



## **Clinical Protocol No. NAB-BC-3781-3101**

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

**US IND 106594 (Intravenous)  
US IND 125546 (Oral)**

**EudraCT Number 2014-005169-63**

<b>Protocol Status</b>	<b>Version</b>	<b>Date</b>
Original	1.0	01 July 2015
Amendment 1	2.0	06 October 2015
Amendment 2	3.0	04 March 2016
Amendment 3	4.0	15 March 2016

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## SPONSOR-RELATED CONTACT DETAILS

### A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Lefamulin (BC-3781) Versus Moxifloxacin (With or Without Adjunctive Linezolid) in Adults With Community-Acquired Bacterial Pneumonia (Protocol NAB-BC-3781-3101 with Amendments 1, 2 and 3)

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**PROTOCOL REVIEW AND APPROVAL FORM****SUBMISSION OF PROTOCOL NAB-BC-3781-3101 WITH AMENDMENTS 1, 2, AND 3**

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

**15 March 2016**

<b>NAME</b>	<b>TITLE</b>	<b>SIGNATURE</b>	<b>DATE</b>
Leanne Gasink, MD	Senior Director, Clinical Development and Medical Affairs		16 March 2016

## INVESTIGATOR SIGNATURE PAGE

### **A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Lefamulin (BC-3781) Versus Moxifloxacin (With or Without Adjunctive Linezolid) in Adults With Community-Acquired Bacterial Pneumonia (Protocol NAB-BC-3781-3101 with Amendments 1, 2, and 3)**

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.

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Investigator's Name (Please Print)

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Investigator's Signature

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Date

## AMENDMENT 3: 15 MARCH 2016

Amendment 3 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  $\geq 2$  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  $\geq 28$  days after the last dose of study drug. If a male partner has been surgically sterile for  $\geq 1$  year, a single contraception method may be used. **NOTE: The use of contraceptives containing progesterone is not permitted.**

### Section 6.8 – Prohibited Medications

Bullet #6

- Strong p-glycoprotein inhibitors and strong CYP3A inhibitors or inducers (see Appendix 4) **[NOTE: The use of contraceptives containing progesterone is not permitted.]**

## AMENDMENT 2: 04 MARCH 2016

Amendment 2 addresses two key revisions to the protocol (Parts 1 and 2), as well as changes to better describe planned analyses (Part 3), clarifications, corrections, and consistency across the lefamulin clinical development program (Part 4), and a revision based on availability of new data (Part 5).

**Part 1.** A change to the treatment duration for community-acquired bacterial pneumonia (CABP) not caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

**Part 2.** A decrease in the sample size.

**Part 3.** Changes to more clearly describe planned analyses.

**Part 4.** Clarification and corrections to existing language within the protocol and/or to ensure alignment with other studies in the lefamulin clinical development program.

**Part 5.** Revision based on availability of new data.

Rationales for all components of this amendment are provided. 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 3). 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.

## **Part 1. Treatment durations for CABP not caused by MRSA**

Treatment durations for CABP (other than CABP caused by MRSA) have been streamlined to minimize the number of different treatment scenarios which would be encountered in the study. This change was taken in order to simplify study delivery. The complexity of the treatment regimens was exacerbated by the difference in treatment duration for the majority of subjects (i.e., 5 days of lefamulin versus 7 days of moxifloxacin), which created the need to use IV lefamulin placebo on Days 6 and 7 to maintain the blind. A thorough search of the literature supports a treatment regimen of 5 to 7 days for most cases of CABP. As a result, treatment of all CABP-associated pathogens, other than MRSA, will be 7 days for both lefamulin and moxifloxacin. Thus, the protocol regimens now are more consistent with current recommendations, eliminate complications associated with maintaining the blind on Days 6 and 7, and minimize the number of different treatment regimens to which subjects would be assigned.

### **All changes related to the treatment duration for CABP not caused by MRSA are provided below.**

#### **Section 5.5.1 – Duration of Treatment**

It is estimated that the duration of blinded study drug administration for the majority (~90%) of subjects will be 7 days **of active treatment as shown in Table 4 (Section 5.5.4)**. ~~Subjects with CABP due to MRSA randomized to lefamulin will receive 10 5 days of active treatment and 2 days of placebo; subjects randomized to moxifloxacin will receive 7 days of active treatment as shown in Table 5 (Section 5.5.4).~~ Subjects with CABP due to *L. pneumophila*, *S. pneumoniae* with accompanying bacteremia, MRSA, or those subjects with confirmed *S. aureus* bacteremia will have their treatment adjusted as described below.

