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)

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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)

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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
Leanne Gasink, MD	Senior Director, Clinical Development and Medical Affairs		17 March 16

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.

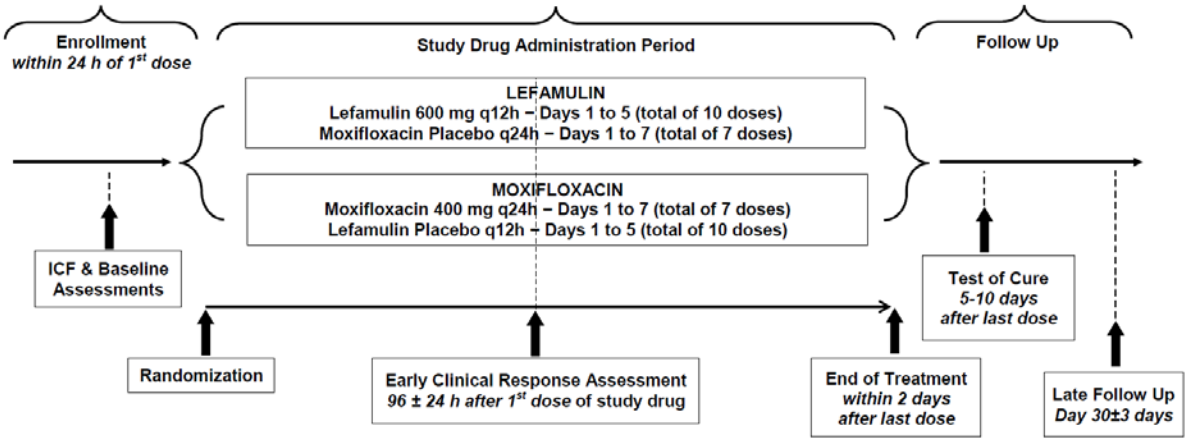
Subjects will be consented for the study prior to study assessments being performed and confirmation of eligibility. Screening assessments will be performed within 24 hours before first dose of study drug.

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.

TABLE OF CONTENTS

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