in rats and monkeys resulted in NOAELs of 75 and 120 mg/kg daily dose, respectively, the highest doses tested. The NOAEL in pivotal 4-week oral repeat-dose toxicity studies in rats and cynomolgus monkeys was 300 and 70 mg/kg daily dose, respectively. In both species, the pivotal repeat-dose toxicity studies did not indicate any systemic target organ toxicity.

Intravenous administration to rats resulted in local effects at the infusion site. These reversible local effects are likely induced by inflammatory irritation caused by the indwelling catheter together with lefamulin. The effect might have been more pronounced due to the small vessel size and the lower blood flow/volume in rats. Intravenous administrations to monkeys up to and including 120 mg/kg/day did not show any signs of local intolerance.

Oral administrations in monkeys up to and including 70 mg/kg/day were well tolerated by the gastrointestinal (GI) tract. Doses of 200 mg/kg/day caused emetic periods and diarrhea associated with body weight loss and poor physical condition. Gastrointestinal tract intolerability following oral dosing of 600 and 450 mg/kg/day was also described in rats. The dose of 70 mg/kg/day corresponds to 4 200 mg daily in 60 kg humans and exceeds the maximum intended daily dose of 1 200 mg. Lefamulin did not evidence any genotoxic potential, as demonstrated by *in vitro* and *in vivo* mutagenicity and clastogenicity assays.

No treatment-related changes were noted in female or male reproductive organs of rats or monkeys following 14 or 28 days repeated dosing. Embryo-fetal development toxicity studies with lefamulin performed in rats and rabbits did not indicate a potential for teratogenicity and the corresponding NOAELs were set at the highest doses tested, 100 and 60 mg/kg/day (IV), respectively. Fertility studies performed in rats did not show any adverse effect on reproductive indices and the NOAEL was established at 75 mg/kg/day (IV), the highest dose tested in both genders.

BC-8041, the main human metabolite of lefamulin, did not demonstrate a potential for QT/QTc prolongation (hERG assay) or genotoxicity (Ames and mouse lymphoma assay), and exhibited no teratogenicity in a rat embryo-fetal development toxicity study.

The safety and toxicology program provided sufficient and pertinent information on the safety profile of lefamulin and its main human metabolite, BC-8041, concluding that the drug candidate has no indices of toxicity in animals that would preclude its use in humans. These studies are described in more detail in the Investigator's Brochure.

1.5 Summary of Clinical Data

Lefamulin has been administered as single or multiple-doses orally and by IV infusions to healthy subjects in 17 completed Phase 1 studies and IV to subjects with ABSSSI in a completed Phase 2 study. In these studies, lefamulin was found to be well tolerated at the doses that exceed those to be used in the current study (i.e., 600 mg per oral administration).

In the 17 Phase 1 studies, 321 male and female healthy subjects were exposed to lefamulin, 12 of whom were ≥ 65 years of age. In the Phase 2 study, 141 subjects (95 male, 46 female) were exposed to lefamulin, 7 of whom were ≥ 65 years of age (4 in the 100 mg group, 3 in the 150 mg group) (Prince et al., 2010; Prince et al., 2013; Wicha et al., 2010; Zeitlinger et al., 2011).

1.5.1 Pharmacokinetics in Humans

Tissue distribution studies in healthy volunteers showed rapid lefamulin distribution achieving therapeutic exposures in relevant target tissues for the treatment of both respiratory tract and skin infections following IV and PO administration. Following a single 150 mg IV infusion, lefamulin showed higher exposure in epithelial lining fluid (ELF) as compared to the penetration into skin tissues (Zeitlinger et al., 2016). This pattern of tissue distribution has also been observed in ELF of mice. Therefore, the exposures in plasma and in ELF were used for the determination of the AUC/MIC ratio for target attainment analyses.

The plasma concentration-time curve of intravenously administered lefamulin in humans showed a multi-phasic decline. Following the end of infusion (i.e., the maximal concentration [C_{max}]), there is a rapid distribution phase over 0.5 h followed by an extended elimination phase with a mean half-life ($t_{1/2}$) of 8.6 h to 11.8 h. The major elimination route for lefamulin was non-renal. There were no statistically significant effects of age, demographics (body weight, height, or body mass index) or gender on the PK parameters of lefamulin. In addition, no significant influence of the health status on the total body clearance or drug distribution of lefamulin was observed.

Oral administered lefamulin is characterized by a plasma concentration time curve with a rapid absorption describing a bimodal peak, suggesting a mixed order absorption. The initial peak plasma concentration occurs 20-60 minutes after administration, followed by a second peak observed between 1-4 hours after dosing. Following every 12 hour intravenous infusion or oral administration, steady-state is achieved after two days and thereafter, trough levels (C_{min}) remain consistently linear throughout the duration of the treatment. After oral

administration of an immediate-release (IR) tablet containing 600 mg of lefamulin, exposure — as measured by AUC (the driver of efficacy) — was equivalent to a 150 mg IV dose, the higher of 2 doses evaluated in the Phase 2 study of lefamulin in the treatment of ABSSSI (NAB-BC-3781-2001) (Wicha et al., 2013).

Lefamulin was best absorbed when taken on an empty stomach. A food-effect study involving administration of lefamulin to healthy female and male volunteers under fasting conditions and with a high-fat meal indicated an effect of food on the absorption process and bioavailability of lefamulin. The CI_{90} % for both C_{max} and AUC were outside of the recommended acceptance range of 80 %-125 %. While the reduced C_{max} is seen as not clinically relevant in terms of efficacy, the effect of the decreased AUC was evaluated using PK/PD analysis. Exposure response (PK/PD) analysis based on an oral popPK model, robust surveillance data, and pre-clinically derived free plasma AUC/MIC ratio targets against *S. pneumoniae* and *S. aureus* showed a high probability of success of ≥ 99.4 % regardless of food. However, in the simulation of lung exposures in ELF (AUC_{ELF}/MIC) using the modified popPK model overall probability dropped down to ≥ 85.6 % in the fed population on Day 1, with a morning and an evening dose after a high fat, high calorie meal. Although we believe that the probability analysis based on the simulated fed state data represent a worst case scenario for oral absorption and that the prediction of ELF exposures might be underestimated, to mitigate any risk associated with co-administration of oral lefamulin with food during the Phase 3 oral trial, we plan to recommend in the protocol that study drug be administered at least 1 hour before a meal or 2 hours after a meal.

Overall, lefamulin metabolism is low. In general, the PK profiles of the metabolites in plasma resemble the profiles of the parent drug, resulting in similar or shorter terminal $t_{1/2}$ values. BC-8041 was the only metabolite that could be identified exceeding the limit of 10 % of total drug related systemic exposure at steady-state when lefamulin was given orally. Therefore, accumulation of any metabolite is unlikely. BC-8041 exposure at steady-state in humans at lefamulin therapeutic doses is covered by toxicology studies in the cynomolgus monkey. In drug-interaction studies performed with lefamulin, no issues of clinical significance have been identified so far. In drug-interaction studies with midazolam or ketoconazole, lefamulin can be classified as having only a weak interaction with CYP3A after IV administration. Oral co-administration of ketoconazole and lefamulin resulted in a moderate interaction, likely as a result of a reduced first-pass effect in the gut wall. Based on the current safety profile of lefamulin and its main metabolite, BC-8041, it is not expected that a drug-drug interaction with potent CYP3A and p-gp inhibitors will be of sufficient clinical significance to justify a dose adjustment.

Most recently, a Phase 1 study (NAB-BC 3781-1107) evaluating the safety, absolute and relative bioavailability, and the potential effect of co-administration of food on the pharmacokinetics of lefamulin administered as a 600 mg immediate release tablet compared with the IV formulation and a capsule formulation containing lefamulin API was completed. This study demonstrates that the AUC of lefamulin achieved with the 600 mg IR tablet formulation in the fasted state is comparable with that observed following administration of a 150 mg IV dose. A lower C_{max} (901 ng/mL), $AUC_{0\text{-}inf}$ (6 630 ng·h/mL), and bioavailability (21.0% versus 25.8 %) were observed with the 600 mg IR tablet in the fed compared with the fasted state.

1.5.2 Efficacy

The efficacy of lefamulin in humans has been demonstrated in a Phase 2 study of 207 subjects with ABSSSI comparing 2 lefamulin doses (100 mg and 150 mg IV) with vancomycin (≥ 1000 mg) over 5-14 days. This study enrolled subjects with moderate to severe skin infection, excluding any subjects with minor and uncomplicated infection. In total, 90.8 % of subjects in the modified ITT population had *S. aureus* infection; 69.1 % of subjects had MRSA.

In all populations evaluated, lefamulin 100 mg (IV) and 150 mg (IV) demonstrated consistently high clinical and microbiological success rates at several time points including the Early Clinical Response visit (Day 3) and Test of Cure (TOC), and 7 to 14 days after the completion of therapy (modified ITT population: 82.0 % and 82.4 % for 100 mg and 150 mg q12h treatment arms, respectively; 82.4 % for vancomycin).

There were no significant differences in clinical success rates and microbiological eradication rates when assessed by baseline pathogen, particularly *S. aureus* and MRSA. Furthermore, no development of decreasing susceptibility was observed for lefamulin during the study (Paukner et al., 2012; Prince et al., 2013; Rubino et al., 2015).

1.5.3 Safety

No changes in safety laboratory parameters, blood pressure (BP), heart rate (HR), or body temperature in any subject at any session in any study were of clinical concern. After IV administration, pain and erythema at the infusion site were the most frequently reported findings. The oral administration of lefamulin was generally well tolerated; infrequent mild and reversible gastrointestinal findings (nausea, abdominal pain and diarrhea) were reported. There were no systemic AEs of clinical concern and no drug-related SAEs in any study conducted to date. None of the subjects met withdrawal or stopping criteria.

In the Phase 2 study in subjects with ABSSSI, lefamulin (100 mg and 150 mg) administered intravenously over 5 to 14 days was generally well tolerated. The incidence of treatment-emergent adverse events (TEAEs) considered related to study drug was comparable across lefamulin treatment arms (34 % and 39 % in the 100 and 150 mg groups, respectively) versus subjects treated with vancomycin (53 %). The types of TEAEs were consistent with a subject population under treatment for ABSSSI. The most frequently reported treatment-related TEAEs in subjects receiving lefamulin were headache, nausea, and diarrhea. Phlebitis at the infusion site was reported in 4 subjects in the lefamulin 100 mg group and 2 subjects in the 150 mg group. There was no increased incidence of phlebitis with increased dose. The most frequently reported treatment-related TEAEs for the vancomycin group were headache, nausea, pruritus, generalized pruritus, and diarrhea. All other related TEAEs were reported by 3 or fewer subjects in each treatment group.

In the Phase 2 study, study drug was discontinued due to an AE for 6 subjects (8 events). These AEs were hyperhidrosis, vomiting, headache, respiratory failure (an SAE), cellulitis, infusion site pain, and dyspnea in the lefamulin groups; and drug eruption in the vancomycin group. Six of these 8 events were considered related to study drug (hyperhidrosis, vomiting,

headache, infusion site pain, and dyspnea in the lefamulin groups and drug eruption in the vancomycin group). Five subjects experienced an SAE; none was considered related to study drug. These SAEs were abscess, respiratory failure, and cellulitis in the lefamulin groups; and accidental overdose (narcotics) and convulsion in the vancomycin group (Prince et al., 2013).

The effect of lefamulin on the cardiac conduction parameters of RR, QT, and QTcF has been closely monitored in all clinical studies. A C_{max}-dependent, predictable, and reproducible prolongation of the QT/QTcF interval has been observed. A thorough analysis of ECGs in the Phase 2 study demonstrated that lefamulin prolonged cardiac depolarization and repolarization duration, but otherwise had a similar cardiac safety profile to that of vancomycin based on evaluations of 12-lead ECGs. Therefore, it is expected that lefamulin will not produce large effects on cardiac de- and repolarization duration. No drug-related cardiac AE — such as increase in ectopic ventricular activity or other cardiac arrhythmia — or clinically relevant ECG findings was reported during the conduct of the studies. None of the protocol-defined stopping criteria (i.e., QTcF > 500 ms and ΔQTcF > 60 ms) was reached in any clinical study.

In summary, the results of the Phase 2 study provide the first proof of concept for the systemic use of a pleuromutilin antibiotic in subjects and support the further clinical evaluation of lefamulin for therapy of serious infections. Pharmacokinetic/ pharmacodynamic analyses suggest that lefamulin 150 mg IV q12h is an efficacious dosing regimen for Phase 3 studies. Based on available safety data, lefamulin 150 mg IV q12h produced therapeutic exposures and demonstrated an acceptable benefit/risk profile for the treatment of infected subjects. Oral doses of 600 mg lefamulin produced similar systemic exposures to 150 mg IV with a similar benefit/risk profile and were well tolerated in Phase 1 studies with no signs or symptoms of clinical concern.

This is the first Phase 3 study to be conducted in subjects with CABP to be treated only with oral administration of pleuromutilin antibiotic. Subjects will receive treatment with either lefamulin or moxifloxacin, a standard of care treatment for CABP.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- 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 **(FDA endpoint).**
- Demonstrate the NI of lefamulin versus comparator with respect to the Investigator's Assessment of Clinical Response at Test of Cure (TOC) (i.e., 5-10 days after the last dose of study drug) in the modified-ITT (mITT) and Clinically Evaluable at TOC (CE-TOC) Analysis Sets **(EMA endpoint)**.

2.2 Secondary Objectives

- Evaluate the Early Clinical Response in the Microbiological Intent-to-Treat (microITT) Analysis Set.
- Evaluate the Investigator's Assessment of Clinical Response at TOC in the microITT and Microbiologically Evaluable at TOC (ME-TOC) Analysis Sets.
- Evaluate 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.

2.3 Additional Objectives

- Evaluate the Early Clinical Response by baseline pathogen in the microITT Analysis Set.
- Evaluate the Investigator's Assessment of Clinical Response at the End of Treatment (EOT) (i.e., within 2 days after the last dose of study drug) and at LFU in the mITT and 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 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 Early Clinical Response PLUS improvement in vital signs in the ITT Analysis Set.
- Evaluate the plasma pharmacokinetics (PK) of lefamulin and its main metabolite, BC-8041, in the PK Analysis Set.
- Explore a variety of health utilization variables and an investigational patient reported outcome (PRO) measure in subjects receiving lefamulin compared with subjects receiving comparator.

3 STUDY DESIGN

This multicenter, multinational, randomized, double-blind, double-dummy, active-controlled efficacy and safety study in subjects with CABP will be conducted at approximately 160 centers. The planned enrollment is 738 subjects (369 subjects in the lefamulin group and 369 subjects in the moxifloxacin group) with PORT Risk Class II, III, or IV. Eligible subjects will be randomized 1:1 to lefamulin or moxifloxacin, using an interactive response technology (IRT). Subject randomization will be stratified according to PORT Risk Class (Risk Class II vs. III/IV), geographic region (US vs. ex-US), and prior (single dose) short-acting antibiotic therapy for CABP vs. none.

Subjects will be consented for the study prior to study assessments being performed and confirmation of eligibility (see Section 4). Screening assessments will be performed within 24 hours before first dose of study drug.

Subjects will be assessed for response at the following time points during the study:

- Early Clinical Assessment (ECA): 96 ± 24 hours after the first dose of study drug.
- End of Treatment (EOT): within 2 days after the last dose of study drug (NOTE: every attempt should be made to conduct the EOT visit within 1 day after the last dose of study drug. However, if this is not logistically feasible [e.g., visit would need to be conducted over a weekend], then conducting the visit within 2 days is acceptable.).
- Test of Cure (TOC): 5-10 days after the last dose of study drug.
- Late Follow Up (LFU): Day 30 (±3 days).

As discussed in detail in Section 6.11, assessment of the 4 cardinal symptoms of CABP (dyspnea, cough, purulent sputum production, and chest pain) will be conducted daily; an assessment at 96 ± 24 hours after the first dose of study drug will determine Early Clinical Response (ECR) (as defined in the Primary Objective - FDA). NOTE: ECR will be determined programmatically based upon the Investigator's assessment of the 4 cardinal symptoms of CABP; the decision to maintain the subject on study drug therapy will be made by the Investigator, based on all available data and his or her best clinical judgment. In addition, as discussed in Section 6.12, the Investigator's Assessment of Clinical Response (IACR) will be performed at the EOT, TOC and LFU visits (Success, Failure and Indeterminate at EOT and TOC; Sustained Success, Relapse and Indeterminate at LFU).

Microbiological assessments will be performed at Screening, and throughout the study as clinically indicated (see Section 6.15). Samples will be taken for Gram's staining, for diagnostic tests (serology, urine antigen tests, molecular tests), and for culture and antimicrobial susceptibility testing. Subjects who have confirmed *S. aureus* bacteremia must be withdrawn from the study.

Safety will be assessed by monitoring vital signs and oxygen saturation, ECG measurements, safety laboratory parameters, and recording of adverse events (AEs) (see Sections 6.5, 6.4, 6.13, and 7). A Data Monitoring Committee (DMC) will review the safety data throughout the study (see Section 10.2).

Blood samples for PK analyses will be collected from all subjects (see Section 6.14).

Exploratory evaluation of a variety of health utilization variables (e.g., length of hospital stay, duration of antibiotic therapy, discharge status, discharge destination) as well as a PRO instrument (SF-12) will be administered. The schedule of study procedures and an overview of study designs are provided in the synopsis (Table 1. Schedule of Assessments and Procedures and Figure 1. Study Design Overview).

3.1 Study Rationale

Lefamulin (BC-3781), a semi-synthetic pleuromutilin, represents a new class of antibiotics for systemic use in the treatment of bacterial infections in humans. Based on the antibacterial spectrum, safety and tolerability and PK in several Phase 1 and Phase 2 clinical studies, lefamulin should be a viable option for the treatment of CABP. The adverse event profile observed in Phase 1 and 2 studies conducted to date demonstrates that lefamulin is well tolerated when administered IV at single doses up to 400 mg and q12h dosing for up to 10 days. Also, the oral safety profile observed in studies conducted to date demonstrates that 600 mg of lefamulin is well tolerated when administered as single and repeat doses. In the first study in which a systemically available pleuromutilin antibiotic was administered to a patient population, Study NAB-BC-3781-2001, lefamulin was found to be safe and effective in treating skin and skin structure infections and supported the continued clinical evaluation of lefamulin for serious infections. In animal models of lung infections caused by *S. pneumoniae* or *S. aureus*, lefamulin showed enhanced activity when compared to the outcome in the murine thigh infection model. Tissue distribution studies in healthy volunteers showed rapid lefamulin distribution, achieving therapeutic exposures in relevant target tissues for the treatment of both respiratory tract and skin infections. Following a single 150 mg IV infusion, lefamulin showed higher exposure in epithelial lining fluid (ELF) as compared to the penetration into skin tissues (Zeitlinger et al., 2016). Lefamulin is therefore being examined further in subjects with CABP.