#### **Section 5.5.2 – Post-Baseline Treatment Modifications**

##### Bullet #1 (deleted)

- ~~• Subjects who have *S. pneumoniae* as a causative pathogen without accompanying bacteremia will receive 7 days of study drug therapy (Table 5). Subjects whose microbiological results confirm *S. pneumoniae* as a causative pathogen with accompanying bacteremia will receive 10 days of active treatment in both the lefamulin and moxifloxacin treatment groups as shown in Table 6 below.~~

##### Bullet #4

- Subjects who were suspected to have MRSA at Screening and whose microbiological results do NOT confirm MRSA will have linezolid or matching placebo discontinued and will continue treatment with study drug for 7 days as shown in **Table 4** below. ~~or for 10 days as shown in Table 6 below.~~

##### Bullet #6 (deleted)

- ~~• Subjects whose microbiological results confirm *L. pneumophila* as a causative pathogen will receive 10 days of active treatment in both the lefamulin and moxifloxacin treatment groups as shown in Table 6 below.~~

**Section 5.5.4 – Treatment Scenarios****Table 4 5. CABP (not caused by MRSA, *S. pneumoniae* with accompanying bacteremia or *L. pneumophila*)**

Study Drug	Regimen	Duration/Additional Dosing Information
Lefamulin	150 mg IV q12h	Total duration of blinded study drug = 7 days ;5 days of active treatment. Days 1-3 = IV; Days 4-7 = IV or PO ( <del>see note below</del> ) If IV study drug administration is switched to oral, moxifloxacin placebo will be administered q24h through Day 7.
	600 mg PO q12h	
Moxifloxacin	400 mg IV q24h	Total duration of blinded study drug = 7 days of active treatment. Days 1-3 = IV; Days 4-7 = IV or PO Separate, alternating doses of IV placebo will be administered q24h such that IV study drug is administered q12h; If IV study drug administration is switched to oral, lefamulin placebo will be administered q12h through Day 7 5.
	400 mg PO q24h	

NOTE: Subjects in the lefamulin treatment arm who remain on IV treatment through days 6 and 7 will receive IV lefamulin placebo q12h on days 6 and 7 to maintain the blind. Subjects in the lefamulin treatment arm who have switched to oral treatment by day 6 will only receive oral moxifloxacin placebo q24h on days 6 and 7.

NOTE: Subjects with confirmed *Staphylococcus S. aureus* bacteremia should have study drug discontinued and appropriate alternate therapy should be initiated promptly. If possible, blood samples should be collected for microbiological culture prior to switching to alternate therapy.

**Table 6. CABP (caused by *S. pneumoniae* with accompanying bacteremia or *L. pneumophila*)**

Table 6 has been deleted.

**Table 5 6. CABP (MRSA suspected at Baseline and confirmed Post-baseline)**

Two table NOTES have been edited.

NOTE #1: If results of baseline respiratory tract cultures do not confirm MRSA as an etiological pathogen, then linezolid or matching placebo will be discontinued and the subject will complete 7 days of study drug as shown in Table 4 5 above. ~~or 10 days of study drug as shown in Table 6 above.~~

NOTE #3: Subjects who are confirmed to have *Staphylococcus aureus* MRSA bacteremia should have study drug discontinued and appropriate alternate therapy should be initiated promptly. If possible, blood samples should be collected for microbiological culture prior to switching to alternate therapy.

**Section 5.6 – Timing of Dose and Dose Administration**

Paragraph 2, Sentences 6 and 7: ~~Subjects who require a 10-day course of study drug (i.e., those with CABP caused by MRSA, *S. pneumoniae* with accompanying bacteremia, or *L. pneumophila*) and who receive only a single dose of study drug on Day 1 will receive their final dose in the morning on either Day 8 (to complete a 7-day course) or on Day 11 (to complete a 10-day course). Subjects who require a 7-day course of study drug and who receive only a single dose of study drug on Day 1 will receive their final dose on Day 7. A final dose in the morning of Day 8 is not required as subjects in both treatment arms will have already received a full course of therapy by Day 7.~~

Example 2, Sentences 4 to 6: Subjects who require a 7-day course of study drug and who receive only a single dose of study drug on Day 1 will receive their final dose in the morning on Day 8 (to complete a 7-day course). Subjects who require a 10-day course of study drug and who receive only a single dose of study drug on Day 1 will receive their final dose ~~in the morning~~ on Day 11 (to complete a 10-day course). ~~Subjects who require a 7-day course of study drug and who receive only a single dose of study drug on Day 1 will receive their final dose on Day 7.~~

**Section 8.4 – Placebo**

[Rationale: Lefamulin placebo (Days 6 & 7) has been deleted from table below.]

[NOTE: The Sponsor will now provide IV placebo to the investigative sites.]

Paragraph 1, Sentence 1: The following IV placebos will be **supplied by the Sponsor and** utilized to maintain the blind.

Drug Product	Route	Dosage Form/Strength
Moxifloxacin placebo	IV	0.9% NaCl for Injection (Given as alternating doses with IV moxifloxacin) <i>NOTE: This is to be supplied by each clinical site</i>
Linezolid matching placebo	IV	0.9% NaCl for Injection <i>NOTE: This is to be supplied by each clinical site</i>
Lefamulin placebo	IV	0.9% NaCl for Injection (Given on Days 6 and 7 for subjects who do not switch to oral treatment and have CABP not due to MRSA, <i>L. pneumophila</i> , or <i>S. pneumoniae</i> with accompanying bacteremia) <i>NOTE: This is to be supplied by each clinical site</i>

[NOTE: Information on preparing the placebo saline provided by the Sponsor has been added to Section 5.7 (Preparation of Infusions) and for storing the placebo saline has been added to Section 8.6 (Storage of Study Drug).]

**Part 2. Decrease in the sample size**

The change in the sample size reflects a change in the non-inferiority margin (NI) for the FDA endpoint of Early Clinical Response (ECR) from 10% to 12.5%. The 12.5% NI margin for ECR in the proposed study population (subjects with CABP and PORT risk class  $\geq$ III) is consistent with FDA guidance and allows the study to be completed more quickly while still providing a valid assessment of non-inferiority vs. moxifloxacin. In the event that additional lefamulin-exposed subjects are required, the study will enroll up to 626 subjects (313 in the lefamulin treatment arm). The resized study provides at least 80% power to demonstrate non-inferiority of lefamulin vs. moxifloxacin in both FDA and EMA endpoints using the respective recommended NI margins. The original assumptions for response rate in all primary endpoints, as well as evaluability (Clinically Evaluable at Test of Cure Analysis Set) were used.

**All changes related to the decrease in sample size are provided below:****Section 3 – Study Design**

Paragraph 1, Sentences 2 & 3: The planned enrollment is ~~550~~ 738 subjects with Pneumonia Outcomes Research Team (PORT) Risk Class  $\geq$ III. **However, if based upon regulatory requirements additional subjects exposed to lefamulin are needed, up to 626 subjects may be enrolled.**

**Section 9.2 – Sample Size Determination**

Paragraph 1, Sentences 1 & 2: A total of ~~550~~ 738 subjects will be randomized in this study (~~275~~ 369 in each treatment group). **However, if based upon regulatory requirements additional subjects exposed to lefamulin are needed, up to 626 subjects may be enrolled.**

Paragraph 4: Utilizing an anticipated ECR responder rate of 79% in the ITT Analysis Set, and a ~~one- two-~~ sided alpha of 0.025, a sample size of ~~550 738~~ subjects (~~275 369~~ in each treatment group) provides >90% power to establish the NI of lefamulin to moxifloxacin for ECR using a NI margin of ~~12.5% 10%~~ 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 ~~80% 91%~~ power for demonstration of NI for IACR at the TOC Visit using a 10% NI margin. **If the sample size is increased to 626 subjects, it will provide >95% power for demonstration of NI for ECR and 85% power for demonstration of NI for IACR at the TOC Visit.**

**Table 1143. Power Calculations for the Primary and Secondary Efficacy Outcomes**

Analysis Set	Primary Outcome (FDA) (ECR 96 ± 24 h After the First Infusion of Study Drug)	Secondary Outcome (Investigator’s Assessment of Clinical Response at TOC- Primary for EMA)	
	ITT	mITT	CE-TOC
N	<del>550 738</del>	<del>550 738</del>	<del>440 590</del>
Outcome Rate	79%	80%	85%
Evaluability Rate	NA	NA	80%
Power	<del>93.8% 90%</del>	<del>80.6% 91%</del>	<del>80% 91%</del>

**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%~~, the null hypothesis will be rejected and the NI of lefamulin to moxifloxacin will be concluded.

**Section 9.9 – Interim Analysis and Independent Interim Analysis Committee**

Paragraph 1, Sentence 1: In order to ensure that the point estimate of the ECR responder **and IACR success rates** used in the estimation of the sample size is valid for this study, an interim analysis for sample size re-estimation will be performed when ECR data at 96 ± 24 h post first dose are available for approximately 60% of randomized subjects (~~330 443~~ subjects) (see Section 9.4.1).

**Part 3. Changes made to more clearly describe planned analyses.**

**Section 2.3 – Additional Objectives**

Bullet #2

- 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-EOT Analysis Sets (**CE-EOT for IACR at EOT and CE-LFU for IACR at LFU**).

Bullet #3

- Evaluate the Investigator’s Assessment of Clinical Response by baseline pathogen at TOC **and LFU** in the microITT and ME-TOC Analysis Sets (**ME-TOC for IACR at TOC and ME-LFU for IACR at LFU**).

**Section 3 – Study Design**

Paragraph 5: 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**).