This study will examine whether lefamulin is non-inferior to moxifloxacin for the treatment of CABP in adults ≥ 18 years of age. The comparison between lefamulin and comparator will be made with respect to the following assessments: ECR (96 ± 24 hours after the first dose of study drug), as well as IACR at TOC. The study will also compare safety between treatment groups and evaluate PK parameters of lefamulin in this population.

This protocol is designed to address both the FDA and European Medicines Agency (EMA) regulatory requirements for the development of antibacterial agents to treat CABP, which differ regarding the preferred primary endpoint. The EMA supports assessment of clinical response by Investigators at a test of cure (TOC) visit, while the FDA adopted assessment of clinical signs and symptoms of CABP on Days 3 to 5 as the recommended primary endpoint. To adequately accommodate these differences, 2 separate regional Statistical Analysis Plans (SAPs) will be utilized to analyze the data collected during this study.

4 STUDY POPULATION

4.1 Inclusion Criteria

Each subject must:

1. Be male or female ≥ 18 years of age.
2. Provide written informed consent and be willing and able to adhere to the study-specified procedures and restrictions. NOTE: Consent may be provided by the subject's legally authorized representative in accordance with local regulations.

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.
4. Have at least 2 of the following vital sign abnormalities:
   - Fever (body temperature > 38.0 °C (100.4 °F) measured orally or equivalent temperature from an alternate body site) or hypothermia (body temperature < 35.0 °C (95.0 °F) 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).
5. Have at least 1 other clinical sign or laboratory finding of CABP:
   - Hypoxemia (i.e., 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 (e.g., crackles, egophony, dullness).
   - White blood cell (WBC) count > 10 000 cells/mm^3 or < 4 500 cells/mm^3 or >15 % immature neutrophils (bands) regardless of total WBC count.
6. Have radiographically-documented pneumonia within 48 hours before enrollment (i.e., infiltrates in a lobar or multilobar distribution or diffuse opacities on chest x-ray or chest computed tomography scan consistent with acute bacterial pneumonia).
7. Have a Pneumonia Outcomes Research Team (PORT) Risk Class of II, III, or IV and be an appropriate candidate for oral antibiotic therapy as treatment for the current episode of CABP.
8. If female, meets the following criteria:
   - Surgically sterile or ≥ 2 years postmenopausal, or if of childbearing potential (including being < 2 years postmenopausal), has a negative pregnancy test, and if participating in sexual activity that may lead to pregnancy, agrees to use an effective dual method of contraception (e.g., condom plus diaphragm, condom plus spermicide, intrauterine device plus spermicide) during the study and for ≥ 28 days after the last dose of study drug. If a male partner has been surgically sterile for ≥ 1 year, a single contraception method may be used. NOTE: The use of contraceptives containing progesterone is not permitted.
   - Agrees not to breastfeed during the study and through ≥ 28 days after the last dose of study drug.

9. If male, meets the following criteria:
    - If not surgically sterile and if participating in sexual activity that may lead to pregnancy, agrees to use an effective dual method of contraception (e.g., condom plus diaphragm, condom plus spermicide, intrauterine device plus spermicide, oral contraceptive plus condom) during the study and through ≥ 28 days after the last dose of study drug. If surgically sterile for ≥ 1 year, a single contraception method may be used.

4.2 Exclusion Criteria

Each subject must NOT:

1. Have received more than a single dose of a short-acting oral or IV antibacterial for CABP within 72 hours before randomization (See Appendix 2).
    - 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 (i.e., 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.
2. Require concomitant systemic antibacterial therapy potentially effective against CABP pathogens (See Section 6.9).
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.
4. Have confirmed or suspected CABP caused by a pathogen known to be resistant to any of the study drugs (e.g., MRSA, *Pseudomonas aeruginosa*, any pathogen of the *Enterobacteriaceae* Family) or attributable to etiologies other than community-acquired bacterial pathogens (e.g., ventilator-associated pneumonia, hospital-acquired bacterial pneumonia, bacterial aspiration pneumonia, *Pneumocystis jiroveci* pneumonia or other fungal pneumonia, viral or mycobacterial infection of the lung).
5. Have a noninfectious cause of pulmonary infiltrates (e.g., pulmonary embolism, chemical pneumonitis from aspiration, hypersensitivity pneumonia, congestive heart failure, bronchial obstruction, lung cancer, cystic fibrosis).
6. Have confirmed or suspected pleural empyema (does not include sterile parapneumonic effusions).
7. Have or be at risk for major cardiac events or dysfunction including, but not limited to, the following:
    - Known prolonged QT interval or family history of long QT syndrome
    - Clinically significant hypokalemia which has not been treated prior to randomization
    - Clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling pacemaker

- Complete left bundle branch block
- Receipt within 7 days before enrollment of Class IA or Class III anti-arrhythmic medication or, in the opinion of the Investigator, subject may require such medication during the study. (Class 1A: Quinidine, Procainamide, Disopyramide; Class III: Amiodarone, Dofetilide, Ibutilide, Sotalol)
- Receipt within 7 days before enrollment of medication that has the potential of prolonging the QT interval or, in the opinion of the Investigator, subject may require such medication during the study (see Appendix 5).

8. Be receiving a strong p-glycoprotein inhibitor or a strong CYP3A inducer or inhibitor (see Appendix 4).
9. Have a history of tendon disease/disorder, myasthenia gravis, or known or suspected central nervous system (CNS) disorders (severe cerebrovascular arteriosclerosis, epilepsy, or other risk factors that may predispose to seizures).
10. Have a history of any hypersensitivity or allergic reaction to any fluoroquinolone, or any drug in the pleuromutilin class (i.e., retapamulin).
11. Have severely impaired renal function, defined as estimated creatinine clearance (CrCl) ≤30 mL/min as calculated by the Cockcroft-Gault formula.
12. Have evidence of significant hepatic, hematologic, or immunologic disease including any of the following:
    - Known acute hepatitis, including acute viral hepatitis.
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 5 times the upper limit of normal (ULN),
    - Total bilirubin > 3 times the ULN (unless known Gilbert's disease).
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 3 times the upper limit of normal (ULN) and total bilirubin > 2 times the ULN.
    - History of cirrhosis of the liver.
    - Manifestation of end-stage liver disease, such as ascites or hepatic encephalopathy.
    - Current or anticipated neutropenia (<500 neutrophils/mm^3).
    - Thrombocytopenia (<50,000 platelets/mm^3).
    - Known infection with human immunodeficiency virus and a CD4 count < 200/mm^3.
13. Have known severe immunosuppression, including but not limited to receipt of corticosteroid therapy (≥20 mg of prednisone/day or equivalent for >4 weeks) within the previous 8 weeks; solid organ or bone marrow transplantation within the previous 12 months; or currently receiving cytotoxic chemotherapy.
14. Have a life expectancy of ≤ 3 months because of any disease other than the current episode of CABP (e.g., current or impending respiratory failure, acute heart failure, shock, acute coronary syndrome, unstable arrhythmia, hypertensive emergency, clinically

relevant gastrointestinal bleeding, profound metabolic abnormality, or acute cerebrovascular event).

15. Have participated in any study involving administration of an investigational agent or device within 30 days or ≤ 5 terminal elimination half-lives of the previous investigational medicinal product, whichever is longer, before enrollment.
16. Have been previously treated with lefamulin or previously enrolled in this study.
17. Have any condition that, in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data.

5 STUDY DRUG ADMINISTRATION

See Section 8 for a complete description of study drugs. Instructions for the preparation of study drugs will be provided in a Pharmacy Manual.

5.1 Selection of Lefamulin Doses

This is the first study of an all oral regimen of lefamulin in subjects with CABP. Based on results obtained from *in vitro*, animal and human experiments conducted to date, lefamulin is predicted to be well tolerated and efficacious in CABP. To further explore and validate these findings, a pharmacometric approach was employed to assess a lefamulin dosing regimen of 150mg IV q12h for the treatment of subjects with CABP caused by *S. pneumoniae* or *S. aureus*. This approach has been utilized previously to support dose selection decisions in antibacterial drug development (Bhavnani et al., 2005; Bhavnani et al., 2009; Van Wart et al., 2009). An oral dose of 600 mg q12h (also being used in the IV-to-Oral Phase 3 study, NAB-BC-3781-3101) has been shown to provide similar exposure (e.g., AUC) as the 150 mg IV dose. Since the primary PD driver of lefamulin efficacy is total drug exposure (AUC), 600 mg q12h given as an oral tablet is expected to provide equivalent therapeutic coverage as the 150 mg IV q12h regimen.

A population PK model describing the disposition of lefamulin, non-clinical PK/PD targets for lefamulin activity against *S. pneumoniae* and *S. aureus* (derived from robust surveillance data for both pathogens), and Monte Carlo simulation were utilized to carry out PK/PD target attainment analyses.

The population PK model used to conduct Monte Carlo simulations was developed using PK data from 11 Phase 1 studies of subjects who received IV or oral lefamulin and 1 Phase 2 study of infected subjects with ABSSSI who received IV lefamulin. Importantly, this dataset includes data describing the disposition of lefamulin in epithelial lining fluid (ELF) (obtained from a Phase 1 study; the relevant site for treatment of CABP) as well as in subjects experiencing active infection (the Phase 2 ABSSSI study). Thus, the data used to construct the population PK model, the parameter estimates and associated variability incorporated into the Monte Carlo simulations are reflective of patients with CABP.

Non-clinical PK/PD targets were identified using PK/PD relationships for efficacy derived from data from a neutropenic murine-lung infection model. For these analyses, focus was

given to median 24 h AUC $_{ELF}$/MIC ratio targets for *S. pneumoniae* and *S. aureus* associated with a 1-$\log_{10}$ CFU reduction from baseline as it has been demonstrated that patients with CABP who attain a 1-$\log_{10}$ CFU reduction from baseline have a higher rate of successful response compared to those patients who did not attain such PK/PD targets. Lastly, in order to make inferences about dose for patients with *S. pneumoniae* or *S. aureus* bacteremia arising from CABP, the above-described analyses were also carried out using 24 h *f*AUC/MIC ratio targets for a 1-$\log_{10}$ CFU reduction from baseline efficacy for both pathogens. The MIC distributions utilized were based on large, contemporary isolate libraries that represent > 1400 *S. pneumoniae* and > 5500 *S. aureus* isolates, accrued globally.

Based on pharmacokinetic data derived from subjects receiving lefamulin 600 mg orally in the fasted state, the percent probabilities of attaining the median AUC_{ELF}/MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline by MIC were >95 % at a MIC of 0.5 µg/mL for *S. pneumoniae* and >97 % at a MIC of 0.25 µg/mL for *S. aureus*. In the fed state (i.e. when subjects ingest a high-calorie, high-fat meal), the percent probabilities of achieving similar AUC_{ELF}/MIC ratio targets were >85% and >91% for *S. pneumoniae* and *S. aureus*, respectively. Based upon these analyses, oral lefamulin will be administered in the current study either 1 hour before a meal or 2 hours after a subject ingests a meal to mitigate against any potential negative effect associated with co-administration with food.

The results obtained from PK/PD target attainment analyses using a population PK model describing the disposition of lefamulin, non-clinical PK/PD targets for lefamulin against *S. pneumoniae* and *S. aureus*, robust surveillance data, and Monte Carlo simulation support the selection of lefamulin 600 mg PO q12h as well-tolerated, having a high probability of efficacy and an appropriate dosing regimen to be studied for the treatment of adult subjects with CABP.

5.2 Selection of Comparator

The Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) treatment guidelines recommend the use of an anti-pneumococcal fluoroquinolone for hospitalized patients (not in the ICU) with CABP. The guidelines also recommend a fluoroquinolone for outpatients with certain co-morbid conditions, outpatients who have used antimicrobials in the previous few months, and outpatients in regions with high rates of macrolide-resistant *S. pneumonia* regardless of co-morbidities or prior antibiotic use. *The European Society of Clinical Microbiology and Infectious Diseases* also supports the use of fluoroquinolones for outpatient treatment of CABP in areas with increased bacterial resistance rates to tetracyclines and macrolides, as well as for empiric therapy in hospitalized patients with CABP. These guidelines also note that respiratory quinolones may offer advantages over other therapy options for *Legionella* infection and that moxifloxacin has the highest antipneumococcal activity.

Therefore, in order to provide a robust comparison of oral lefamulin to an oral CABP treatment regimen that would be appropriate in multiple regions and in patients with and without co-morbidities, respiratory fluoroquinolones were considered the comparator of choice. Moxifloxacin was chosen over other respiratory fluoroquinolones because the labels of other fluoroquinolones have variable dose and/or treatment durations for CABP depending

on the specifics of approved labels in other countries. In addition, other respiratory fluoroquinolones require adjustment in settings of renal dysfunction which would complicate treatment regimens and create challenges with maintaining the blind.

5.3 Randomization

Qualified subjects will be randomized to receive lefamulin or moxifloxacin in a 1:1 allocation ratio. Randomization may occur following the required assessments and prior to administration of the first dose of study drug.

Randomization will be stratified by PORT Risk Class (Risk Class II vs. III and IV; see Section 6.3), geographic region (US vs. ex-US), and prior (single dose) short-acting antibiotic therapy for CABP vs. none using blocked randomization via IRT. (NOTE: No more than 25 % of randomized subjects will have received a single dose of a short-acting antibiotic). A minimum of 50% of the total number of subjects randomized will have a PORT Risk Class of III or IV.

The randomization schedule will be generated by Nabriva (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. Prior to dosing, study personnel will contact the IRT system to obtain a treatment assignment. Subjects are considered randomized once a randomization number has been assigned regardless of whether the subject receives study drug. Randomized subjects who do not receive study drug or who discontinue participation in the study for any reason will not be replaced.

5.4 Study Drug Treatment

The duration of blinded study drug administration will be 7 days.

Subjects randomized to lefamulin will receive oral lefamulin 600 mg q12h for 5 days (10 doses) and oral moxifloxacin placebo q24h for 7 days (7 doses). Subjects randomized to moxifloxacin will receive oral moxifloxacin 400 mg q24h for 7 days (7 doses) and oral lefamulin placebo q12h for 5 days (10 doses).

On Day 1, study personnel will administer the first dose of study drug at the study site to all subjects, as soon as possible after the diagnosis of CABP and completion of all required Day 1 procedures as outlined in Table 1. While subjects are hospitalized, all doses of study drug will be administered by hospital staff or study personnel.

For Outpatients, or in the event a subject is discharged from the hospital during the study drug administration period, an adequate supply of study drug will be dispensed for self-administration at home. Subjects will be provided instructions regarding the dosing schedule. Subjects may self-administer oral study drug at home with the following exception: Study personnel will advise subjects who are Outpatients that they must return to the study site to assess CABP signs and symptoms at 96 ± 24 hours after the first dose of study drug (see Section 6.11). Study personnel will inform Outpatients as to the timing of

this required study site visit. Subjects will be advised not to take their first dose of study drug at home that day, rather to bring their blister packs (used and unused) to the study site where they will take their dose while supervised, so that specific assessments can be performed both prior to and after taking the dose (see Sections 6.4 [ECGs] and 6.14 [PK]).

On Study Day 1, if q12h dosing is not feasible, the 1st and 2nd doses may be administered as close as 8 hours apart, in order to allow 2 doses to be given on Day 1. In this circumstance, the subject's dosing schedule should be adjusted on Day 2 to a regular q12h morning and evening schedule. Subsequently, every effort should be made to maintain a q12h dosing schedule. When this is not possible, it is acceptable to administer doses within 4 hours of the scheduled dosing time (i.e., a minimum of 8 hours between doses).

Study drug should be administered at least 1 hour before a meal or 2 hours after a meal. However, in the event that a subject has taken any of the following − antacids containing aluminum, products containing iron, or multivitamins containing zinc − study drug should be administered 2 hours before or 4 hours after consuming any of these medications. Doses should be administered with approximately 240 mL (8 ounces) of water.

The lot numbers and expiration dates of all study drugs supplied will be recorded.

5.5 Blinding

This is a double-blind, double-dummy study.

The study personnel, Sponsor (except as specified), and subject will not know what study drug is being administered.

Study drugs will be provided in blister packs and all study drug administration will utilize a "double-dummy" technique. Details about the double-dummy design and blinding are provided in a Study Procedure Manual. Lefamulin or matching placebo tablets will be provided by the Sponsor. Moxifloxacin will be over encapsulated; matching placebo tablets will also be provided by the Sponsor.

A member(s) of the Sponsor's Clinical Pharmacology group (or designee) will be unblinded to treatment assignment, as appropriate, in order to perform PK/PD assessments. A Data Monitoring Committee (DMC) will review study data by masked treatment group in accordance with the DMC Charter. In addition, as needed to meet regulatory reporting requirements on a country-by-country basis, designated pharmacovigilance personnel may be unblinded to treatment status of individual patients. In this circumstance, and if there are no other concerns, neither the Sponsor nor study personnel will be unblinded to treatment status.

5.6 Unblinding of Therapy Assignments

Unblinding of therapy assignment may be requested in an emergency if unblinding is considered necessary for medical management of the subject. In such a case, the Investigator must contact the Sponsor (or designee) and document the reason(s) for the request to unblind.

The Sponsor (or designee) must document any such communication with an Investigator. The IRT system will record the date of any unblinding of individual therapy assignments.

The study will be unblinded for all analyses after the study database is locked, which will occur after the last subject randomized in the study has completed the 30-day post treatment follow-up assessment period.

5.7 Adherence

If subjects are Inpatient, hospital staff or study personnel will administer all doses of study drug and will record the date and time of dosing. In addition, for Outpatients, any doses administered under supervision of study personnel in conjunction with assessments/ procedures (e.g., PK sampling, ECGs), study personnel will also record the date and time of those doses.

Outpatient subjects will be instructed to bring all used and unused blister packs to each study visit so that drug accountability can be reviewed by study personnel. Study personnel will collect all blister packs (empty or containing unused study drug) at the EOT visit (see Section 8.3.3). The total number of pills dispensed on Day 1 and returned at the EOT visit will be recorded in the eCRF.

5.8 Occupational Safety

Lefamulin and moxifloxacin being used in this study are not expected to pose a significant occupational safety risk to study personnel under normal conditions of use and administration.

A Material Safety Data Sheet describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from Nabriva Therapeutics AG.

6 STUDY ASSESSMENTS AND PROCEDURES

A schedule of study procedures is presented in Table 1. Subjects meeting the eligibility criteria listed in Section 4 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily given by the subject or the subject's legally authorized representative in accordance with local regulations.

Study personnel must complete all screening procedures after informed consent is signed and prior to the first dose of study drug. Note: Assessments performed as part of routine standard of care prior to consent (e.g., 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.

During the Study Drug Administration Period, the first dose of study drug is counted as 0 Hour on Day 1. The Investigator should make every effort to perform procedures at the

scheduled times and to record the actual time of the procedures, where appropriate, in the subject's eCRF.

For subjects who are screened (i.e., those with signed written informed consent) but who are not randomized, the reason for screening failure will be recorded.

6.1 Inpatient and Outpatient Assessments

As shown in the Schedule of Assessments and Procedures (see Table 1), the timing of assessments and procedures during the Study Drug Administration Period (Days 1-7) may differ between subjects who are Inpatient versus Outpatient.

Hospitalization is not a requirement for this study (i.e., subjects do not need to be admitted to the hospital to participate and those who are admitted may be discharged at any time at the discretion of the investigator).

While Inpatient, all assessments and procedures (including daily study drug administration) will be conducted at the study site/hospital in accordance with the schedule shown in Table 1 (Screening/Baseline through LFU). While Outpatient, the study site must contact the subjects by telephone daily to assess CABP signs and symptoms, assess for the presence of AEs, and determine changes in concomitant medications (see Sections 6.11, 7, and 6.8.2).

All subjects, including Outpatients, must be evaluated by at the investigational site by study personnel at the following time points/visits: Screening/Baseline; Day 1; 96 ± 24 hours after the first dose of study drug; EOT; TOC; and LFU (see Table 1).

6.1.1 Outpatient Visit for ECR Assessment and Other Site Procedures

Outpatients must return to the site for a face-to-face visit with study personnel 96 ± 24 hours (i.e., 72 to 120 hours) after the first dose of study drug. Study personnel will inform Outpatients as to the timing of this required study site visit in the course of the daily telephone contacts.

The purpose of this site visit is to assess CABP signs and symptoms which will be used to programmatically determine the ECR, as well as to perform other procedures that cannot be done by telephone (i.e., ECG, blood samples for PK analysis, blood samples for safety assessments, vital signs, and physical examination).

ECGs and blood samples for PK analysis must be performed within specified time windows before and after study drug administration. Therefore, it is **critical** that the subject be instructed to not take their first dose of study drug at home that day, rather to bring all their blister packs (used and unused) to the study site. The dose associated with the outpatient visit for ECR assessment and other site procedures will be taken under supervision of study personnel. In addition, as discussed in Sections 5.4 and 6.17, study personnel will remind subjects regarding adherence to the food and supplement restrictions when scheduling this visit.

6.2 Medical/Surgical History and Physical Examination

A medical and surgical history will be taken at Screening. All medical history findings that have been present or active within the 5 years prior to enrollment will be entered into the eCRF regardless of clinical relevance or presence at study start. Medical history findings that have not been present within the 5 years prior to enrollment will be recorded if deemed clinically relevant by the Investigator to the conduct of the study. The medical history should include drug allergy history, past and present smoking status, influenza virus and pneumococcal vaccination history, as well as the presence of influenza virus infection during the current illness.

A complete physical examination will be performed by the Investigator at Screening. At the time points specified in Table 1, subsequent directed physical examinations will be performed according to standard institutional practices and must be documented in source documents.

Body weight and height will be measured at Screening only.

6.3 PORT Risk Class Assessment

Study personnel will determine the subject's PORT Score (Table 2) and subsequent PORT Risk Class (Table 3) at Screening only.

Table 2. PORT Score Determination

Patient Characteristic	Point Assignment
Age	1 point for each year of age
Female	–10 if yes
Neoplastic disease history	+30 if yes
Liver disease	+20 if yes
Congestive heart failure	+10 if yes
Cerebrovascular disease	+10 if yes
Renal disease	+10 if yes
Altered mental status	+20 if yes
Respiratory rate ≥ 30 breaths/min	+20 if yes
Systolic blood pressure < 90 mmHg	+20 if yes
Temperature < 35 ºC (95 ºF) or ≥ 40 ºC (104 ºF)	+15 if yes
Pulse ≥125 beats/min	+10 if yes
pH <7.35 (from ABG)	+30 if yes (+0 if ABG not obtained)
Blood urea nitrogen > 30 mg/dL (Urea > 11 mmol/L)	+20 if yes
Sodium < 130 mmol/L	+20 if yes
Glucose ≥ 250 mg/dL (≥14 mmol/L)	+10 if yes
Hematocrit < 30 %	+10 if yes
Partial pressure of arterial O_2 < 60 mmHg (from ABG if medically indicated) or O_2 saturation < 90 % (by pulse oximetry)	+10 if yes
Pleural effusion on radiograph	+10 if yes
PORT SCORE	**Sum of Applicable Numbers Above**

Table 3. PORT Risk Class Determination

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

6.4 Electrocardiograms

Triplicate 12-lead ECGs will be performed within a 5-minute interval at time points specified in Table 1. The subject should be stabilized in a supine position for 5 minutes before recording the ECG. ECG recordings should allow a full assessment of QT intervals. Machine-read values for QTc/QTcF will be evaluated for determination of eligibility at Screening. If the quality of the ECG is insufficient then it must be repeated. All ECG data must be reviewed by the Investigator or designee and any findings of clinical significance found following Screening will be recorded as AEs in the eCRF. In addition, advice may be sought from appropriate cardiologists, if necessary. ECGs will be made available to the Sponsor for review and will be sent to a Cardiac Core Laboratory for further evaluation.

If Screening and Day 1 are on the same day, the Screening ECG can serve as the Day 1 ECG prior to the first dose of study drug; an additional ECG must be performed 1-3 hours after administration of first dose.

On Day 4 (Inpatients) or 96 ± 24 hour post first dose (Outpatients), ECGs in triplicate are required prior to the first dose of study drug and again within 1-3 hours after the first dose of study drug. Thus, Outpatients will be advised not to take their first dose of study drug at home that day, rather to bring their blister packs (used and unused) to the study site where they will take their dose while supervised so that the ECGs can be performed both prior to and after taking the dose.

As discussed in detail in Section 6.18.3, if at any time the subject demonstrates an average QTcF value > 500 ms (mean of 3 ECGs at any time point), or an average QTcF value > 480 ms 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.

6.5 Vital Signs and Oxygen Saturation

Vital signs (HR, BP, respiratory rate and body temperature) and oxygen saturation will be recorded at time points specified in Table 1. Blood pressure and heart rate assessments will be performed according to standard practice at the clinical sites. Vital signs associated with the highest temperature after the first dose of study drug will be recorded in the eCRF.

In addition, if the subject is receiving supplemental oxygen therapy, the amount given will be recorded in the eCRF.

All subjects will have vital signs and O_2 saturation evaluated at Screening/Baseline and Day 1. If screening/baseline and Day 1 occur on the same calendar day, vital signs and O_2 saturation do not need to be repeated. All subjects will also have assessments at EOT and TOC; at LFU, vital signs should be performed if medically indicated. 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 (i.e., as part of the EOT assessment).

For Inpatients, in addition to the above time points, vital signs and O_2 saturation will be measured daily and recorded. If multiple vital signs are taken on a study day, the highest

temperature and the vital signs associated with that high temperature will be recorded. For Outpatients, in addition to the above time points, vital signs and saturation will be measured at the study visit scheduled 96 ± 24 hour after the first dose of study drug (see Section 6.1.1).

Vital signs measurements are to be repeated if clinically significant changes or machine errors occur. Out of range BP and HR will be repeated at the Investigator's discretion. Semi-supine BP and HR will be measured more frequently if warranted by the clinical condition of the subject.

6.6 Chest X-Ray or CT Scan

Chest x-ray will be performed at the Screening/Baseline visit as specified in Table 1 and evaluated by the Investigator (or designee) to qualify a subject for enrollment; however, the imaging study must also be interpreted by a radiologist. If a chest computed tomography scan has been performed within 48 hours of enrollment and demonstrates findings consistent with pneumonia, it can be used in place of a chest x-ray. The test type and date and the Investigator's and radiologist's reading/interpretation will be recorded in the eCRF.

6.7 Arterial Blood Gases

Study sites are not required to measure arterial blood gases (PaO_2, $PaCO_2$) or pH. However, if these data are available, they should be recorded in the eCRF.

6.8 Prior and Concomitant Medications

Prior and concomitant medications that will be recorded include prescription medications, dietary supplements/vitamins, and over-the-counter medications. Topical medications will be recorded only if used as treatment for an AE. The minimum requirement is that drug name, indication and the stop and start dates of administration are to be recorded. For the following agents, the drug dose, route and frequency will also be collected in the eCRF:

- Systemic antibacterial agents
- Corticosteroids

Additionally, for systemic antibacterial agents start time and stop time will be recorded.

6.8.1 Prior Medications

A medication history will be taken at Screening. All medications taken within 1 week prior to Day 1 will be entered into the eCRF.

6.8.2 Concomitant Medication

All concomitant medications taken during the study will be recorded in the subject's eCRF.

In the case that additional antibiotic treatment is required for the current episode of CABP, the subject's study drug will be discontinued and they will be considered to have an IACR of

Failure; however, subjects will continue to be followed for safety as detailed in Section 6.18.1.

Other systemic antibacterial agents that are potentially effective against pathogens associated with CABP should not be administered during the study except in the case of CABP treatment failure or when medically necessary for treatment of a concomitant infection. The following antibacterial agents are permitted:

- Anti-tuberculosis drugs isoniazid, ethambutol and pyrazinamide
- Cinoxacin
- Dapsone
- Enoxacin
- Fidaxomicin
- Methenamine Mandelate
- Metronidazole
- Naladixic Acid
- Nitrofurantoin
- Norfloxacin
- Oral Vancomycin

Although all drugs that are metabolized by CYP3A4 are not prohibited, they should only be used when necessary and with appropriate subject monitoring. *In vitro* studies demonstrated that lefamulin may inhibit the metabolism of substrates of CYP3A4; however, results obtained from Phase 1 drug interaction studies performed demonstrate that lefamulin has a marginal effect on CYP3A4 inhibition in humans and no change in lefamulin's dose is required. In addition, all drugs that are P-glycoprotein substrates are not prohibited; however, they should only be used when necessary and with appropriate subject monitoring. A list of drugs that are CYP3A4 substrates and P-glycoprotein substrates is provided in Appendix 3.

Close monitoring is recommended in subjects who require medication that can reduce potassium levels (e.g., loop and thiazide-type diuretics, laxatives and enemas [high doses], corticosteroids, amphotericin B) or medication that is associated with clinically significant bradycardia.

6.9 Prohibited Medications

The following medications are prohibited:

- Prior (within 72 hours before randomization) oral or IV antibacterials for CABP.
  - NOTE: Up to 25 % of subjects may have a single dose of a short-acting antibiotic for the current episode of CABP within 72 hours of randomization.

- EXCEPTION: A subject who has received > 48 hours of prior systemic antibacterial therapy for the current episode of CABP with unequivocal evidence of treatment failure (i.e., worsening signs and symptoms) and the 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.

- Agents that prolong the QT interval (see Appendix 5)
- Systemic corticosteroids at a dose ≥ 20 mg per day (prednisone equivalent)
- Anti-epilepsy or seizure medication
- Strong p-glycoprotein inhibitors (see Appendix 4) [NOTE: The use of contraceptives containing progesterone is not permitted.]
- Strong CYP3A inhibitors or inducers (see Appendix 4)

6.10 Nonpharmacologic Treatments and Procedures

Nonpharmacologic treatments and procedures (e.g., surgical, diagnostic) that occur during the study will be entered into the eCRF, including the date and reason for the treatment/procedure.

6.11 Assessment of Clinical Signs and Symptoms of CABP

Clinical signs and symptoms of CABP will be assessed at the time points specified in Table 1. Signs and symptoms are not obtained at TOC or LFU if the subject previously had an IACR of Failure.

The intensity of each symptom (dyspnea, cough, sputum production, and chest pain) will be evaluated and recorded as absent, mild, moderate or severe based on the definitions in Table 4 below. While Inpatient, all subjects will have clinical signs and symptom of CABP assessed daily.

Subjects who are discharged to home will be contacted by phone to assess signs and symptoms of CABP daily while on study drug with the following exception:

> **All subjects must have a study site visit 96 ± 24 hours after the first dose of study drug to assess CABP signs and symptoms.** Study personnel will inform Outpatients as to the timing of this required study site visit (see Section 6.1.1).

Table 4. Definitions of Symptom Intensity

Symptom	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Dyspnea	Resolution (to pre-CABP baseline) or absence of dyspnea	Dyspnea on exertion (e.g., climbing stairs)	Dyspnea with normal/routine activities (e.g., walking)	Dyspnea at rest or requiring oxygen therapy
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

The assessment of the clinical signs and symptoms of CABP will be used to determine ECR which will be calculated **programmatically**. The decision to maintain a subject on study drug therapy will be made by the Investigator, based on all available data and his or her best clinical judgment.

Subjects will be programmatically defined as a **Responder** if the following 4 criteria are met:

- Alive.
- Improvement in at least 2 of the 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 of any symptom.
- Did not receive a concomitant antibiotic for the treatment of CABP.

Subjects will be programmatically defined as a **Non-Responder** if any of the following criteria are met:

- Did not show an improvement in at least 2 of the 4 cardinal symptoms of CABP the subject presented with at Baseline. Improvement is defined as a decrease by at least 1 level in severity; or
- Worsening of any of the 4 cardinal symptoms of CABP. Worsening is defined as an increase by at least 1 level in severity for any symptom; or
- Received a concomitant antibiotic for the treatment of CABP; or
- Died from any cause.

Subjects will be programmatically defined as an **Indeterminate** if the following criterion is met:

- The symptom data are missing such that a response or non-response cannot be determined.

6.12 Investigator's Assessment of Clinical Response (IACR)

The Investigator will assess Clinical Response at time points specified in Table 1.

6.12.1 Investigator's Assessment of Clinical Response (IACR) at End of Treatment and Test of Cure

The Investigator's Assessment of Clinical Response will be classified as Success, Failure or Indeterminate at EOT and TOC based on the following criteria:

- **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.

NOTE: Subjects who have an IACR of Failure at EOT will not have an IACR assessed at TOC and will be considered to have an IACR of Failure at TOC.

6.12.2 Investigator's Assessment of Clinical Response (IACR) at Late Follow Up

For subjects who do not have an IACR of Failure at TOC, a determination of Clinical Response (Sustained Success, Relapse or Indeterminate) will be made at LFU based on the following criteria:

- **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.
- **Indeterminate**: Insufficient information is available to determine Sustained Success or Relapse, specifically lost to follow-up.

6.13 Clinical Laboratory Tests (Safety)

Safety laboratory tests will be performed at the time points specified in Table 1 and sent to a Central Laboratory. 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. Blood and/or urine will be collected at LFU only if the subject had an abnormal (high/low flag) result at TOC. Additional tests may be performed at the discretion of the Investigator if deemed clinically appropriate. Subjects treated as outpatients must agree to return to the site for blood draws as indicated in Table 1 (i.e., 96 ± 24 hour post first dose [see Section 6.1.1], EOT, and TOC visits).

A full list of the clinical laboratory tests that will be performed and analyzed can be found in Appendix 1. A urine pregnancy test will be performed at the site on all females unless surgically sterile or at least 2 years post-menopausal. A negative urine pregnancy test is required prior to randomization. Serum must be collected on Day 1 prior to 1st dose and sent to the central lab for confirmatory testing.

Any safety laboratory results outside the normal range will be repeated at the discretion of the Investigator and will be evaluated by the Investigator or designee as "clinically significant" or "not clinically significant." Any clinically significant value should be repeated as necessary and followed until resolution.

6.14 Sample Collection for Pharmacokinetic Analysis

Blood samples for PK analysis of lefamulin and its main metabolite, BC-8041, will be collected in association with the first dose of study drug on Day 1 and Day 4 (see Table 5).

If PK sampling for Inpatients on Day 4 is not feasible, it can be done relative to the first dose on Day 5. For Outpatients, PK sampling will be done during the 96 ± 24 hours post 1st dose visit. Subjects will be instructed to not take their first dose of study drug at home that day, 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.

Table 5. Sample Collection Time Points for the Determination of Lefamulin Plasma Concentrations following Oral Administration

PK Sample Time Point	Day 1 and Day 4 or 96 ± 24 hours post 1st dose [a,b]
Within 1 h prior to the first dose of study drug	X
1-2 h after the first dose of study drug	X
3-4 h after the first dose of study drug	X
8-9 h after the first dose of study drug [c]	X

a: Day 1 [all subjects] and Day 4 [Inpatients] or 96 ± 24 hours post first dose [Outpatients]

b: If Day 4 PK sampling for Inpatients is not feasible, it can be done relative to the morning dose on Day 5.

c: The 8-9 h sample is required for inpatients. The 8-9 h sample is optional for outpatients; however, it should be obtained if logistically feasible.

NOTE: It is essential to record the exact time of dosing on those days when PK samples are obtained (see Section 5.7 – Adherence). Documentation of the exact blood sampling time points for population PK analysis is also essential.

6.14.1 Sample Collection Methodology

Blood samples for PK analysis will be collected into tubes containing K_3EDTA, immediately chilled on crushed ice, and then centrifuged to separate plasma. Promptly following centrifugation, plasma specimens (2 aliquots: 1 for bioanalysis and 1 for backup) will be immediately deep frozen and stored at -20 ºC or cooler until transported to the central laboratory. The total time period from blood withdrawal to storage of plasma at -20 ºC should not exceed 60 minutes

Additional information and instructions for blood sample collection is provided in the Laboratory Manual.

6.14.2 Assay Methodology

Plasma samples from subjects who received lefamulin will be analyzed for the concentration of lefamulin and its main metabolite, BC-8041, using a validated liquid chromatography-tandem mass spectrometry method at the bioanalytical laboratory A&M GmbH (Bergheim, Germany). Samples from subjects who did not receive lefamulin (i.e., received the comparator) will not be analyzed. Scientists at the bioanalytical laboratory will be unblinded before bioanalysis.