<p><b>Section 6.10 – Assessment of Clinical Signs and Symptoms of CABP</b></p> <p><u>Paragraph 3, Bullet #2, Sub-Bullet #3 and #4:</u></p> <ul style="list-style-type: none"> <li>– Received a concomitant antibiotic (other than adjunctive linezolid) for the treatment of CABP <del>up through 120 hours after the first dose of study drug;</del></li> <li>– Died from any cause <del>through 120 hours after the first dose of study drug.</del></li> </ul>
<p><u>Paragraph 3, Bullet #3 (added):</u></p> <ul style="list-style-type: none"> <li>• <b>Subjects will be programmatically defined as an Indeterminate if the following criterion is met:</b> <ul style="list-style-type: none"> <li>• <b>The symptom data are missing such that a response or non-response cannot be determined.</b></li> </ul> </li> </ul>
<p><b>Section 6.11.2 – Investigator’s Assessment of Clinical Response (IACR) at Late Follow Up</b></p> <p><u>Paragraph 2 (added):</u> <b>NOTE: Subjects who have an IACR of Failure at EOT or TOC will not have an IACR assessed at LFU and will be considered to have an IACR of Failure at LFU.</b></p>
<p><b>Section 9.3.5 – Clinically Evaluable Analysis Set</b></p> <p>The CE Analysis Sets (CE-EOT, <del>and</del> CE-TOC, <b>and</b> 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 <del>and</del>, at TOC for the CE-TOC Analysis Set, <b>and at LFU for the CE-LFU Analysis Set</b>), did not receive concomitant antibacterial therapy (other than adjunctive linezolid) 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), <del>and</del> through the TOC Visit (CE-TOC Analysis Set), <b>and through the LFU Visit (CE-LFU Analysis Set)</b>, and for whom there are no other confounding factors that interfere with the assessment of the outcome.</p>
<p><b>Section 9.3.6 – Microbiologically Evaluable Analysis Set</b></p> <p>The ME Analysis Set (ME-EOT, <del>and</del> ME-TOC, <b>and</b> ME-LFU) will include all subjects who meet the criteria for inclusion both the microITT and CE-EOT (ME-EOT) Analysis Set, <del>or</del> the CE-TOC (ME-TOC) Analysis Set, <b>or the CE-LFU (ME-LFU) Analysis Set.</b></p>
<p><b>Section 9.4.1 – Primary Efficacy Analysis Variable</b></p> <p><u>Bullet #4</u></p> <ul style="list-style-type: none"> <li>• Did not receive a concomitant antibiotic (other than adjunctive linezolid) for the treatment of CABP <del>up through 120 hours after the first dose of study drug.</del></li> </ul>
<p><u>Paragraph 3, Sentence 3 (added):</u> <b>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.</b></p>
<p><b>Section 9.4.2.1 – Clinical Outcome</b></p> <p><u>Paragraph 1, Sentence 3 (added):</u> <b>All-cause mortality will be evaluated in the ITT Analysis Set.</b></p>
<p><b>Section 9.6.1 – Primary Efficacy Analysis</b></p> <p><u>Paragraph 4, Sentence 6 (added):</u> <b>Subgroup analyses of the primary efficacy outcome will also be conducted for descriptive purposes and will be detailed in the SAP.</b></p>

<p><u>Paragraph 6 (added)</u>: <b>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.</b></p>
<p><b>Section 9.6.2 – Secondary Efficacy Analysis</b></p> <p><u>Paragraph 1, Sentence 2</u>: 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 <del>and will be based on a 12.5% NI margin.</del></p>
<p><u>Paragraph 2 (added)</u>: <b>The number and percentage of subjects categorized as Responder, Non-responder and Indeterminate for ECR plus improvement in vital signs will also be presented for the ITT Analysis Set and a 2-sided unstratified 95% CI for the difference in responder rate will be calculated using a continuity-corrected Z-statistic.</b></p>
<p><b>Section 9.6.3 – Additional Efficacy Analysis</b></p> <p><u>Paragraph 2</u>: <del>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 data. The number and percentage of subjects who are a Responder for ECR (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, 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 success at LFU will be presented by baseline pathogen in the microITT, ME-TOC (IACR only), and ME-LFU (sustained success only) Analysis Sets.</del></p>
<p><u>Paragraph 3, Sentences 2 &amp; 3</u>: The number and percentage of subjects with a Sustained Success, Relapse, <b>Failure</b>, and Indeterminate response as assessed by the Investigator at the LFU Visit will be summarized for the mITT and CE-LFU <del>TOC</del> Analysis Sets. <b>Failure is at LFU defined as a subject who had an IACR of failure at the TOC visit.</b></p>
<p><b>Section 9.8 – Handling of Missing Data</b></p> <p><u>Paragraph 2</u>: For the outcome measure of IACR at EOT, <del>and</del> TOC, <b>and</b> 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, <b>CE-LFU</b>, ME-EOT, <del>and</del> ME-TOC, <b>and</b> ME-LFU Analysis Sets.</p>
<p><u>Paragraph 3 (added)</u>: <b>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.</b></p>
<p><u>Paragraph 4 (added)</u>: <b>Handling of missing data for other efficacy and safety outcomes will be presented in the SAP.</b></p>

## **Part 4. Clarifications, corrections, and alignment with other studies in the lefamulin clinical development program**

### **Table 3. Schedule of Assessments and Procedures**

*[Rationale: Two footnotes related to timing of physical examinations and safety laboratory assessments have been updated to provide flexibility.]*

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

**om:** For **all** subjects ~~receiving a 7-day course of therapy~~, collect blood and urine at Screening, Day 4 (**Day 3 is acceptable for outpatients who are not able to return on Day 4**), EOT, and TOC. **In addition**, ~~For~~ subjects receiving a 10-days course of therapy study drug, collect blood and urine on ~~at Screening, Day 4, Day 7~~ (**Day 8 is acceptable for outpatients who are not able to return on Day 7**), ~~EOT, and TOC~~.

### **Section 3 – Study Design**

*[Rationale: Edited for clarity.]*

Paragraph 4, Sentence 1: Assessment of the 4 cardinal symptoms of CABP (dyspnea, cough, purulent sputum production and chest pain) will be conducted **daily (see Section 6.10); an assessment at 96 ± 24 hours after the first dose of study drug will be used** to determine Early Clinical Response (ECR) (as defined in the Primary Objective - FDA) (Section 9.4.1).

*[Rationale: Instructions added to provide clarity in assessment of daily CABP signs and symptoms for inpatients and outpatients.]*

Paragraph 4, Sentences 3 & 4 (added): **CABP signs and symptoms will be assessed in person while subjects are hospitalized. Outpatients may have signs and symptoms assessed daily by telephone; however, they must also have a study site visit 96 ± 24 hours after the first dose of study drug to assess CABP signs and symptoms in person.**

### **Section 4.2 – Exclusion Criteria**

*[Rationale: Window expanded to 72 hours to minimize prior antibiotic use as a confounding factor in assessing treatment effect.]*

#1 Have received more than a single dose of a short-acting oral or IV antibacterial for CABP within **72 24-hours** before randomization (See Appendix 2).