6.15 Microbiological Assessment

The following microbiological assessments will be performed at the time points described in Table 1. Details regarding storage of samples and shipment to the central laboratory can be found in the Laboratory Manual.

6.15.1 Sputum Samples

- A sputum sample will be taken at Screening for Gram's staining, culture and susceptibility testing at the local/regional laboratory. 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 repeat 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.
- 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.
- Sputum samples will only be taken at subsequent visits when clinically indicated.
- All organisms isolated from sputum samples which are not considered contaminants will be sent to the central laboratory for confirmatory identification and susceptibility testing. The following organisms, if isolated, will always be sent to the central laboratory for confirmatory identification and susceptibility testing: *S. pneumoniae, S. aureus, S. pyogenes, Haemophilus* spp.*, M. catarrhalis, L. pneumophila, C. pneumoniae, and M. pneumoniae.* Further details regarding organisms which should be sent to the central microbiology laboratory, including a list of organisms which if isolated will be classified as contaminants, can be found in the Laboratory Manual.
- 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.
- A portion of each Screening sputum sample taken will be frozen until shipment to the central laboratory. Frozen samples will be analyzed by the central microbiological laboratory using real-time quantitative PCR for common CABP pathogens. Additionally, for subjects who have a positive urinary antigen test for *Legionella* spp. the frozen sputum will be utilized for *L. pneumophila* isolation and susceptibility testing.

6.15.2 Bronchoalveolar Lavage Samples (BAL)

A BAL sample is not required per the protocol and will be collected only if clinically indicated per the Investigator, and sent to the local/regional laboratory for Gram's staining, culture and susceptibility testing. However, if the subject undergoes a repeat bronchoscopy as clinically warranted per the investigator, a repeat BAL sample should be sent for Gram's staining and culture. All organisms isolated from BAL samples, which are not considered contaminants, will be sent to the central laboratory for confirmatory identification and

susceptibility testing. Culture results from the local/regional laboratory will be recorded in the eCRF.

6.15.3 Pleural Fluid Samples

A pleural fluid sample is not required per the protocol, and will be collected only if clinically indicated per the Investigator and sent to the local/regional laboratory for Gram's staining, culture and susceptibility testing. However, if the subject undergoes a repeat thoracentesis as clinically warranted per the Investigator, a repeat pleural fluid sample should be sent for Gram's staining and culture. If possible, pleural fluid samples should be incubated in blood culture bottles for optimal pathogen recovery. All organisms isolated from pleural fluid samples which are not considered contaminants will be sent to the central laboratory for confirmatory identification and susceptibility testing. Culture results from the local/regional laboratory will be recorded in the eCRF.

6.15.4 Blood Cultures

Two sets of blood cultures via venipuncture will be obtained at Screening and sent to the local/regional laboratory. Repeat blood samples for culture should be taken as clinically indicated during the study. Blood cultures should be repeated after a positive result until sterilization is documented. All organisms isolated from blood cultures which are not considered contaminants will be sent to the central laboratory for confirmatory identification and susceptibility testing. Subjects who have confirmed bacteremia should have blood samples collected for microbiologic culture prior to switch to alternate appropriate therapy. Subjects who have confirmed *S. aureus* bacteremia must be withdrawn from the study. Culture results from the local/regional laboratory will be recorded in the eCRF.

6.15.5 Serological Testing

Blood samples will be collected at Screening and LFU, and sent frozen to the central laboratory for serologic tests for *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*.

6.15.6 Urine Antigen Test

A urine sample will be taken at Screening and tested at the clinical site for *L. pneumophila* and *S. pneumoniae* antigen. Results will be recorded in the eCRF. Clinical sites that are unable to perform urinary antigen testing will send urine to the central laboratory for testing. Subjects who have urinary antigen test positive for *L. pneumophila* at Screening, or sites that are sending urine to the central laboratory for urinary antigen testing, will have a portion of the sputum sample collected at Screening sent to the central laboratory for *L. pneumophila* testing as described above (Section 6.15.1).

6.15.7 Oropharyngeal Specimen

An oropharyngeal specimen (2 swabs) will be obtained at Screening and sent to the central laboratory/specialty laboratory for *M. pneumoniae* culture, susceptibility testing, as well as identification by PCR. Oropharyngeal specimens must be frozen until shipment to the central laboratory.

6.15.8 Nasopharyngeal Specimen

A nasopharyngeal specimen (1 swab) will be obtained at Screening and sent to the central laboratory/specialty laboratory for *S. pneumoniae* culture, susceptibility testing, as well as identification by PCR. Culture, susceptibility testing, as well as identification by PCR may also be performed for *H. influenzae*. Nasopharyngeal specimens must be frozen until shipment to the central laboratory.

6.16 Health Utilization and Patient Reported Outcome

Exploratory evaluation of a variety of health utilization variables (e.g., length of hospital stay, duration of antibiotic therapy, discharge status, discharge destination) as well as a PRO instrument (SF-12) will be administered. Details for this exploratory analysis will be presented in a separate SAP and results will be presented in a stand-alone clinical study report.

6.17 Food and Beverage Restrictions

Subjects should refrain from drinking alcohol throughout study drug administration period.

In addition, as discussed in Section 5.4, study drug should be administered at least 1 hour before a meal or 2 hours after a meal. However, in the event that a subject has taken any of the following − antacids containing aluminum, products containing iron, or multivitamins containing zinc − study drug should be administered 2 hours before or 4 hours after consuming any of these medications.

6.18 Discontinuation from Treatment or Study

Subjects are free to withdraw from the study at any time for any reason. Subjects may be withdrawn from study at the discretion of the Principal Investigator or Sub-Investigator at any time. Once a subject has been withdrawn from the study they may not be re-entered. Subjects who withdraw or who are withdrawn from the study will not be replaced. If a subject is discontinued from treatment or from the study, the reason for discontinuation will be collected in the eCRF.

6.18.1 Discontinuation from Treatment

A subject may be discontinued prematurely from study drug treatment for the following reasons:

- Lack of efficacy (i.e., requirement for additional non-study antibacterial therapy to treat the current episode of CABP)
- Adverse event
- Withdrawal by subject [specify reason in the eCRF]
- Lost to follow-up

- Physician decision (i.e., Investigator decision based on protocol violation, assessment that it is not in the subject's best interest to continue, or other reason) [specify reason in the eCRF]
- Sponsor decision [specify reason in the eCRF]

If a subject is prematurely withdrawn from study drug treatment, the Investigator should make every effort to retain the subject in the study and perform all procedures scheduled for the EOT, TOC, and LFU visits. Any subject withdrawn from treatment due to an AE, SAE, or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or a monitoring physician, and will be treated and/or followed up until the symptoms or values have either resolved or are assessed as stable by the Investigator.

6.18.2 Discontinuation from Study

A subject may be discontinued prematurely from the study for the following reasons:

- Withdrawal by subject [specify reason in the eCRF]
- Lost to follow-up
- Death
- Physician decision (i.e., assessment that it is not in the subject's best interest to continue, or other reason) [specify reason in the eCRF]
- Sponsor decision [specify reason in the eCRF]

Every attempt will be made to contact subjects who withdraw from the study in order to determine their vital status (alive or dead) at Day 28.

6.18.3 Individual Stopping Criteria

Subjects will be withdrawn from the study drug treatment for any of the following reasons:

- The subject demonstrates an average QTcF value > 500 ms (mean of 3 ECG's at any time point) as assessed locally by the Investigator. Such subjects should be observed until the ECG normalizes with repeat ECG's taken at the discretion of the investigator.
- The subject demonstrates an average QTcF value > 480 ms with a concurrent increase in average QTcF value of > 60 ms (mean of 3 post-dose ECGs compared to mean pre-dose ECGs taken on that day) as assessed locally by the Investigator.
- The subject has confirmed *S. aureus* bacteremia.

If a subject is prematurely withdrawn from study treatment, the Investigator should make every effort to retain the subject in the study and to perform all procedures scheduled for the EOT, TOC, and LFU visits. Any subject withdrawn from treatment due to an AE, SAE, or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or a

monitoring physician, and will be treated and/or followed up until the symptoms or values have either resolved or are assessed as stable by the Investigator.

6.18.4 Lost to Follow-up

Every reasonable attempt should be made to retain subjects in the study. If a subject does not report to the study site for a scheduled visit, study personnel will make 4 contact attempts: 3 telephone contact attempts and, if these are unsuccessful, a certified letter will be sent to the subject. The subject will be considered lost to follow-up if (1) upon receipt of delivery confirmation of the certified letter the subject does not contact the site or (2) the certified letter is returned as undeliverable. Every attempt will be made to contact subjects who withdraw from the study in order to determine their status (alive or dead) at Day 28.

7 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product.

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e., before informed consent) should be recorded as medical/surgical history. Any medical occurrences which are new or worsened from the time of informed consent and up to and including the final visit must be reported as AEs or SAEs. All AEs and SAEs must be recorded irrespective of whether they are considered drug related. NOTE: lack of efficacy/clinical failure does not have to be recorded as an AE unless it is an SAE.

Subjects will be monitored throughout the study for adverse reactions to the study medications and/or procedures at each study visit. Questions will be posed in a non-leading manner so as not to bias the response. In addition to questioning at specific time points, subjects will be encouraged to spontaneously report any AEs. Any subject with an AE, SAE or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or a monitoring physician, and will be treated and/or followed up until the symptoms or values have resolved or are assessed as stable by the by the Investigator. A physician, either at the Investigative site or at a nearby hospital emergency room, will administer treatment of any SAEs. Where appropriate, medical tests and examinations may be performed to ensure that an AE has fully resolved.

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. Study personnel will monitor AEs for subjects who are Outpatients in conjunction with daily telephone contacts for CABP signs/symptoms as well as at all site visits (see Table 1). Study personnel will follow unresolved AEs and SAEs present at LFU until resolution or stabilization.

Whenever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the subject's eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the subject's eCRF.

Each AE or SAE reported will be assessed for intensity and the date and time of onset (if available), time relationship to dosing, duration, and outcome of each event will be noted.

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.

The Investigator will exercise medical and scientific judgment in deciding whether an abnormal clinical laboratory finding or other abnormal assessment is clinically significant.

7.1 Assessment of Severity (Intensity)

The following definitions for rating severity (intensity) will be used:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but the subject is still able to function

Severe: The type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

7.2 Assessment of Relationship to Study Drug

The Investigator will use his/her clinical judgment to explain each adverse event and determine its relationship, if any, to study drug treatment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator will also consult the Investigator's Brochure in the determination of his/her assessment. Causality should be assessed using the following categories:

Not related The event could readily be explained by factors not involving the study drug and a temporal relationship with the study drug did not exist.

Possibly Related There was some temporal relationship between the event and the administration of the study drug and the event was unlikely to be explained by the subject's medical condition or other therapies.

Probably Related The temporal relationship between the event and the administration of the study drug was suggestive, and the event was less likely to be explained by the subject's medical condition or other therapies.

Definitely Related The event followed a reasonable temporal sequence from administration of the study drug, followed a known or suspected response pattern to the study drug, was confirmed by improvement upon stopping the study drug (dechallenge) and reappeared upon repeated exposure (rechallenge). (NOTE: this was not to be construed as requiring re-exposure of the subject, however, a category of definitely related could only be used when recurrence was observed.).

7.3 Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening. NOTE: The term 'life threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Results in persistent or significant disability/incapacity.
- Requires in subject hospitalization or prolongation of existing hospitalization.
  NOTE: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after entry into the study, should not be classified as SAEs. For example, admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Is a congenital anomaly/birth defect.
- Is an important medical event.
  NOTE: Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

All SAEs will be collected from the time of informed consent until 30 days after the last study treatment regardless of study drug relationship, and must be reported to Nabriva Therapeutics AG or their representative (Covance Pharmacovigilance & Drug Safety Services [PV & DSS]) within 24 hours of knowledge of the event (this refers to any AE that meets one or more of the aforementioned serious criteria).

Safety Contact Information (24 hours/day):

Location	Phone	Fax
United States	+1-888-724-4908	1-888-887-8097
Latin America	+55-11-3750-3900	+0800-892-1513
Europe	+44-1628-548-171	+44-1628-540028
Asia Pacific	+61-2-8879-2000	+61-2-9888-8322

When the SAE form is completed in EDC, Nabriva Therapeutics AG or their representative (Covance PV & DSS) will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the system, sites must email or fax the completed paper SAE report form to Covance PV&DSS at drugsafety@covance.com. The emailed report should include all available information requested on the SAE form. The SAE form will collect data surrounding the event, e.g., the nature of the symptom(s), time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was interrupted or discontinued. The Investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic reports, and procedures, as well as all pertinent medical information related to the event, will also be collected.

Covance PV&DSS will forward SAE queries directly to the Investigator requesting incomplete or missing information. It is the Investigator's responsibility to be diligent in providing this information back to the Covance PV&DSS as soon as it is available. Initial reports of SAEs should never be left on telephone voicemails.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report to Nabriva Therapeutics AG, or their representative. However, it is very important that the Investigator always makes an assessment of causality for every event prior to transmission of the SAE report form to Nabriva Therapeutics AG, or their representative. The Investigator may change his/her opinion of causality in light of follow-up information, amending the SAE report form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The Investigator will provide the assessment of causality as per instructions on the SAE form in the subject's eCRF. SAEs that are determined by the Investigator to be related to the study drug must be reported even if more than 30 days after the last administration of study drug.

The sponsor will not routinely unblind the therapy assignment for an individual subject in the event of a serious adverse event. However, unblinding of an individual subject may occur if this information is requested by the Investigator, if the Sponsor determines that the information is necessary to adequately assess safety, or if this information is required for reporting to local regulatory authorities (see Section 5.6).

All serious adverse events and suspected unexpected serious adverse events (SUSARs) will be reported by the sponsor to the relevant competent authorities in accordance with the European Directive 2001/20/EC, as applicable.

7.4 Symptoms of the Disease Under Study

In this study, clinical signs and symptoms of pneumonia which are assessed daily per protocol (i.e., dyspnea, cough, sputum production, and chest pain) will not be reported as adverse events unless they meet the definition of a serious adverse event.

7.5 Other Reportable Events

Certain events that occur should be reported to the Sponsor as Other Reportable Events. These include the following:

- Potential Hy's Law (PHL)
  - The investigator is responsible for prompt reporting of any patients who has had both (1) AST or ALT > 3 x ULN and (2) total bilirubin > 2 x ULN at any point in the study (i.e., meets criteria for Potential Hy's Law). The investigator must complete the Hy's Law eCRF. Liver laboratory results should be followed locally every several days until resolution or stabilization of the laboratory abnormalities and reported using an unscheduled laboratory eCRF. If subsequent to the initial report of PHL, the investigator determines that the case meets serious criteria, it should be reported as an SAE using standard reporting procedures.
- Pregnancy exposure (subject becomes pregnant while taking study drug)
  - Subjects who are pregnant at Screening are not permitted to take part in this study, however, Nabriva Therapeutics AG or their representative must be notified of any subjects that become pregnant while participating in this study (or the partner of a male subject). Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator or designee to report any pregnancy in a subject that occurs during this study to Nabriva Therapeutics AG or their representative.
- Lactation exposure (subject was taking study drug while nursing an infant)
- Accidental exposure (someone other than the study subject was exposed to study drug)
- Overdose (subject received more than the prescribed dose of study drug within a given timeframe)
- Other medication errors that potentially place subjects at a greater risk of harm than was previously known or recognized (e.g., study drug was administered by an incorrect route).

8 DRUG SUPPLIES

8.1 Lefamulin (BC-3781)

The active substance being investigated in this study is lefamulin (BC-3781), present in the drug product as the acetate salt (BC-3781.Ac). Physicochemical properties can be found in the Lefamulin Investigator's Brochure.

Oral lefamulin is supplied by the Sponsor as 600 mg yellow oval film coated immediate-release tablets. Details of the composition are provided in the Lefamulin Investigator's Brochure.

8.2 Moxifloxacin

The oral dose of moxifloxacin is provided by the Sponsor as an over-encapsulated film coated tablet containing 400 mg as hydrochloride.

Additional details regarding moxifloxacin are found in the product monograph.

8.3 Placebo

The following oral placebo tablets will be supplied by the Sponsor: lefamulin placebo tablet and moxifloxacin placebo capsule.

Further details may be found in the Study Pharmacy Manual.

8.3.1 Packaging and Labeling

Study drugs will be packaged and labeled in accordance with the applicable regulatory authority requirements.

8.3.2 Storage of Study Drugs

Access to all study drugs at the site must be restricted to designated study personnel throughout the study.

Oral study medication will be supplied in blister packs. Two different blister packs will be provided:

- Lefamulin tablets and moxifloxacin placebo capsules.
- Over-encapsulated moxifloxacin tablets and lefamulin placebo tablets

The two blister packs must be stored at controlled room temperature (15 to 25 °C).

8.3.3 Product Accountability

The Investigator is responsible for study medication accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or

designated study personnel must maintain study drug accountability records throughout the course of the study. This person(s) will document the amount of study drug received from the supplier, the amounts dispensed to subjects as well as lot numbers and expiration / retest date of study medications.

At the conclusion of the study, any unused study drug will be returned to either a Sponsor-designated recipient or destroyed at the site after discussion with the Sponsor. If no supplies remain, this will be recorded in the drug accountability section of the final monitoring report.

9 STATISTICAL ANALYSIS

Inferential statistical analyses of the primary and secondary outcomes will be conducted as outlined below. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Additional statistical analyses, other than those described in this section, may be performed if deemed appropriate. A description of the statistical analysis performed on the study data will be outlined in the SAP.

As a consequence of differing regulatory requirements for the choice of primary efficacy analysis variable and statistical analyses of this study, 2 separate regional comprehensive SAPs will be prepared (FDA and EMA) and finalized before database lock and analysis of the data.

Exploratory evaluation of a variety of health utilization variables (e.g., length of hospital stay, duration of antibiotic therapy, discharge status, discharge destination) as well as a PRO instrument will be performed. Details for this exploratory analysis will be presented in a separate SAP and results will be presented in a stand-alone clinical study report.

9.1 Treatment Comparison of Interest

All comparisons will be for lefamulin versus comparator therapy (moxifloxacin).