*[Rationale: Edited for clarity]*

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 unless the resistance organism is not resistant** to fluoroquinolones and, in the case of methicillin-resistant *Staphylococcus aureus* (MRSA), oxazolidinones.

*[NOTE: Both changes noted above were also made to Section 6.8 (Prohibited Medications)].*

*[Rationale: Edited for clarity.]*

#9 Be receiving a strong p-glycoprotein **inhibitor** or a **strong** CYP3A inducer or inhibitor (see Appendix 4).

### **Section 5.6 – Timing of Dosing and Dose Administration**

*[Rationale: Guidance provided on minimum number of hours between doses.]*

Paragraph 5, Sentence 2: On days when this is not feasible, doses should be given within 4 hours of the scheduled dosing time (**i.e., a minimum of 8 hours between doses**).

<p><i>[Rationale: Infusion rate corrected.]</i></p> <p><u>Paragraph 8, Sentence 1:</u> Infusions will be administered via an infusion set and IV catheter at a controlled rate <b>over approximately 60 minutes</b> (<del>approximately 60 mL/min</del>).</p> <p><i>[NOTE: This change was also made to Section 5.8 (Blinding).]</i></p>
<p><b>Section 5.8 – Blinding</b></p> <p><i>[Rationale: Provide clarity that safety data provided to DMC will be masked, not unblinded.]</i></p> <p><u>Paragraph 2, Sentence 3:</u> An DMC will review summary safety data by <b>masked</b> treatment group throughout the study.</p> <p><i>[NOTE: This change was also made to Section 10.2 (Independent DMC)].</i></p>
<p><b>Section 5.10 – Adherence</b></p> <p><i>[Rationale: Clarification regarding eCRF data reporting updated.]</i></p> <p><u>Paragraph 1, Sentence 2:</u> The date, start and stop time of each IV dose, the date and time of the first oral dose, <b>the date of the last oral dose</b>, and the number of tablets/capsules taken for the oral dose will be recorded in the eCRF.</p>
<p><i>[Rationale: Edited for clarity.]</i></p> <p><u>Paragraph 4:</u> The site of care/site of <b>IV</b> study drug administration (e.g., emergency room, IV infusion center, subject’s home, etc.) will be recorded on each study day.</p>
<p><b>Section 6 – Study Assessments and Procedures</b></p> <p><i>[Rationale: Removed to avoid confusion regarding timing of procedures.]</i></p> <p><u>Paragraph 2, Sentence 3 (deleted):</u> <del>When multiple procedures are performed at the same time points, the preferred sequence of order is: vital signs, ECG, and plasma PK/blood draw.</del></p>
<p><i>[Rationale: Edited to ensure clarity regarding the need for a face-to-face visit for ECR.]</i></p> <p><u>Paragraph 4 (added):</u> <b>NOTE: All subjects <u>must have an in person 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.</u> Subjects who are receiving oral medication at home will be informed as to the timing of this visit by study personnel.</b></p>
<p><b>Section 6.4 – Vital Signs and Oxygen Saturation</b></p> <p><i>[Rationale: Collection of supplemental oxygen therapy data has been added to the protocol and eCRF.]</i></p> <p><u>New paragraph (Paragraph 2) was added:</u> <b>In addition, if the subject is receiving supplemental oxygen therapy, the amount given will be recorded in the eCRF.</b></p>
<p><b>Section 6.6 – Arterial Blood Gases</b></p> <p><i>[Rationale: FiO2 is not being collected on the eCRF as part of the results of arterial blood gases.]</i></p> <p>Study sites are not required to measure arterial blood gases (PaO<sub>2</sub>, PaCO<sub>2</sub>) (<del>and FiO<sub>2</sub></del>) or pH. However, if these data are available, they should be recorded in the eCRF.</p>
<p><b>Section 6.7.2 – Concomitant Medications</b></p> <p><i>[Rationale: Edited for clarity.]</i></p> <p><u>Paragraph 3, Sentence 1:</u> Although <b>all</b> drugs that are metabolized by CYP3A4 are not prohibited, they should only be used when necessary and with appropriate subject monitoring.</p>
<p><i>[Rationale: Edited for clarity.]</i></p> <p><u>Paragraph 3, Sentences 3 &amp; 4:</u> <b>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.</b> A list of drugs that <del>which</del> are CYP3A4 substrates and P-glycoprotein substrates is provided in Appendix 3.</p>

**Section 6.8 – Prohibited Medications**

*[Rationale: Instructions added to provided clarity regarding prohibited medications.]*

Bullet #3

- Other systemic antibacterial agents that are potentially effective against pathogens associated with CABP except in the case of treatment failure **or when medically necessary for treatment of a concomitant infection.**

Bullet #6

- Strong p-glycoprotein inhibitors **and strong CYP3A inhibitors** or inducers (see Appendix 4).

**Section 6.10 – Assessment of Clinical Signs and Symptoms of CABP**

*[Rationale: Instructions provided to ensure that subjects have a face-to-face study visit at time of ECR assessment.]*

Paragraph 3 (added): **NOTE: All subjects must have a face-to-face assessment of CABP signs and symptoms 96 ± 24 hours after the first dose of study drug. Subjects who are receiving outpatient study drug (IV or oral) during this timeframe MUST have a visit at the study site for this assessment. Study personnel will inform outpatients as to the timing of this required study site visit.**

**Section 6.13 – Sample Collection for Pharmacokinetic Analysis**

*[Rationale: To clarify that PK analysis will include lefamulin's main metabolite, BC-8041.]*

Paragraph 1, Sentence 1: Blood samples for PK analysis of lefamulin **and its main metabolite, BC-8041**, in plasma following IV dosing will be collected in association with the morning dose of study drug on Study Day 3 as specified in Table 9 ~~4~~below.

*[Rationale: Instructions added to provided clarity in PK sample collection for outpatients.]*

Paragraph 3 (added): **Outpatients who have consented for oral drug PK samples will return to the clinical site for PK blood collection relative to the first morning dose of oral drug. These subjects should be instructed to not take their first morning 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.**

**Section 6.14.1 – Sputum Samples**

*[Rationale: Edited for clarity.]*

Bullet #3, Sentence 1:

- **To be adequate**, Gram's stains of sputum samples should have >25 polymorphonuclear (PMN) cells AND <10 squamous epithelial cells per LPF.

*[Rationale: Edited so that all organisms that are non-contaminants are sent to the central lab for confirmation.]*

Bullet #4, Sentence 1:

- All organisms isolated from sputum samples which are not considered contaminants ~~(with the exception of *Pseudomonas* spp. and organisms in the *Enterobacteriaceae* Family)~~ will be sent to the central laboratory for confirmatory identification and susceptibility testing.

*[Rationale: Corrected to indicate that PCR will only be performed on baseline pathogens.]*

Bullet #6, Sentences 1 & 2:

- A portion of each **Screening** sputum sample taken (~~all Screening samples, plus any additional samples collected as clinically indicated~~) 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 including *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* as well as atypical pathogens including *L. pneumophila*, *C. pneumoniae*, and *M. pneumoniae*.

### **Section 6.17.2 – Discontinuation from Study**

*[Rationale: Instructions provided to investigative sites to minimize missing data for analysis of 28 day all-cause mortality.]*

Paragraph 2 (added): 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.

*[NOTE: This change was also made to Section 6.17.4 (Lost to Follow-up).]*

### **Section 6.17.3 – Individual Stopping Criteria**

*[Rationale: Added for clarity and consistency with Section 5.5.2 (Post-Baseline Treatment Modifications).]*

Bullet #3 (added):

- **The subject has confirmed *S. aureus* bacteremia.**

### **Section 7.5 – Other Reportable Events**

*[Rationale: Other reportable events are reported regardless of whether or not the investigator considers it an adverse event.]*

Paragraph 1, Sentence 1: Certain events that occur ~~in the absence of an adverse event~~ should be reported to the Sponsor as Other Reportable Events.

*[Rationale: Based on FDA Guidance to Industry (July 2009), Potential Hy's Law was added as an "Other Reportable Event" to evaluate and monitor any potential drug-induced hepatotoxicity that may be observed in this study.]*

Bullet #1 (added):

- **Potential Hy's Law (PHL)**
  - **The investigator is responsible for prompt reporting of any patient 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.**

### **Section 9.4.2.2 – Microbiological Assessment**

*[Rationale: Revised for clarity and consistency.]*

Paragraph 1, Bullet #3

Indeterminate: The IACR was Indeterminate, and ~~no~~ culture was not **repeated** obtained.

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

Paragraph 3, Bullet #3:

- Development of Decreasing Susceptibility: Increase in MIC ( $\geq 4x$ ) or  $\geq 6$  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 9.4.4 – Pharmacokinetic Analysis Variables**

*[Rationale: Minor edits made to clarify the popPK analysis.]*

Sentence 3: Individual 24h AUC values from Day 1 **obtained from the population PK model** will be used for the PK/PD analysis **focusing on efficacy**.

#### **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 Bazett~~, 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 9.9 – Interim Analysis and Independent Interim Analysis Committee**

*[Rationale: Interim analysis applies to primary outcome measures for both regulatory authorities.]*

Paragraph 1, Sentence 3: The interim analysis will involve a sample size re-estimation to either confirm the initial sample size estimate is adequate or increase the sample size (number of randomized subjects) to ensure the study has adequate power for determining whether lefamulin is non-inferior to moxifloxacin for the primary outcome measures **for the FDA and EMA**.

#### **Section 19 – List of References**

Zeitlinger et al., 2014 (poster presentation) has been published in *J Antimicrob Chemother* (2016).

Reference and citations for Zeitlinger et al., 2014 have been updated to Zeitlinger et al., 2016.

A reference for FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation (2009) was added to support addition of Potential Hy's Law to Section 7.5 (Other Reportable Events).

**Appendix 3** (Closely Monitored CYP3A4 Substrates and P-Glycoprotein Substrates [excluding strong CYP3A inducers and inhibitors and excluding strong P-glycoprotein inhibitors]) and **Appendix 4** (Prohibited Strong P-Glycoprotein Inhibitors and Strong CYP3A Inducers and Inhibitors) have been re-structured for clarity. In addition, efavirenz and nevirapine were moved from the list of Strong CYP3A inducers to the list of CYP3A substrates that should be closely monitored reflecting their correct classification.