9.2 Sample Size Determination

A total of 738 subjects will be randomized in a ratio of 1:1 (lefamulin:moxifloxacin) resulting in 369 subjects in the lefamulin arm and 369 in the moxifloxacin arm in this study. 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 as well as 2 recent clinical trials in CABP indicate the point estimates for an ECR responder at Days 3-5 range from 72% to 81% (FDA, 2011; Barrera et al., 2016; Cempra, 2015; Oldach et al., 2015**)**. Thus, it is reasonable to assume that in a prospective study of subjects with CABP, the proportion 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 (MAA) to the EMA will be the proportion 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% to 93% (Cempra, 2015) and in the ITT Analysis Set ranged from 85% to 89% depending on the antibiotics under study and the severity of the CABP. 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, a 1:1 randomization ratio, a two-sided alpha of 0.025, and a continuity corrected Z-test with unpooled variance, a sample size of 738 subjects (369 subjects in the lefamulin group and 369 in the moxifloxacin group) provides 90% power to establish the NI of lefamulin to moxifloxacin for ECR using a NI margin of 10.0% at the ECA. 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 91% power for demonstration of NI for IACR at the TOC Visit using a 10% NI margin.

The calculated power in each analysis set for the primary and secondary outcomes is provided in Table 6 below.

Table 6. Power Calculations for the Primary and Secondary Efficacy Outcomes

	Primary Outcome (FDA) (ECR 96 ± 24 hours After the First Dose of Study Drug)	Secondary Outcome (Investigator's Assessment of Clinical Response at TOC- Primary for EMA)	
Analysis Set	ITT	mITT	CE-TOC
NI Margin	10%	10%	10%
N	738 (369:369)	738	590
Outcome Rate	79%	80%	85%
Evaluability Rate	NA	NA	80%
Power	90%	91 %	91%

CE = clinically evaluable; ITT = intent to treat; mITT = modified ITT; TOC = test of cure

9.3 Analysis Populations

9.3.1 Intent-to-Treat Analysis Set (ITT)

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.

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

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

9.3.3 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.

9.3.4 Microbiological Intent-to-Treat Analysis Set (microITT)

The microITT Analysis Set will consist of all subjects in the ITT Analysis Set who have at least 1 baseline "typical" bacterial pathogen known to cause CABP, *Legionella pneumophila* from an appropriate microbiological specimen, or who have CABP caused by *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae*.

9.3.5 Clinically Evaluable Analysis Set

The CE Analysis Sets (CE-EOT, CE-TOC and CE-LFU Analysis Sets) will be a subset of the ITT Analysis Set that will include subjects who meet the criteria for CABP described in Inclusion Criteria Nos. 3-7, and who received at least the pre-specified minimal amount of the intended dose of study drug and duration of treatment, do not have an indeterminate response based on the IACR (at EOT for the CE-EOT Analysis Set, at TOC for the CE-TOC Analysis Set and at LFU for the CE-LFU Analysis Set), did not receive concomitant antibacterial therapy that is potentially effective against CABP pathogens (except in the case of clinical failure) from the first dose of study drug through the EOT Visit (CE-EOT Analysis Set), through the TOC Visit (CE-TOC Analysis Set) and through the LFU Visit (CE-LFU Analysis Set), and for whom there are no other confounding factors that interfere with the assessment of the outcome.

9.3.6 Microbiologically Evaluable Analysis Set

The ME Analysis Sets (ME-EOT, ME-TOC and ME-LFU) will include all subjects who meet the criteria for inclusion in both the microITT and CE-EOT (ME-EOT) Analysis Sets, the CE-TOC (ME-TOC) Analysis Set, or the CE-LFU (ME-LFU) Analysis Set.

9.3.7 Pharmacokinetic Analysis Set

All subjects who receive any amount of study drug will be included in the formal analysis of PK parameters providing they have at least 1 evaluable PK sample.

9.4 Criteria for Evaluation

9.4.1 Primary Efficacy Analysis Variable

The primary efficacy variable (FDA) is the proportion of subjects in the ITT Analysis Set with an ECR of Responder at 96 ± 24 hours post first dose.

Subjects will be defined as an ECR of Responder if the following 4 criteria are met:

- Alive
- Improvement in at least 2 of the 4 cardinal symptoms of CABP (Section 6.11), 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 from Baseline by at least 1 level of severity of any symptom.
- Did not receive a concomitant antibiotic for the treatment of CABP.

The primary efficacy variable for the EMA (and secondary efficacy variable for the FDA) is the proportion of subjects with an IACR of Success at TOC in the mITT and CE-TOC Analysis Sets (see Section 6.12). An IACR of Success is defined as a subject whose 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. Subjects who have an IACR of Failure at EOT will not have an IACR assessed at TOC and will be considered to have an IACR of Failure at TOC.

9.4.2 Secondary Efficacy Analysis Variables

9.4.2.1 Clinical Outcome

The Investigator's Assessment of Clinical Response will be evaluated in the microITT and ME-TOC Analysis Sets at TOC as described in Section 6.12. ECR will be evaluated in the microITT Analysis Set. All-cause mortality will be evaluated in the ITT Analysis Set.

9.4.2.2 Microbiological Assessment

The By-Pathogen Microbiological Response will be assessed in the micro-ITT and ME Analysis Sets for each causative organism using the categories for outcome as follows.

- **Success** includes**:**
  - Eradication: the baseline causative pathogen was absent from repeat culture(s).
  - Presumed eradication: the IACR was Success, and culture was not repeated.
- **Failure** includes**:**
  - Persistence: the baseline causative pathogen was isolated in repeat culture(s).
  - Presumed persistence: the IACR was Failure and a culture was not repeated.

- **Indeterminate:**
  - The IACR was Indeterminate, and culture was not repeated.

9.4.3 Safety Analysis Variables

Safety will be assessed by monitoring vital signs, ECG measurements, clinical laboratory parameters, and AEs.

9.4.4 Pharmacokinetic Analysis Variables

Population PK modeling will be performed to determine the model-predicted plasma concentration time curves of lefamulin for each subject. Calculated PK will enable descriptive statistical analysis of PK variables such as the maximum observed drug concentration (C_{max}) and area under the concentration-time curve (AUC) for lefamulin and its main metabolite, BC-8041. Individual AUC values from Day 1 and Day 4 [i.e., 96 ± 24 hours post first dose] (collected pre-dose, 1-2 h post dose and 3-4 h post dose, and 8-9 h post dose (8-9 h post dose is required for inpatients; optional for outpatients) will be used for the PK/PD analysis. The population PK analysis as well as a PK/PD analysis will be reported separately.

9.4.5 Other Variables

The Investigator's Assessment of Clinical Response at EOT and at LFU will be evaluated in the mITT and CE Analysis Sets.

The By-Subject Microbiological Response will be programmatically determined at TOC for each subject using the By-Pathogen Microbiological Response for each baseline causative pathogen. For a subject to have a By-Subject Microbiological Response of Success, the response for each baseline pathogen must be Success (i.e., Eradication or Presumed Eradication). If the response for any Baseline pathogen is Failure (i.e., Persistence or Presumed Persistence), the subject will be considered to have a By-Subject Microbiological Response of Failure. A By-Subject Microbiological Response of Indeterminate will be assigned if all baseline pathogens have a Microbiological Response of Indeterminate.

New bacteria isolated from respiratory or blood culture will be assessed separately from the outcomes listed above as follows:

- **Superinfection:**
  - New respiratory (i.e., from sputum, pleural fluid or BAL specimen) pathogen(s) (i.e., pathogen(s) not present at baseline) identified in post-baseline culture(s) through the TOC Visit with persistent signs and symptoms of CABP (i.e., IACR of Failure at the TOC Visit, such that additional antibacterial therapy is necessary for the current episode of CABP).
- **Colonization:**
  - New respiratory (i.e., from sputum, pleural fluid or BAL specimen) pathogen(s), (i.e., 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, (i.e., 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:**
  - Increase in MIC (≥ 4x) or 6 mm decrease from baseline in disk inhibition zone diameter to the study drug received for a pathogen isolated at baseline and subsequently isolated from a blood or lower respiratory tract specimen.

ECR plus improvement in vital signs (i.e., body temperature, blood pressure, heart rate, respiratory rate), if abnormal at Baseline will be evaluated in the ITT Analysis set. If vital signs are normal at Baseline (i.e., 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]
- 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 bpm
- Tachypnea: defined as respiratory rate > 20 breaths/min

Exploratory evaluation of a variety of health utilization variables (e.g., length of hospital stay, duration of antibiotic therapy, discharge status, discharge destination) as well as a PRO instrument will be performed. Details for this exploratory analysis will be presented in a separate SAP and results will be presented in a stand-alone clinical study report.

9.5 Demographic and Baseline Characteristics

Enrollment, protocol deviations, and discontinuations from the study drug and the study will be summarized by treatment group. Demographics (age, race, ethnicity and sex), medical and surgical history, baseline assessment of the clinical signs and symptoms, microbiological assessment, and study drug administration will also be summarized by treatment group. Differences between treatment groups will be analyzed using the chi-square or Fisher's exact test for dichotomous variables and the Wilcoxon Rank Sum test for ordinal and continuous variables.

9.6 Efficacy Analysis

For all efficacy analyses, subject data will be analyzed in the group to which the subject was randomized. For the stratified analysis of the primary efficacy outcome and for the primary

analysis for the EMA, subjects who are randomized to the wrong stratum will be analyzed in the stratum to which they were randomized.

9.6.1 Primary Efficacy Analysis

The primary efficacy outcome (FDA) is the proportion of responders for ECR at 96 ± 24 hours following 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 assessments of CABP signs and symptoms Subjects who are missing data required to determine an ECR 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 responder rate. Thus, subjects with an ECR of Indeterminate are considered non-responders for the primary analysis. The number and percentage of subjects in each treatment group in each response category 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 ECR (lefamulin group minus the moxifloxacin group). The CI will be calculated using an unadjusted continuity corrected Z-statistic. If the lower limit of the 95 % CI for the difference in responder rates in the ITT Analysis Set is greater than -10.0 %, the null hypothesis will be rejected and the NI of lefamulin to moxifloxacin will be concluded.

Additional analyses of the primary efficacy outcome will be conducted. ECR will be assessed separately across the geographic regions, prior antibiotic use, and PORT risk class strata. 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 ECR include determination of a stratified 95% CI (adjusted for the randomization stratification factors) and considering all subjects with missing data (i.e., Indeterminates) at 96 ± 24 hours after the first dose of study drug as responders for ECR (these subjects are considered non-responders in the primary analysis). For the second sensitivity analysis, an unstratified 95% CI will be computed for the difference in the responder rates between lefamulin and moxifloxacin. Subgroup analyses of the primary efficacy outcome will also be conducted for descriptive purposes and will be detailed in the SAP. For both ECR and IACR, additional analyses will be conducted whereby failures will be reclassified as Indeterminate if they received less than 48 hours of study medication.

For the EMA primary analysis (secondary analysis for the FDA), the number and percentage of subjects in each treatment group with an IACR of Success, Failure and Indeterminate (by definition Indeterminates are not included in the CE-TOC Analysis Set) at TOC will be reported in the mITT and CE-TOC Analysis. Subjects who have an IACR of Failure at EOT will be considered to have an IACR of Failure at TOC. The primary analysis for the EMA will utilize 2-sided stratified (for the randomization stratification factors) 95% CIs calculated using the method of Miettinen-Nurminen. If the lower limit of the 95% CI for the difference in success rates in both the mITT and CE-TOC Analysis Sets is greater than -10%, the NI of lefamulin to moxifloxacin will be concluded. Two-sided unstratified 95% CIs will be calculated for the difference in success rates at TOC in the mITT and CE-TOC Analysis Sets (FDA secondary outcome).

Additional analyses of the EMA primary efficacy outcome will be conducted. IACR at TOC will be assessed separately across the geographic regions, prior antibiotic use, and PORT risk class strata in the mITT and CE-TOC Analysis Sets. For each geographic region, prior antibiotic use, and PORT risk class stratum, a 2-sided 95% CI for the observed difference success rates will be calculated for the ITT and CE-TOC Analysis Sets. Sensitivity analyses of IACR include determination of unstratified 95% CI and considering all subjects with missing data (i.e., Indeterminates) as successes for IACR (these subjects are considered failures in the EMA primary analysis). For the second sensitivity analysis, a stratified 95% CI will be computed for the difference in the success rates between lefamulin and moxifloxacin. Subgroup analyses of the EMA primary efficacy outcome will also be conducted for descriptive purposes and will be detailed in the EMA SAP.

9.6.2 Secondary Efficacy Analyses

The number and percentage of subjects categorized as Responder, Non-responder and Indeterminate for the primary FDA efficacy outcome of ECR will also be presented for the microITT Analysis Set and a 2-sided unstratified 95 % CI for the difference in responder rate will be calculated using a continuity-corrected Z-statistic. However, the formal test of NI will be conducted in the weighted (based on the inverse variance of each effect size) pooled population from this study and a second study in CABP.

The number and percentage of subjects in each treatment group with an IACR of Success, Failure and Indeterminate (by definition Indeterminates are not included in the ME-TOC Analysis Set) at TOC will be reported in the microITT and ME-TOC Analysis Sets. Subjects who have an IACR of Failure at EOT will be considered to have an IACR of Failure at TOC. Two-sided unstratified 95 % CIs will be calculated for the difference in success rates.

The By-Pathogen Microbiologic Response (by definition, subjects with an Indeterminate Microbiologic Response are excluded from the ME-TOC Analysis Set) will be provided for the microITT and ME-TOC Analysis sets at TOC.

All-cause mortality (ACM) through Day 28 will also be summarized in the ITT Analysis Set. Subjects who are lost to follow-up will be considered deceased for this analysis. A 2-sided unstratified 95 % CI will be calculated for the treatment difference in ACM.

9.6.3 Additional Efficacy Analyses

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

The number and percentage of subjects who are a Responder for ECR, the number and percentage of subjects who have an IACR of Success at TOC, and the number and percentage of subjects who are a sustained response at LFU will be presented by baseline pathogen in the microITT Analysis Set, ME-TOC (IACR only) and ME-LFU (sustained success only) Analysis Sets.

The number and percentage of subjects in each treatment group with an IACR of Success, Failure and Indeterminate (by definition subjects with an IACR of Indeterminate are not included in the CE-EOT Analysis Set) at EOT in the mITT and CE-EOT Analysis Sets. Two-sided unstratified 95 % CIs will be calculated for the difference in IACR success rates. The number and percentage of subjects with a Sustained Success, Relapse, Failure and Indeterminate response as assessed by the Investigator at the LFU Visit will be summarized for the mITT and CE-LFU Analysis Sets. Failure is defined as a subject who had an IACR of Failure at the TOC Visit.

The By-Subject Microbiologic Response (by definition, subjects with an Indeterminate Microbiologic Response are excluded from the ME-TOC Analysis Set) will be provided for the microITT and ME-TOC Analysis sets at TOC. Two-sided unstratified 95 % CIs will be provided for the difference in the By-Subject Microbiologic Response success rate.

Early Clinical Response, including improvement in vital signs at 96 ± 24 hours after the first dose of study drug will be derived programmatically from the eCRF assessment of CABP signs and symptoms data. The number and percentage of subjects who are a Responder (including vital signs) will be tabulated by treatment group in the ITT Analysis Set. A 2-sided unstratified 95 % CI will be calculated for the treatment difference for the responder rate.

9.7 Safety Analysis

Safety will be evaluated in the Safety Analysis Set by presenting summaries of AEs, routine clinical laboratory evaluations, ECGs, and vital signs in the 2 treatment groups. Subjects who receive the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received.

Summary tables will be provided for all TEAEs. A TEAE is defined as an AE with a start date and time on or after the first dose of study drug. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of subjects with TEAEs will be tabulated by system organ class (SOC) and MedDRA Preferred Term for each treatment group and by severity and relationship to treatment.

Adverse events leading to premature discontinuation from the study drug and serious TEAEs will be presented either in a table or a listing.

Change from baseline to each scheduled evaluation and the overall worst post-baseline in clinical laboratory variables will be summarized by treatment group. The number and percent of subjects with treatment-emergent potentially clinically significant (PCS) laboratory values will be tabulated for each treatment group. Treatment-emergent PCS laboratory tests are those in which the Baseline value is not PCS and the post-baseline value is PCS. PCS will be defined based on the pre-specified criteria outlined in the SAP.

Change from baseline to each scheduled evaluation and the overall worst post-baseline for RR interval, PR interval, QRS interval, QT interval, and QT interval corrected with Fridericia from the ECG will be summarized for each treatment group with the mean, standard deviation, minimum value, and maximum value. The triplicate values will be averaged for each subject before analysis. An outlier analysis will also be provided based on the worst post-baseline value.

Descriptive statistics of vital signs and the change from baseline to each scheduled evaluation will be summarized by treatment group at each study visit and the worst overall post-baseline. The number and percent of subjects with treatment-emergent PCS values will be tabulated for each treatment group.

9.8 Handling of Missing Data

For the primary outcome measure (FDA), if any data field needed to determine ECR is missing, the subject will be assigned a response of Indeterminate. Imputations for the missing times will be provided in the SAP. For analyses of the primary outcome, subjects with an indeterminate response are included in the denominator, and thus are considered Non-responders. A sensitivity analysis of the primary outcome will be conducted in which subjects with an indeterminate response are considered Responders.

For the outcome measure of IACR at EOT, TOC and LFU, missing data are considered as a response of Indeterminate. For analysis in the ITT, mITT and microITT Analysis Sets, indeterminate outcomes are included in the denominator and are thus, considered clinical Failures. By definition, subjects with an IACR of Indeterminate are excluded from the CE-EOT, CE-TOC, CE-LFU, ME-EOT, ME-TOC, and ME-LFU Analysis Sets.

A missing microbiological response is considered a presumed response based on the IACR. For analysis in the microITT Analysis Set, indeterminate outcomes are included in the denominator and are thus, considered microbiological failures. By definition, subjects with an IACR of Indeterminate are excluded from the ME Analysis Sets.

Handling of missing data for other efficacy and safety outcomes will be presented in the SAP.

9.9 Pharmacokinetic Analyses

Measured plasma concentrations of lefamulin and its main metabolite, BC-8041, will be summarized descriptively by the actual time point of collection. Summary statistics in the

tabulation will include *n*, mean, standard deviation, CV [%], median, minimum and maximum.

Population PK modeling will be used to determine the individual model-predicted concentrations of lefamulin. Simulation of model output will enable descriptive statistical analysis of PK variables such as the C_{max}, C_{min} and AUC for lefamulin.

A description of the population PK analysis will be described in a separate SAP. Results of this analysis will be reported separately.

9.10 Health Utilization Variables and Patient Reported Outcome

Exploratory evaluation of a variety of health utilization variables (e.g., length of hospital stay, duration of antibiotic therapy, discharge status, discharge destination) as well as a PRO instrument, the SF-12, will be performed. In addition, other PRO instruments may be utilized in this study, as feasible. Details for this exploratory analysis will be presented in a separate SAP and results will be presented in a stand-alone clinical study report

10 STUDY MONITORING

10.1 Clinical Monitoring

All aspects of the study will be carefully monitored by the Sponsor's authorized individuals, acting as agents of the sponsor with respect to current Good Clinical Practice and Standard Operating Procedures for compliance with applicable government regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the principal investigator.

Frequent communication between the study site and the Sponsor is essential to ensure that the subject safety is monitored adequately. The Investigator will make safety assessments on an ongoing basis. The Sponsor's medical monitor will review safety information from all study sites as it becomes available throughout the study. Should any safety concerns be identified, the Data Monitoring Committee (DMC) will be asked to review the data and determine what action is recommended.

10.2 Independent Data Monitoring Committee (DMC)

An independent DMC will be constituted for this study to monitor important aspects of study conduct, including safety results on an ongoing basis. The DMC will consist of 3 members who will be selected by the Sponsor but will be independent from the Sponsor. The clinicians on the committee will not participate in the study as Principal or Co-investigators, and should be isolated from the study if their institution is a study site. The DMC members receive no financial incentives for their participation, but are reimbursed only for customary consultative and administrative support fees.

DMC meeting frequency and conduct is outlined in a separate DMC Charter. An independent unblinded statistician will provide the committee with masked data for review

(treatment A versus treatment B), but will not be a member of the committee. All members of the DMC will treat study data, reports, meeting discussions, and conclusions as confidential.

11 IEC/IRB APPROVAL

The Principal Investigator agrees to provide the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) with all appropriate material, including a copy of the informed consent. The study will not be initiated until the Investigator obtains written approval of the research plan (protocol) and the informed consent document from the appropriate IEC/IRB and copies of these documents are received by Nabriva Therapeutics AG.

It is the Investigator's responsibility to obtain IEC/IRB approval for all subsequent major changes to the protocol, in compliance with local law. Appropriate reports on the progress of this study will be made by the Investigator to the IEC/IRB and Sponsor in accordance with applicable government regulations and in agreement with policy established by the Sponsor.

12 ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in compliance with this Protocol, the guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Fortaleza, Brazil, October 2013), the guidelines of International Conference on Harmonization (ICH) Good Clinical Practice (GCP) (CPMP/ICH/135/95), European Union (EU) Clinical Trials Directive 2001/20/EC, EU Commission Directive 2005/28/EC, and Code of Federal Regulation (CFR) Title 21, CFR Part 50, 56 and 312, designated Standard Operating Procedures, and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

13 INFORMED CONSENT

The International Conference on Harmonization (ICH) has issued guidelines to provide protection for human subjects in clinical investigations. The ICH Tripartite Guideline for Good Clinical Practice establishes the general requirements for informed consent.

A properly executed, written informed consent in compliance with the terms of these guidelines shall be obtained from each subject before entering the study, or before performing any unusual or non-routine procedure in relation to the study. The purpose of the study, procedures to be carried out, and potential hazards will be described to each potential subjects in non-technical terms. Subjects (or their legally authorized representative) will be required to read, voluntarily sign, and date an informed consent form summarizing the discussion at Screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects (or their legally authorized representative) will sign and date 1 copy of the informed consent form which will be photocopied. In accordance with local regulations, the original and copies of the signed and dated consent may be retained by the subject (or their legally authorized representative) and/or retained on file by the Investigator, as applicable.

The consent form must be approved by the appropriate IEC/IRB and Sponsor before study initiation at a study site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IEC/IRB and Sponsor before implementation.

14 QUALITY ASSURANCE AND QUALITY CONTROL

Standard Operating Procedures belonging to Nabriva Therapeutic AG or designee(s) will be adhered to for all activities relevant to the quality of the study and are routinely monitored by the Quality Assurance (QA) Division.

Data will undergo quality control checks prior to clinical database lock. Sponsor-designated, independent monitors will be responsible for the monitoring of the study and its data within the eCRFs.

A QA audit of this study may be conducted by the Sponsor or Sponsor's designee. The QA auditor will have access to all medical records, the Investigator's study-related files and correspondence, information in the informed consent documentation of this study, and study drug storage facilities.

An inspection of this study may be conducted by a regulatory agency. The Investigator agrees to contact the Sponsor as soon as possible, but not later than within 1 week, upon notification of an inspection by a regulatory agency. The Investigator agrees to allow the Inspector direct access to all relevant documents and to allocate his/her time and that of study personnel to the Inspector to discuss findings in any relevant issues. The Investigator will allow Sponsor personnel to be present as an observer during a regulatory inspection, if requested.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Handling

Data will be recorded at sites using eCRFs and reviewed by the Sponsor or designee during monitoring visits. The recorded data in the EDC system will be verified with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. eCRFs will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for. Data collected at baseline will only be entered into the eCRF if the subject is eligible for study participation following review of the data by the Investigator or designee.

Adverse events, concomitant medication data and clinical observations will be in the subjects' hospital notes, or recorded on source data forms, and will be transferred into the eCRF after assessment by the Investigator or designee.

Data produced by automatic devices with original print-outs (e.g., clinical laboratory test results, ECG traces, BP measurements) will be included in the source documentation. Clinical laboratory parameters are to be reviewed, signed and dated by the Investigator or

designee. Any results outside the normal range should be designated by the Investigator or designee as not clinically significant (NCS) or clinically significant (CS).

15.2 Subject Confidentiality

Investigator and his/her staff will be required to manage subject data collected for the study in accordance with applicable laws and regulations on personal data protection.

US: All US-based investigational sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. An investigational site that is not a Covered Entity as defined by HIPAA must provide documentation of this fact to Nabriva Therapeutics AG.

EU: Data collected during this study may be used to support the development, registration or marketing of lefamulin. Nabriva Therapeutics AG will control all data collected during the study, and will abide by the EU Directive on Data Privacy concerning the processing and use of subjects' personal data. For the purpose of data privacy legislation, Nabriva Therapeutics AG will be the data controller.

After subjects have consented to take part in the study their medical records and the data collected during the study will be reviewed by Nabriva Therapeutics AG or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of Nabriva Therapeutics AG; third parties with whom Nabriva Therapeutics AG may develop, register or market lefamulin; national or local regulatory authorities and the IRB/IECs that gave approval for this study to proceed.

Subjects will be known by a unique number; however, their date of birth can also be collected if not in contradiction with any requirements (e.g., from IECs) and used to assist Nabriva Therapeutics AG to verify the accuracy of the data, for example, that the laboratory results are assigned to the correct subject. The results of this study may be recorded and transferred to and used in other countries throughout the world, which may not afford the same level of protection that applies within the EU. The purpose of any such transfer would be to support regulatory submissions in other countries.

15.3 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

15.4 Data Entry

Data must be recorded using the EDC system as the study is in progress. All study personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with the Title 21 Code of Federal Regulations (21 CFR Part 11) for US sites and EU Directives 2001/20/EC and 2005/28/EC for EU sites. All passwords will be strictly confidential.

15.5 Data Validation

Validation checks programmed within the EDC system as well as supplemental validation performed via review of the downloaded data will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

eCRFs must be reviewed and electronically signed by the Investigator who signed the protocol.

15.6 Record Keeping

Raw data generated in connection with this study as well as an original copy of the final clinical study report, will be retained in archive until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of lefamulin. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

As required under European Directive 2005/28/EC, Article 17, all 'essential documents' (as described in the ICH GCP Guidelines) must be retained by Nabriva Therapeutics AG and the Investigator for at least 5 years after the completion of the clinical study. Therefore all studies, independent of where they were conducted in the world, must follow this requirement in the event a submission is ever made in the EU. These documents may be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Nabriva Therapeutics AG. It is the responsibility of Nabriva Therapeutics AG to inform the Investigator as to when these documents no longer need to be retained. The Investigator must obtain written permission from Nabriva Therapeutics AG prior to the destruction of any study document.

The retention of investigator study records is an investigator responsibility and Nabriva Therapeutics AG will neither arrange nor pay for this activity. Any transfer of ownership of the content of the clinical trial master file is the responsibility of the investigator or site representative, and shall be documented. The new owner shall assume the responsibilities set forth in the applicable regulations.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US Food and Drug Administration (FDA) in accordance with 21 CFR 312.68 or other national or foreign Regulatory Authorities in accordance with regulatory requirements.

16 TERMINATION OF STUDY

The Sponsor reserves the right to discontinue this study at any time.

17 FINANCING AND INSURANCE

The costs necessary to perform the study will be agreed with each Investigator and will be documented in a separate financial agreement that will be signed by the Investigator and Nabriva Therapeutics AG (or designee), prior to the start of the study. A statement regarding insurance/indemnity such as Association of British Pharmaceutical Industry (ABPI) should also be included.

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the results or outcome of the study. The following information will be collected: any significant payments of other sorts from Nabriva Therapeutics AG, (e.g., money to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria); any proprietary interest in lefamulin; any significant equity interest in Nabriva Therapeutics AG as defined in 21 CFR 54 2(b).

In consideration of participation in the study, Nabriva Therapeutics AG will pay the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

18 PUBLICATION POLICY

It is intended that the results of the study may be published as scientific literature. Results may also be used in submissions to Regulatory Authorities. The following conditions are to protect commercial confidential materials (e.g., patents, etc.), not to restrict publication.

All information concerning lefamulin (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator by Nabriva Therapeutics AG and not previously published) is considered confidential by Nabriva Therapeutics AG and shall remain the sole property of Nabriva Therapeutics AG. The Investigator agrees not to use it for other purposes without Nabriva Therapeutics AG written consent.

It is understood by the Investigator that Nabriva Therapeutics AG will use the information developed in this clinical study in connection with the development of lefamulin and, therefore, may be disclosed as required to other Nabriva Therapeutics AG Investigators or any appropriate international Regulatory Authorities. In order to allow for the use of information derived from this clinical study, the Investigator understands that he/she has an obligation to provide Nabriva Therapeutics AG with complete test results and all data developed during this study.

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Nabriva Therapeutics AG in advance of submission. The review is aimed at protecting Nabriva Therapeutics AG's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data shall be set out in the agreement between each Investigator and Nabriva Therapeutics AG.

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20 APPENDICES

Appendix 1	Clinical Laboratory Tests (Safety)
Appendix 2	Short Acting Antibiotics
Appendix 3	Closely Monitored CYP3A4 Substrates and P-Glycoprotein Substrates (excluding strong CY3A inducers and inhibitors and excluding strong P-glycoprotein inhibitors)
Appendix 4	Prohibited Strong P-Glycoprotein Inhibitors and Strong CYP3A Inducers and Inhibitors
Appendix 5	Drugs That Prolong QT

Appendix 1 Clinical Laboratory Tests (Safety)

Blood and urine samples for the following laboratory tests will be sent to a central laboratory for testing.

Hematology

Complete blood count (CBC) with RBC indices and WBC differential
Platelet count

Chemistry

BUN
Creatinine
Glucose
Sodium
Potassium
Chloride
Calcium
Magnesium
Phosphorus
AST
ALT
GGT
Alkaline Phosphatase
CPK
Total Bilirubin
Direct Bilirubin
Uric Acid
Albumin
Total Protein

Urinalysis

Specific gravity
pH, glucose, protein, blood, ketones, bilirubin and leukocyte esterase by dipstick
Microscopic examination (all samples)

Other tests

Procalcitonin

Testing at Screening Only

Serum pregnancy test
Urine pregnancy test (testing kit provided by central laboratory; test to be performed at the local site prior to randomization)

Appendix 2 Short Acting versus Long Acting Antibiotics

Short-acting	Long-acting
Cephalosporins	
Cefaclor, Cefadroxil, Cefdinir, Cefepime, Cefixime (200 mg), Cefotaxime, Cefpodoxime, Cefprozil, Ceftazadime, Ceftibuten, Cefditoren, Cefruoxime, Cephalexin, Loracarbef	Cefixime (400 mg), Ceftriaxone
Fluoroquinolones	
Ciprofloxacin, Norfloxacin	Gatifloxacin, Gemifloxacin, Grepafloxacin, Levofloxacin, Moxifloxacin, Sparfloxacin
Macrolides and Ketolides	
Clarithromycin, Erythromycin, Roxithromycin	Azithromycin, Clarithromycin XL (extended release), Dirithromycin, Telithromycin
Penicillins and Carbapenems	
Amoxicillin, Amoxicillin-Clavulanate, Amoxicillin-Sulbactam, Ampicillin, Ampicillin-Sulbactam, Dicloxacillin, Imipenem, Meropenem, Nafcillin, Oxacillin, Penicillin-G, Penicillin-V, Piperacillin, Piperacillin-Tazobactam, Ticaracillin-Clavulanate	Ertapenem, Penicillin-G, Benzathine/Procaine
Tetracyclines	
Doxycycline (100 mg), Minocycline, Tetracycline	Doxycycline (200 mg), Minocycline Extended Release

Appendix 3 Closely Monitored CYP3A4 Substrates and P-Glycoprotein Substrates (excluding strong CY3A inducers and inhibitors and excluding strong P-glycoprotein inhibitors)

Closely Monitored CYP3A4 Substrates		
Alfentanyl	Domperidone	Pimozide
Alprazolam	Eplerenone	Progesterone
Amiodipine	Estradiol	Propranolol
Aprepitant	Fentanyl	Quetiapine
Aripiprazole	Finasteride	Quinine
Astemizole	Gleevec	Reserpine
Buspirone	Haloperidol	Salmeterol
Cafergot	Hydrocortisone	Sildenafil
Caffeine	Lercanidipine	Sirolimus
Chlorpheniramine	Lidocaine	Terfenadine
Cilostazol	Methadone	Testosterone
Cocaine	Midazolam	Trazodone
Codeine	Nateglinide	Triazolam
Dapsone	Nifedipine	Zaleplon
Dexamethasone	Nisoldipine	Ziprasidone
Dextromethorphan	Nitrendipine	Zolpidem
Docetaxel	Ondansetron	

Closely Monitored P-Glycoprotein Substrates		
Apixaban	Fexofenadine	Ranitidine
Carvedilol	Fosamprenavir	Rivaroxaban
Cimetidine	Ivermectin	Saxagliptin
Colchicine	Ledipasvir	Silodosin
Dabigatran	Loperamide	Sitagliptin
Daclatasvir	Losartan	Sofosbuvir
Dasabuvir	Maraviroc	Tetracycline
Dexamethasone	Methylprednisolone	Tipranavir
Digoxin	Methotrexate	Tolvaptan
Domperidone	Morphine	Umeclidinium
Edoxaban	Ombitasvir	Vecuronium
Empagliflozin	Paliperidone	Vilanterol
Estradiol	Paritaprevir	
Ezetimibe	Prazosin	

Appendix 4 Prohibited Strong P-Glycoprotein Inhibitors and Strong CYP3A Inducers and Inhibitors

Prohibited Strong P-Glycoprotein Inhibitors		
Amiodarone	Indinavir	Ranolazine
Atorvastatin	Itraconazole	Reserpine
Boceprevir	Ketoconazole	Ritonavir
Bromocriptine	Linagliptin	Saquinavir
Captopril	Lopinavir and ritonavir	Simeprevir
Carvedilol	Lovastatin	Simvastatin
Cobicistat	Meperidine	Suvorexant
Conivaptan	Methadone	Tacrolimus
Cyclosporine	Nelfinavir	Tamoxifen
Diltiazem	Nicardipine	Telaprevir
Doxazosin	Pentazocine	Ticagrelor
Dronedarone	Progesterone	Verapamil
Felodipine	Quercetin	
Fluvastatin	Quinidine	

Prohibited Strong CYP3A Inhibitors	Prohibited Strong CYP3A Inducers
Indinavir	Efavirenz
Nelfinavir	Nevirapine
Ritonavir	Phenobarbital
Itraconazole	Phenytoin
Ketoconazole	Pioglitazone
Nefazodone	Rifabutin
Saquinavir	Rifampin
Suboxone	St. John’s Wort
Carbamazepine	Troglitazone

Appendix 5 Drugs That Prolong QT

Anticonvulsants	Fosphenytoin; Felbamate
Antihistamines	Azelastine, Clemastine
Anti-infectives	Amantadine, Clarithromycin, Chloroquine, Foscarnet, Erythromycin, Halofantrine, Mefloquine, Pentamidine, Sparfloxacin, Quinine, Trimethoprim-Sulfamethoxazole, Ketoconazole
Antineoplastics	Tamoxifen
Cardiovascular	
Antiarrhythmics	Amiodarone, Bretylium, Disopyramide, Flecainide, Ibutilide, Procainamide, Quinidine, Sotalol, Dofetilide
Calcium Channel Blockers	Bepridil, Israpidine, Nicardipine
Diuretics	Indapamide, Moexipril/ hydrochlorothiazide
Hormones	Octreotide, Vasopressin
Immunosuppressives	Tacrolimus
Migraine: Serotonin Receptor Agonists	Zolmitriptan, Naratriptan, Sumatriptan
Muscle Relaxants	Tizanidine
Narcotic Detoxification	Levomethadyl
Psycotherapeutics	
Antidepressants	Amitriptyline, Desipramine, Fluoxetine, Imipramine, Venlafaxine
Antipsychotics	Chlorpromazine, Haloperidol, Pimozide, Quetiapine, Risperidone, Thioridazine
Antianxiety	Doxepin
Antimanic	Lithium
Respiratory (Sympathomimetics)	Salmeterol
Sedative/Hypnotics	Chloral hydrate

Note: List not exhaustive

A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Oral Lefamulin (BC-3781) Versus Oral Moxifloxacin in Adults with Community-Acquired Bacterial Pneumonia

Protocol: NAB-BC-3781-3102

FINAL

STATISTICAL ANALYSIS PLAN

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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 Oral Lefamulin (BC-3781) Versus Oral Moxifloxacin 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. A separate analysis plan will be written for the health utilization and patient-reported outcome analyses.

Study NAB-BC-3781-3102 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 oral lefamulin (600 mg every 12 hours [q12h]) and oral moxifloxacin (400 mg every 24 hours [q24h]) in the treatment of adult subjects with community-acquired bacterial pneumonia (CABP). The duration of blinded study drug administration is 7 days. Subjects randomized to lefamulin will receive oral lefamulin 600 mg q12h for 5 days (10 doses) and oral moxifloxacin placebo q24h for 7 days (7 doses). Subjects randomized to moxifloxacin will receive oral moxifloxacin 400 mg q24h for 7 days (7 doses) and oral lefamulin placebo q12h for 5 days (10 doses).