## **Part 5. Revision based on availability of new data**

### **Section 5.6 – Timing of Dosing and Dose Administration**

*[Rationale: Based upon the analyses of PK data from a recently completed Phase 1 study of subjects receiving lefamulin 600 mg orally in the fed and fasted states, 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.]*

**Paragraph 6, Sentences 1 & 2 (new): Oral 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.**

*[NOTE: This change was also made to Section 6.16 (Food and Beverage Restrictions).]*

In addition, the Sponsor has made the following minor revisions:

- Amendment 2 is protocol version 3.0, dated 04-Mar-2016.
- Administrative change in the Medical Officer and protocol signatory from Elyse Seltzer, MD to Leanne Gasink, MD.
- Administrative change in the PPD Medical Monitor from Anton Maki Jr, MD to Laura McKain, MD.
- Correction of typographical errors (e.g., definition of ELF), formatting, consistency in terminology (e.g., By-Pathogen Response for microbiological assessment), etc.
- Updated information includes:
  - Section 1.3 - increase in number of clinical isolates tested
  - Section 1.4 – results of *in vitro* drug transporter studies
  - Section 1.5 – increase in number of Phase 1 clinical studies
  - Nabriva US offices
  - List of abbreviations
  - Table numbering
- Clarified throughout the protocol that SF-12 will be the PRO instrument.

## **AMENDMENT 1: 06 OCTOBER 2015**

This amendment addresses changes requested during the Voluntary Harmonization Procedure in Europe for assessment of the original protocol. Three eligibility criteria were revised to further define the study population. These revisions were made to the protocol sections noted below as well as to the study synopsis. Added text is **bolded**.

### **Section 4.1 – Inclusion Criteria**

- #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.**

- #7. Have a Pneumonia Outcomes Research Team (PORT) Risk Class  $\geq$ III **and require IV antibiotic therapy as initial treatment for the current episode of CABP.**

#### Section 4.2 – Exclusion Criteria

- #16. Have participated in any study involving administration of an investigational agent or device within 30 days **or  $\leq$ 5 terminal elimination half-lives of the previous investigational medicinal product, whichever is longer,** before enrollment.

Protocol Sections 6 and 13 were revised as follows for consistency with amended Inclusion Criterion #2.

#### Section 6 – Study Assessments and Procedures

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.**

#### Section 13 – Informed Consent (Paragraph 3)

Subjects **(or their legally authorized representative)** will sign and date 1 copy of the informed consent form which will be photocopied. The copy will be retained by the subject **(or their legally authorized representative)** and the original will be retained on file by the Investigator.

In addition, the Sponsor has made the following revisions to the original protocol. These revisions were made to the protocol sections noted below as well as to the study synopsis, the Schedule of Assessments and Procedures (Table 4), and the Overview of Study Design (Figures 1-3), as applicable. Added text is **bolded**; deleted text is ~~struck through~~.

One eligibility criterion was revised to expand the window for radiographic confirmation of pneumonia. This will minimize radiation exposure in subjects with a recent chest x-ray/CT scan and, additionally, it is consistent with the EMA guidance.

#### Section 4.1 – Inclusion Criteria

- #6 Have radiographically-documented pneumonia within **24 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).

Section 5.5.2 (Post-Baseline Treatment Modifications) has been revised to clarify treatment management (1) among subjects who were suspected to have MRSA at Screening and whose microbiological results confirm MRSA as a causative pathogen during the oral treatment period and (2) among subjects who were suspected to have MRSA at Screening and whose microbiological results do NOT confirm MRSA. Table 7 has been modified accordingly.

#### Section 5.5.2 – Post-Baseline Treatment Modifications (Primary Bullets #3 and #4)

- Subjects who were suspected to have MRSA at Screening and whose microbiological results confirm MRSA as a causative pathogen during the oral treatment period will be managed as follows:

- Subjects randomized to receive moxifloxacin: Oral moxifloxacin should be discontinued. Subjects will continue to receive oral linezolid plus oral lefamulin placebo ~~for~~ **to complete 10 days of study drug therapy** as shown in Table 7 below.
- Subjects randomized to receive lefamulin: Oral moxifloxacin placebo should be discontinued. Subjects will continue to receive oral lefamulin plus oral linezolid placebo ~~for~~ **to complete 10 days of study drug therapy** as shown in Table 7 below.
- Subjects who were suspected to have MRSA at Screening and whose microbiological results do NOT confirm MRSA will have linezolid or matching placebo discontinued and will continue treatment with study drug for 7 days as shown in Table 5 below **or for 10 days as shown in Table 6 below.**

Section 5.6 (Timing of Dosing and Dose Administration, Paragraph 2) has been revised to clarify dosing instructions for subjects randomized to 7 days of study drug (i.e., subjects with CABP not caused by MRSA, *S. pneumonia* with accompanying bacteremia or *L. pneumophila*) and who receive a single dose of study drug on Day 1. A final dose in the morning on Day 8 is not required as subjects in both treatment arms will have already received a full course of therapy by Day 7. Example 2 in this section has been modified accordingly. This change does not affect those subjects randomized to 10 days of study drug (i.e., subjects with CABP caused by MRSA, *S. pneumoniae* with accompanying bacteremia, or *L. pneumophila*) and who receive only a single dose of study drug on Day 1.