A total of 738 subjects with CABP (Pneumonia Outcomes Research Team [PORT] Risk Class II, III, or IV) will be randomized 1:1 to study treatment (369 to each treatment arm) using interactive response technology (IRT). Randomization will be stratified by geographic region (US vs ex-US), prior single dose treatment with a short acting antibiotic vs. none, and by PORT risk class: (PORT II vs. III/IV). Enrollment of subjects receiving prior single dose treatment with a short acting antibiotic will be capped at 25%. A minimum of 50% of the total number of subjects randomized will have a PORT Risk Class of III or IV.

After informed consent is obtained, all potential study participants undergo screening evaluations, which includes a medical history, clinical assessments, and laboratory assessments. 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 on Day 30 (±3 days).

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:** This is the primary efficacy endpoint for the EMA.
- Evaluate the Early Clinical Response in the Microbiological Intent-to-Treat (microITT) 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 Early Clinical Response PLUS improvement in vital signs in the ITT Analysis Set

- Evaluate the plasma pharmacokinetics of lefamulin and its main metabolite, BC-8041, in the Pharmacokinetic Analysis Set
- Explore a variety of health utilization variables and an investigational patient reported outcome measure 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 for microbiologic specimens 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 the administration of the first dose of study drug or the 24 hours after the first dose of study. A Gram stain from a specimen collected at baseline is considered a baseline Gram stain.

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.

In general, the central lab identification of genus and species 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 remains unavailable for an isolate after the lab has requested the isolate be resent, the local laboratory identification will be used. For any discrepancies in genus and/or species identification between the central and local laboratory, the central laboratory identification will be used as the default identification. Thus, it is possible for subjects to have different isolates from both central and local laboratories as a result.

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-PCRof sputum (see Table 1 for cutoff value); or

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 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 per the radiologists interpretation). **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 of II, III or IV and be an appropriate candidate for oral antibiotic therapy as 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 Day 30 (±3 days) 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 from the first dose of study drug through EOT (CE-EOT), through TOC (CE-TOC) or through LFU (CE-LFU) 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.

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, MRSA, *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 16: 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 *Enterobacteriacea* 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 concentration results from at least one pharmacokinetic sample.

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 (as described in Section 6.1) 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 – Day 30 (±3 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 as defined in Section 6.1. 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 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 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 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 are randomized and not treated or 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 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 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 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 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 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.

6.2.4 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
- Proportion of subjects with an ECR of responder PLUS improvement in vital signs in the ITT Analysis Set

Other additional efficacy outcomes specified in this SAP include:

- Percentabe 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 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 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:

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

6.3.2 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 all vital signs (ie, body temperature, blood pressure, heart rate, respiratory rate) that were abnormal at baseline. Improvement is defined as returning to normal. If a vital sign was normal at baseline (ie, not abnormal as per the definitions below), it cannot 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, <36.0°C (96.8°F) measured rectally, or <34.5°C (94.1°F) by axillary measurement
  - 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 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 all vital signs that was abnormal at baseline. 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
  - Systolic blood pressure ≥90 mmHg
  - Heart rate >50 to ≤100 beats/min
  - Respiratory rate ≤20 breaths/min; or
- Received a concomitant antibiotic 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):

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

6.4 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 for subjects in the lefamulin group.

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 738 subjects will be randomized in a ratio of 1:1 (lefamulin:moxifloxacin) resulting in 369 subjects in the lefamulin arm and 369 in the moxifloxacin arm in this study. 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 as well as 2 recent clinical trials in CABP indicate the point estimates for an ECR responder at Days 3-5 range from 72% to 81% (FDA, 2011; Barrera et al., 2016; Cempra, 2015; Oldach et al., 2015**)**. Thus, it is reasonable to assume that in a prospective study of subjects with CABP, the proportion 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 (MAA) to the EMA will be the proportion 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% to 93% (Cempra, 2015) and in the ITT

Analysis Set ranged from 85% to 89% depending on the antibiotics under study and the severity of the CABP. 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, a 1:1 randomization ratio, a one-sided alpha of 0.025, and a continuity corrected Z-test with unpooled variance, a sample size of 738 subjects (369 subjects in the lefamulin group and 369 in the moxifloxacin group) provides 90% power to establish the NI of lefamulin to moxifloxacin for ECR using a NI margin of 10.0%. 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 91% power for demonstration of NI for IACR at the TOC Visit using a 10% NI margin.

The calculated power in each analysis set for the primary and secondary outcomes is provided in Table 7.

Table 7. Power Calculations for the Primary and Secondary Efficacy Outcomes

	Primary Outcome (FDA) (ECR 96 ± 24 hours After the First Dose of Study Drug)	**Secondary Outcome (Investigator's Assessment of Clinical Response at TOC- Primary for EMA)**	
Analysis Set	ITT	mITT	CE-TOC
NI Margin	10%	10%	10%
N	738 (369:369)	738	590
Outcome Rate	79%	80%	85%
Evaluability Rate	NA	NA	80%
Power	90%	91 %	91%

CE = clinically evaluable; ITT = intent to treat; mITT = modified ITT; TOC = test of cure

7.2 Visit Windows

7.2.1 Baseline

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 Screening assessment (since time of assessment is not captured) as long as the date of collection is on or before the date of first dose of study drug.
- For ECGs, baseline is defined as the mean of the triplicates (or duplicate or single, if a triplicate is not obtained) from the last assessment prior to the first dose of study drug, including scheduled and unscheduled visits.
- If no study drug is received, baseline is defined as the measurement taken at the Screening Visit (ie, prior to the randomization date/time)

Study Day 1 is defined as the first calendar day of study drug administration (or the date of randomization if no study drug was received). The calendar day prior to the first dose of study drug (or randomization day if no study drug is received) 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.

7.2.2 Post-Baseline

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). When a nominal visit assessment is unavailable, an unscheduled assessment may be utilized as described in Appendix D.

See Appendix A for a complete description on the timing of the safety assessments. See Appendix D for a summary of visit window definitions for the safety assessments.

7.2.3 Unscheduled 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 as described in Appendix D. 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 should be used. All unscheduled visits not satisfying the analysis visit condition as described in Appendix D will be referred to as "Unscheduled" as their analysis visit designation. For overall worst post-baseline analyses (i.e. minimum, maximum, highest, lowest, any post-baseline, and PCS), all assessments including those obtained on unscheduled (i,e. analysis visit "Unscheduled") and scheduled visits (e.g., analysis visits "Baseline", "Day 1", "Day 4", "TOC", "EOT" and "LFU") will be included. See Section 8.7.2 for a discussion of when to use central and local safety laboratory values.

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 (II vs. III/IV) 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

No interim analyses of efficacy will be conducted.

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.

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 (or date of randomization if no study drug was received). For concomitant medications and prior medications taken on the same day as the first dose of study drug (or date of randomization if no study drug was received), start day will be calculated as the start date of the medication minus the date of the first dose of study drug (or date of randomization if no study drug was received), 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 a post-baseline 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. If the time of assessment of CABP symptoms obtained on or prior to the date of the first dose of study drug is missing, the time will be imputed to 00:00.
- 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:

- If a followup specimen for culture was not obtained, microbiological response at the EOT Visit will be determined based on 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. If a followup specimen for culture was not obtained and the pathogen/subject was not a microbiologic persistence/failure at EOT, microbiological response at the TOC Visit will be determined based on IACR at the TOC Visit. If the IACR at the TOC Visit is indeterminate, the microbiological response at the TOC Visit will be indeterminate, unless a followup specimen for culture was obtained.
- 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. If a followup specimen for culture was not obtained and the pathogen/subject was not a microbiologic persistence/failure at TOC, microbiological response at theLFU Visit will be determined based on IACR at the LFU Visit. If the IACR at the LFU Visit is indeterminate, the microbiological response at the LFU Visit will be indeterminate, unless a followup specimen for culture was obtained.
- 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, Chile, Mexico, Peru), Eastern Europe (Bulgaria, Georgia, Latvia, Russia, Serbia, Ukraine), Western Europe (Hungary, Poland, Spain) and Rest of World (Philippines, South Korea, Taiwan, 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), completing the EOT assessment, completing the TOC assessment, 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 [II, III/IV] as well as calculated from components reported in the eCRF [II, III/IV]), subjects meeting minor and 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 (defined as altered mental status as recorded on the PORT Risk Assessment eCRF)
- 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
- age ≥65 years.

ATS severity and SIRS criteria are derived from the eCRF data and baseline PMNs reported in the central safety laboratory data. The minor 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 (defined as infiltrates present in any two locations, except lingula and left upper loabe is not multilobar. Lingula and other location is multilobar)
- platelets <100,000 cells/mm^3
- temperature <36°C
- systolic blood pressure <90 mmHg.

Modified ATS severity criteria is defined as presence of ≥3 of the following 6 criteria at baseline:

- respiratory rate ≥30 breaths/min
- SpO_2/FiO_2 <274 where SpO_2/FiO_2 = 64+0.84 (PaO_2/Fi O_2)
- BUN ≥20 mg/dL
- Confusion
- Age ≥ 65 years
- multilobar infiltrates.

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 the baseline Gram-stained respiratory specimens (ie, the best Gram stain reading) 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 the 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.

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*.

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 (placebo and/or active, as well as active only) will be summarized for the Safety and mITT 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 1-2 days, ≥3-5 days, and 6-8 days as well as descriptive statistics of the number of days on study drug (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group.

The proportion of subjects receiving all doses of study drug as inpatients, receiving all doses of study drug as outpatients and receiving doses of study drug as both inpatients and outpatients will be presented for the mITT Analysis Set.

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 (or date of randomization if no study drug was received). 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 (or date of randomization if no study drug was received) will be considered concomitant; medications stop dates occurring prior to the date of first dose of study drug (or date of randomization if no study drug was received) 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 (or date of randomization if no study drug was received).

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 (or date of randomization if no study drug was received). 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 (or date of randomization if no study drug was received).

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 (or the next available level if level 4 is not available) 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, mITT 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 (or the next available level if level 4 is not available), 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 number of treatment days (ie, the date of the first and last dose of study drug). Treatment compliance is defined as the number of doses actually received divided by the number of doses expected for the time period between the dates of the first and last doses of study drug (× 100). Subjects are expected to receive 7 days of study drug (5 days of active lefamulin plus 2 days of placebo) or moxifloxacin (7 days of active moxifloxacin). Descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) will be presented for the ITT, microITT, CE-EOT 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 -10%, 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 (II vs. III/IV). 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 (II, III, IV), 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. 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.

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 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.

8.5.3.4 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.*

8.5.3.5 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. A 2-sided unadjusted 95% CI for the difference in IACR sustained success rates will be calculated using a continuity corrected Z-test.

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 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 was performed, the assessment will be summarized both at the study day and the EOT Visit.

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.

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 for the lefamulin 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, 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 (1-3 hours after the first dose of study drug), Day 4 (inpatients)/96±24h after the first dose of study drug (outpatients) (prior to the first dose of study drug) and Day 4 (1-3 hours after the first dose of study drug) will be summarized by treatment group for subjects in the Safety Analysis Set. In addition, Day 4 post-active dose will be summarized. Change from baseline will be calculated for each subject at Day 1 (1-3 hours after the first dose of study drug) and Day 4 (inpatients)/96±24h after the first dose of study drug (outpatients) (prior to and 1-3 hours after the first dose 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).

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APPENDIX A: SCHEDULE OF ASSESSMENTS AND PROCEDURES

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

Assessment or Procedure	*Screening/ Baseline* [a]	*Study Drug Administration*				*EOT* [d]	*Follow-up Visits*	
		Day 1 [b]	*Day 2*	*Day 3*	*Days 4 to 7* [c]	*Visit*	*TOC* [e]	*LFU* [f]
Investigator's Assessment of Clinical Response (IACR) [z]						X	X	X

NOTE: Hospitalization is not a requirement for this study. However, all subjects, including Outpatients, must be evaluated at the investigational site by study personnel at the following time points/visits: Screening/Baseline; Day 1; Day 4 / 96 ± 24 hours after the first dose of study drug; EOT; TOC; and LFU.

a: Perform Screening/Baseline assessments within 24 hours before the first dose of study drug. Administration of study drug should begin as soon as possible after the diagnosis of CABP. ***See Footnote x.*** Assessments performed as part of routine standard of care prior to consent (e.g., 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. Assessments/ procedures on Day 1 should be performed prior to first dose.

c: INPATIENTS will be assessed daily while hospitalized; thus, data required for ECR Assessment (96 ± 24 hours after the first dose of study drug) will be collected.
OUTPATIENTS **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 during the course of daily telephone contact. In addition to the assessment of CABP signs/symptoms, subjects will also have the following procedures/assessments performed at that study site visit: ECGs, physical examination, AE monitoring, review of concomitant medications, vital signs, oxygen saturation, and blood sampling for PK analysis and safety laboratory evaluations. Importantly, study personnel will advise OUTPATIENTS not to take their first dose of study drug at home that day, rather to bring their blister packs (used and unused) to the study site where they will take their dose while supervised; thus, specific assessments can be performed both prior to and after taking the dose (i.e., ECGs and PK). ***See Footnotes i, k, l, m, o, p, and y below for details***.

d: Perform End of Treatment (EOT) assessments at the study site within 1 day (up to 2 days permitted) 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.

e: Perform Test of Cure (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.

f: Perform Late Follow Up (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.

g: Obtain informed consent before initiating any study-specific assessments or procedures.

h: Assessment or procedure may occur at either Screening OR prior to the first dose of study drug on Day 1 once eligibility has been determined.

i: All subjects will have vital signs and O_2 saturation evaluated at Screening/Baseline and Day 1. If screening/baseline and Day 1 occur on the same calendar day, vital signs and O_2 saturation do not need to be repeated. All subjects will also have assessments at EOT and TOC; at LFU, vital signs should be performed if medically indicated. 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 (i.e., as part of the EOT assessment). Record the vital signs associated with the highest temperature after the first dose of study drug.
INPATIENTS: Vital signs, O_2 saturation, and supplemental O_2 usage will be measured daily. If multiple vital signs are taken on a study day, the highest temperature and the vital signs associated with that high temperature will be recorded.
OUTPATIENTS: In addition to the above time points, vital signs, O_2 saturation and, if applicable, supplemental O_2 usage will be measured at the study visit scheduled 96 ± 24 hours after the first dose of study drug.

j: Study personnel will evaluate signs and symptoms of CABP at Baseline, daily while on study therapy, and at EOT, TOC, and LFU Visits. *NOTE*: 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 (i.e., as part of the EOT assessment). Signs and symptoms are not obtained at TOC or LFU if the subject was previously deemed to have an IACR of Failure.
OUTPATIENTS: Study personnel will contact subjects daily by telephone to track signs and symptoms of CABP; **however, subjects must report to the study site for the assessment of CABP signs/symptoms 96 ± 24 hours after the first dose of study drug**. ***See Footnote c***.

k: 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. In addition, study personnel will monitor AEs for OUTPATIENTS in conjunction with daily telephone contacts for CABP signs/symptoms and at the study site visit 96 ± 24 hours after the first dose of study drug. ***See Footnote c.***

l: **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. If Screening and Day 1 are on the same day, the Screening ECG can serve as the Day 1 ECG prior to the first dose of study drug; an additional ECG must be performed 1-3 hours after administration of first dose. ***See Footnote m.***

m: INPATIENTS: The Day 4 ECG in triplicate is required prior to the first dose of study drug and again within 1-3 hours after the first dose of study drug.
OUTPATIENTS: The Day 4 ECG can be performed at the required study site visit 96 ± 24 hours after the first dose. ***See Footnote c.*** The Day 4 ECG in triplicate is required prior to the first dose of study drug and again within 1-3 hours after the first dose of study drug.

n: A complete physical examination is performed at Baseline and directed physical examinations are performed thereafter.

o: INPATIENTS: On Day 4, a directed physical examination will be performed..
OUTPATIENTS: A directed physical examination will be performed at the study site visit scheduled 96 ± 24 hours after the first dose. ***See Footnote c.***

p: 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. Collect blood and/or urine at LFU only if subject had an abnormal (high/low flag) result at TOC.

q: INPATIENTS: On Day 4, blood and urine samples will be collected for safety laboratory evaluations.
OUTPATIENTS: Blood and urine samples will be collected for safety laboratory evaluations at the study site visit scheduled 96 ± 24 hours after the first dose. ***See Footnote c.***

r: A urine pregnancy test will be performed at the site on all females unless surgically sterile or at least 2 years post-menopausal. A negative urine pregnancy test is required prior to randomization. Serum must be collected on Day 1 prior to 1st dose and sent to the central lab for confirmatory testing.

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

t: Collect blood samples (2 sets via peripheral venipuncture) for microbiologic culture and susceptibility testing at the local/regional lab at Baseline 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.

u: All lower respiratory tract and expectorated sputum samples should be sent to the local/regional laboratory for Gram's stain, culture and susceptibility testing. A sputum sample will be taken at Screening for Gram's staining, culture and susceptibility testing at the local/regional laboratory. 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 Baseline sputum samples must be frozen until sent to the central laboratory for quantitative PCR. Subjects with a urinary antigen positive for *Legionella* spp. will also have a portion of their sputum sample sent frozen to the central laboratory for isolation of *L. pneumophila*.

v: 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.

w: An oropharyngeal specimen (2 swabs) and a nasopharyngeal specimen (1 swab) 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. The nasopharyngeal specimen will be used for culture and identification by PCR of *S. pneumoniae,* and potentially, *H. influenzae.*

x: Study personnel will administer the first dose of study drug at the study site, as soon as possible after the diagnosis of CABP and completion of all required pre-dose Day 1 procedures. On Day 1, if q12h dosing is not feasible, the 1st and 2nd doses may be administered as close as 8 hours apart, in order to allow 2 doses to be given on Day 1. In this circumstance, the subject's dosing schedule should be adjusted on Day 2 to a regular q12h morning and evening schedule. Subsequently, every effort should be made to maintain a q12h dosing schedule. When this is not possible, it is acceptable to administer doses within 4 hours of the scheduled dosing time (i.e., a minimum of 8 hours between doses). For Outpatients, or in the event a subject is discharged from the hospital during the study drug administration period, an adequate supply of study drug will be dispensed for self-administration at home. Subjects will be provided instructions regarding the dosing schedule. Subjects may self-administer oral study drug at home with the following exception: Study personnel will advise subjects who are

Outpatients that they must return to the study site to assess CABP signs and symptoms at 96 ± 24 hours after the first dose of study drug. **See Footnote c.** Administration of study drug may occur on the same calendar day as EOT, and if so will be completed before EOT assessments begin.

y: Collect blood samples for PK analysis relative to the first dose of study drug. Blood will be collected within 1 h pre-dose, 1-2 h post dose, and 3-4 h post dose, and 8-9 h post dose. INPATIENTS: PK sampling should occur on Day 4 but, if not feasible, it can be done relative to the first dose on Day 5; the 8-9 h post dose is required. OUTPATIENTS: PK sampling will be done during the 96 ± 24 hours post 1st dose visit. The 8-9 h post dose sample is optional; however, it should be obtained if logistically feasible.

z: Investigator to determine IACR - Success, Failure or Indeterminate (i.e., 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.

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

APPENDIX D: SAFETY ASSESSMENT WINDOWS

Vital Signs:

Analysis Visit	Study Visit	Target Day	If scheduled study visit assessment not available:	
			Consider Unscheduled assessment for Analysis Visit?	Study Days acceptable for Analysis Visit[1]
Baseline	Screening[2]	-	No	-
Day 1	Day 1	1	Yes	1
Day 2	Day 2	2	Yes	2
Day 3	Day 3	3	Yes	3
Day 4	Day 4	4	Yes	4
Day 5	Day 5	5	Yes	5
Day 6	Day 6	6	Yes	6
Day 7	Day 7	7	Yes	7
EOT	EOT	-	Yes	within 2 days after the last dose of study drug (i.e., last day of study drug through 2 subsequent calendar days)
TOC	TOC	-	Yes	5-10 days after last dose of study drug
Unscheduled[3]	-	-	Yes	

Notes: EOT: End of Treatment; TOC: Test of Cure; N/A: Not applicable.
[1] Except for Baseline, if more than 1 measurement is taken during the visit window (and no scheduled is taken) the earliest value will be analyzed..
[2] Provided the date of collection is on or before the date of first dose
[3] Any unscheduled assessments not meeting the criteria for an analysis visit.

ECG:

Analysis Visit and Timepoint	Timepoint	Target Day		
			Consider Unscheduled assessment for Analysis Visit?	Study Days acceptable for Analysis Visit
Baseline	Screening or Day 1 pre-dose or Unscheduled[1]		Yes	-4 to ≤1 *(pre-dose)*
Day 1 post dose	Day 1 post-dose	1	No	-
Day 4 pre dose	Day 4[2] pre-dose	4	No	-
Day 4 post dose[4]	Day 4[2] post-dose	4	No	-
Unscheduled[3]	Unscheduled	-	-	-

Notes: N/A: Not applicable.
[1] Baseline is the mean of the triplicates (or duplicates or single if a triplicate is not obtained) from the last assessment prior to the first dose of study drug.
[2]The timepoint identified as the Day 4 or 96 +/- 24 hour timepoint regardless of visit.
[3] Any unscheduled assessments (i.e., timepoint='Unscheduled') not meeting the criteria for an analysis visit.
[4] In addition, Day 4 post-active dose will be summarized.

Safety Laboratory:

Analysis Visit	Study Visit	Target Day	If scheduled study visit assessment not available:		
			Consider Unscheduled central assessment for Analysis Visit? [1]	Consider Local lab assessments for Analysis Visit?	Study Days acceptable for Analysis Visit
Baseline	Screening[2]	-	Yes	No	-4 to ≤1[2]
Day 4	Day 4[3]	4	Yes	No[4]	3 to 6
EOT[5]	EOT	-	Yes	No[4]	within 2 days after the last dose of study drug (i.e., last day of study drug through 2 subsequent calendar days)
TOC	TOC	-	Yes	No[4]	5-10 days after last dose of study drug
LFU	LFU	30	Yes	No[4]	27 to 33
Unscheduled[6]	-	-	Yes	Yes[4]	-

Notes: EOT: End of Treatment; TOC: Test of Cure; LFU: Late Follow-up; N/A: Not applicable.
[1] Except for Baseline, if more than 1 central measurement is taken during the visit window (and no scheduled is taken) the earliest value will be analyzed.
[2] Provided the date and time of collection is on or before the date and time of first dose
[3] The visit identified as the 96 +/- 24 hour visit (i.e., study visit Day 4, Day 5, or Day 6).
[4] Local labs assessment are to be included in the identification of worst post-baseline values (i.e. minimum, maximum, highest, lowest, any post-baseline, and PCS). See section 8.7.2.
[5] If an EOT assessment is done within the day 4 visit window, and no assessment was done at the study day 4 visit, the assessment will be reported at both the Day 4 and EOT analysis visits.
[6] Any unscheduled assessments not meeting the criteria for an analysis visit.

A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Oral Lefamulin (BC-3781) Versus Oral Moxifloxacin in Adults with Community-Acquired Bacterial Pneumonia

Protocol: NAB-BC-3781-3102

FINAL

STATISTICAL ANALYSIS PLAN ADDENDUM

EUROPEAN MEDICINES AGENCY

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

CABP	Community Acquired bacterial pneumonia
CE	Clinically evaluable
CE-EOT	Clinically Evaluable at End-of-Treatment
CE-TOC	Clinically Evaluable at Test-of-Cure
CE-LFU	Clinically Evaluable at Late Follow Up
CI	Confidence interval
ECR	Early Clinical Response
eCRF	Electronic case report form
EMA	European Medicines Agency
emicroITT	Expanded Microbiological Intent-to-Treat
EOT	End of Treatment
FDA	Food and Drug Administration
IACR	Investigator's Assessment of Clinical Response
ITT	Intent-to-Treat
LFU	Late Follow Up
ME	Microbiologically evaluable
ME-EOT	Microbiologically Evaluable at End-of-Treatment
ME-LFU	Microbiologically Evaluable at Late Follow Up
ME-TOC	Microbiologically Evaluable at Test-of-Cure
microITT	Microbiological Intent-to-Treat
microITT-2	Microbiological Intent-to-Treat-2
mITT	Modified Intent-to-Treat
NI	Non-inferiority
PORT	Pneumonia Outcomes Research Team
SAP	Statistical Analysis Plan
TOC	Test of Cure
US	United States

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 Oral Lefamulin (BC-3781) Versus Oral Moxifloxacin in Adults With Community-Acquired Bacterial Pneumonia." Changes made to the 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.

Protocol NAB-BC-3781-3102 has been designed to address both the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory requirements. As a consequence of different regulatory requirements for the statistical analysis of this study, a Primary SAP and a SAP Addendum have been developed. This SAP Addendum applies to regions outside of the US and is based on requirements of the EMA, while the Primary SAP details the approach for the US FDA. This SAP Addendum addresses the different primary efficacy outcome and analyses for the EMA. For other analyses which are the same for both regions, refer to the Primary SAP.

2.0 STUDY DESIGN

Refer to the Primary SAP.

3.0 STUDY OBJECTIVES

The main difference in study requirements between the US FDA and EMA relates to the primary outcome. The primary outcome for the EMA is a secondary outcome for the US FDA and vice-versa. For the EMA the objectives are:

Primary:

- Demonstrate the non-inferiority (NI) of lefamulin versus comparator with respect to the Investigator's Assessment of Clinical Response (IACR) at Test of Cure (TOC) (ie, 5-10 days after the last dose of study drug) in the modified-Intent-to-Treat (mITT) and Clinically Evaluable at TOC (CE-TOC) Analysis Sets.

Secondary:

- Demonstrate the NI of lefamulin versus comparator with respect to the Early Clinical Response (ECR) (96 ± 24 hours after the first dose of study drug) in the Intent-to-Treat (ITT) Analysis Set. Note: This is the primary efficacy endpoint for the US FDA.

All other secondary and additional objectives remain the same as those in the Primary SAP.

4.0 PATHOGEN IDENTIFICATION

Refer to the Primary SAP.

5.0 ANALYSIS SETS

Refer to the Primary SAP.

6.0 DEFINITIONS OF OUTCOME MEASURES

Although the primary and first secondary efficacy outcomes in this EMA SAP Addendum differ compared to the Primary SAP, the definitions and details surrounding these measurements are identical and are fully described in the Primary SAP.

7.0 STATISTICAL METHODS

7.1 Sample Size

A total of 738 subjects will be randomized in a ratio of 1:1 (lefamulin:moxifloxacin) resulting in 369 subjects in the lefamulin arm and 369 in the moxifloxacin arm in this study. The total number of subjects included in this study is sufficient to achieve the primary and secondary study objectives based on statistical considerations.

The primary efficacy analysis variables used for NI analyses for the Marketing Authorization Application (MAA) to the EMA will be the proportion 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% to 93% (Cempra, 2015) and in the ITT Analysis Set ranged from 85% to 89% depending on the antibiotics under study and the severity of the CABP. 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.

Retrospective analyses of clinical study data for patients with CABP of varying severity as well as 2 recent clinical trials in CABP indicate the point estimates for an ECR responder at Days 3-5 range from 72% to 81% (FDA, 2011; Barrera et al., 2016; Cempra, 2015; Oldach et al., 2015). Thus, it is reasonable to assume that in a prospective study of subjects with CABP, the proportion of subjects who are responders for ECR at 96 ± 24 hours post first dose of study drug will be approximately 79%.

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 91% power for demonstration of NI for IACR at the TOC Visit using a 10% NI margin. Utilizing an anticipated ECR responder rate of 79% in the ITT Analysis Set, a 1:1 randomization ratio, a two-sided alpha of 0.025, and a continuity corrected Z-test with unpooled variance, a sample size of 738 subjects (369 subjects in the lefamulin group and 369 in the moxifloxacin group) provides 90% power to establish the NI of lefamulin to moxifloxacin for ECR using a NI margin of 10.0%.

The calculated power for the primary and secondary outcome measures is provided in Table 1.

Table 1. Power Calculations for the Primary and Secondary Outcome Measures

	Primary Outcome (Investigator's Assessment of Clinical Response - TOC)		Secondary Outcome (Primary for FDA) (Early Clinical Response)
Analysis Set	mITT	CE-TOC	ITT
NI Margin	10%	10%	10%
Evaluability Rate	738	590	738 (369:369)
Outcome Rate	80%	85%	79%
N	NA	80%	NA
Power	91 %	91%	90%

For more details on statistical methods, refer to the Primary SAP.

8.0 STATISTICAL ANALYSES

The changes for this EMA SAP Addendum in this section as compared with the Primary SAP relate to the primary efficacy analysis as well as the methodology for calculating the 95% CIs for the secondary and additional outcomes of IACR.

8.1 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 Pneumonia Outcomes Research Team (PORT) risk class stratum will be analyzed in the stratum to which they were randomized.

8.1.1 Primary Efficacy Analysis

The primary efficacy analyses will be based on the mITT and CE-TOC Analysis Sets. The NI test will be a 1-sided hypothesis test performed at the 2.5% level of significance. This NI test will be based on the lower limit of the 2-sided 95% confidence interval (CI). Co-primary efficacy outcomes are the percentage of subjects with an IACR of success at the TOC Visit in the mITT and CE-TOC Analysis Sets. The primary analysis is adjusted for the randomization stratification factors of geographic region (US vs. ex-US), receipt of prior single dose short-acting antibiotic therapy for CABP (yes vs. no), and by PORT risk class (II vs. III/IV).

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).

The null and alternative hypotheses are as follows:

$$H_0 : p_{1i} - p_{2i} \leq -\Delta \text{ or } p_{1c} - p_{2c} \leq -\Delta$$

$$H_1 : p_{1i} - p_{2i} > -\Delta \text{ and } p_{1c} - p_{2c} > -\Delta$$

where p_{1i} is the primary efficacy outcome rate in the lefamulin treatment group in the mITT Analysis Set, p_{1c} is the primary efficacy outcome rate in the lefamulin treatment group in the CE-TOC Analysis Set, p_{2i} is the primary efficacy outcome rate in the moxifloxacin treatment group in the mITT Analysis Set, p_{2c} is the primary efficacy outcome rate in the moxifloxacin treatment group in the CE-TOC Analysis Set, and Δ is the non-inferiority margin of 10%.

To test the null hypothesis, a 2-sided 95% CI for the observed difference in primary outcome rates (lefamulin treatment group minus moxifloxacin treatment group) will be calculated for the mITT and CE-TOC Analysis Sets. If the lower limit of the 95% CI for the difference in success rates in *both* the mITT and CE-TOC Analysis Sets is greater than –10%, then the null hypothesis will be rejected and the NI of lefamulin to moxifloxacin will be concluded.

The 2-sided 95% CI for NI testing based on the difference of IACR success rates, will be computed using the method proposed with adjustment for the randomization stratification factors by Miettinen and Nurminen (1985). For notation purposes, assume 1 represents the lefamulin group (Group 1) and 2 represents the moxifloxacin group (Group 2). Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI as follows:

$$W_i = \frac{n_{1i} n_{2i}}{n_{1i} + n_{2i}}$$

Based on Miettinen and Nurminen, the 2-sided 95% CI is given by the roots for $RD = p_1 - p_2$ of the following equation.

$$\chi_\alpha^2 = \frac{(\hat{p}_1 - \hat{p}_2 - RD)^2}{\sum_i \left(\frac{W_i}{\sum_i W_i} \right)^2 \tilde{V}_i}$$

where χ_α^2 is the cut point of size α from the chi-square distribution (χ_α^2=3.84 for 2-sided 95% CI); RD is the difference between the 2 true rates ($RD = p_1 - p_2$); $\hat{p}_1$ = the observed weighted average (across the i strata) proportion in Group 1; $\hat{p}_2$ = the observed weighted average (across the i strata) proportion in Group 2; and

$$\widetilde{V}_i = \left[\frac{\widetilde{p}_{1i}(1-\widetilde{p}_{1i})}{n_{1i}} + \frac{\widetilde{p}_{2i}(1-\widetilde{p}_{2i})}{n_{2i}} \right] \frac{n_{1i}+n_{2i}}{n_{1i}+n_{2i}-1}$$

where n_{1i} = number of subjects in Group 1 in the ith stratum; n_{2i} = number of subjects in Group 2 in the ith stratum; $\widetilde{p}_1 = \widetilde{p}_2 + RD$; and $\widetilde{p}_2$ is the maximum likelihood estimate for p_2 as a function of RD and under the constraint $p_1 = p_2 + RD$.

As stated above, the 2-sided 95% CI for the difference in rates is given by the roots for $RD = p_1 - p_2$ from the equation above, but this equation does not allow for explicit solution for RD. Therefore, a numerical algorithm will be used to obtain the 2 roots (CI) for RD. This CI approach corresponds to the NI test (a p-value approach) proposed by Farrington and Manning (1990).

8.1.2 Additional Analyses of the Primary Efficacy Outcome

Sensitivity analyses of IACR at the TOC Visit include:

- Subjects with an indeterminate response will be reclassified as a clinical success. The number and percentage of subjects in each treatment group determined to have an IACR of success or failure at the TOC Visit will be presented for the mITT Analysis Set. An adjusted (for the randomization stratification factors) 95% CI will be computed using the method of Miettinen and Nurminen for the difference in the IACR success rates between lefamulin and moxifloxacin. A second unadjusted 95% CI will be computed using a continuity corrected Z-test.
- Subjects with an indeterminate response at the End of Treatment (EOT) Visit are considered an indeterminate response at the TOC Visit. The number and percentage of subjects in each treatment group determined to have an IACR of success, failure, or indeterminate at the TOC Visit will be presented for the mITT and CE-TOC Analysis Sets. An adjusted (for the randomization stratification factors) 95% CI will be computed using the method of Miettinen and Nurminen for the difference in the IACR success rates between lefamulin and moxifloxacin. A second unadjusted 95% CI will be computed using a continuity corrected Z-test.
- Subjects who are failures and receive less than 48 hours total duration of study drug will be reclassified as indeterminates and the number and percentage of subjects An adjusted (for the randomization stratification factors) 95% CI will be computed using the method of Miettinen and Nurminen for the difference in the IACR success rates between lefamulin and moxifloxacin. A second unadjusted 95% CI will be computed using a continuity corrected Z-test. Subjects who do not receive at least 48 hours total duration of study drug are excluded from the CE Analysis Sets.

Investigator's assessment of clinical response will be assessed separately across the geographic regions, prior antibiotic use and PORT risk class strata. For each geographic region, prior antibiotic use and PORT risk class stratum, 2-sided 95% CIs for the observed difference in IACR success rates will be calculated using a continuity corrected Z-test for the mITT and CE-TOC Analysis Sets.

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

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.

Subgroup analyses of IACR, including treatment differences and 95% CIs (computed using a continuity corrected Z-test), in the mITT and CE-TOC Analysis Sets will also be conducted for descriptive purposes. These include but are not limited to PORT Risk Class per the eCRF (II, III, IV), prior antibiotic use in the 72 hours before randomization per the eCRF (use, no use), SIRS (yes, no), meeting minor ATS criteria (yes, no), meeting modified ATS criteria (yes, no) CURB-65, gender, age group (<65, 65-74, ≥75 years), renal impairment category and bacteremic subjects. Exploratory analyses in other subgroups may also be conducted. A Forest plot of the treatment difference in IACR clinical success rate at the TOC Visit in the mITT and CE-TOC Analysis Sets and CIs by the stratification factors and subgroups will also be provided.

8.1.3 Secondary Efficacy Analyses

8.1.3.1 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 at the TOC Visit will be presented for the microITT and ME-TOC Analysis Sets. Two-sided adjusted (for the randomization stratification factors) 95% CIs for the difference in success rates will be calculated using the method of Miettinen and Nurminen.

8.1.4 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.

8.1.4.1 Clinical Outcome Measures

The number and percentage of subjects in each treatment group determined to have an IACR of success, failure, or indeterminate at the TOC Visit in the microITT-2 and emicroITT Analysis Sets will be presented. Two-sided adjusted (for the randomization stratification factors) 95% CIs for the difference in success rates will be calculated using the method of Miettinen and Nurminen.

The number and percentage of subjects in each treatment group determined to have an IACR of success, failure, or indeterminate at the EOT Visit in the mITT, microITT, CE-EOT and ME-EOT Analysis Sets will be presented. Two-sided adjusted (for the randomization stratification factors) 95% CIs for the difference in success rates will be calculated using the method of Miettinen and Nurminen.

9.0 REFERENCES

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