#### Section 5.6 – Timing of Dosing and Dose Administration (Paragraph 2)

The first dose of study drug will be administered on Day 1, as soon as possible after the diagnosis of CABP and completion of all required Day 1 procedures as outlined in Table 4; subsequent study days are consecutive calendar days. Every attempt should be made to administer 2 doses of study drug on Study Day 1. On Day 1, if q12h dosing is not feasible, the 1<sup>st</sup> and 2<sup>nd</sup> 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. Despite this, there may still be instances where it is not possible to administer 2 doses on Day 1. ~~Subjects who receive only a single dose of study drug on Day 1 will receive their final dose in the morning on either Day 8 (to complete a 7-day course) or Day 11 (to complete a 10-day course).~~ **Subjects who require a 10-day course of study drug (i.e., those with CABP caused by MRSA, *S. pneumoniae* with accompanying bacteremia, or *L. pneumophila*) and who receive only a single dose of study drug on Day 1 will receive their final dose in the morning on Day 11 (to complete a 10-day course). Subjects who require a 7-day course of study drug and who receive only a single dose of study drug on Day 1 will receive their final dose on Day 7. A final dose in the morning of Day 8 is not required as subjects in both treatment arms will have already received a full course of therapy by Day 7.**

This protocol does not require the measurement of arterial blood gases. Additionally, PaO<sub>2</sub> is not required for calculation of PORT Risk Class. Thus, Section 6.6 (Arterial Blood Gases) has been modified to remove instructions on calculating PaO<sub>2</sub>.

### Section 6.6 – Arterial Blood Gases

Study sites are not required to measure arterial blood gases (PaO<sub>2</sub>, PaCO<sub>2</sub>) (and FiO<sub>2</sub>) or pH. However, if these data are available, they should be recorded in the eCRF. ~~If a direct measurement is not available, study personnel will calculate PaO<sub>2</sub> based on O<sub>2</sub> saturation as measured by oximetry to assign PORT Risk Class at Screening, and as clinically indicated during the study.~~

Instructions for pregnancy testing at Screening have been modified because serum pregnancy results from the Central Laboratory will not be available prior to randomization. Thus, Section 6.12 (Clinical Laboratory Tests) has been modified to require a urine pregnancy test prior to randomization and confirmation with a serum pregnancy test as soon as possible. Appendix I (Clinical Laboratory Tests [Safety]) has been modified accordingly.

### Section 6.12 – Clinical Laboratory Tests (Safety) (Paragraph 2)

A full list of the clinical laboratory tests that will be performed and analyzed can be found in Appendix 1. A pregnancy test will be performed on all females who are not surgically sterile or post-menopausal for at least 2 years. ~~If serum pregnancy test results are not available at the time of enrollment,~~ a A negative urine pregnancy test is required **prior to randomization** and must be confirmed as soon as possible using a serum pregnancy test.

An additional microbiological assessment – a nasopharyngeal specimen – will be obtained at Screening to test for *S. pneumoniae*. A new section was added to the protocol (Section 6.14.8).

### Section 6.14.8 – Nasopharyngeal Specimen

**A nasopharyngeal specimen 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. Nasopharyngeal specimens must be frozen until shipment to the central laboratory.**

Appendix I (Clinical Laboratory Tests [Safety]) has been modified to remove the requirement that glucose testing be performed in a fasted state. In addition, the Sponsor has made administrative changes that include a change in the US study manager from Lisa Goldberg to John Saviski, correction of typographical errors, and consistency in formatting.

## SYNOPSIS

**Study Title:** A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Lefamulin (BC-3781) Versus Moxifloxacin (With or Without Adjunctive Linezolid) in Adults With Community-Acquired Bacterial Pneumonia (CABP) (Protocol NAB-BC-3781-3101).

### Study Objectives:

#### Primary Objectives

- Demonstrate the non-inferiority (NI) of lefamulin versus comparator with respect to the Early Clinical Response ( $96 \pm 24$  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 Early Clinical Response PLUS improvement in vital signs in the ITT Analysis Set.
- Evaluate the Investigator's Assessment of Clinical Response at TOC in the microITT and Microbiologically Evaluable at TOC (ME-TOC) Analysis Sets.
- 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-EOT 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-TOC Analysis Sets (ME-TOC for IACR at TOC and ME-LFU for IACR at LFU).
- Evaluate the By-Subject Microbiologic Response at TOC in the microITT and ME-TOC Analysis Sets.

- Evaluate the plasma pharmacokinetics (PK) of lefamulin in the PK Analysis Set.
- Explore a variety of health utilization variables and an investigational patient reported outcome (PRO) measure (SF-12) in subjects receiving lefamulin compared with subjects receiving comparator.

**Study Population:**Inclusion Criteria

Each subject must:

1. Be male or female  $\geq 18$  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 ( $\leq 7$  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  $>38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) measured orally or equivalent temperature from an alternate body site) or hypothermia (body temperature  $<35.0^{\circ}\text{C}$  ( $95.0^{\circ}\text{F}$ ) 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.,  $\text{O}_2$  saturation  $<90\%$  on room air or while receiving supplemental oxygen at subject's baseline requirement or  $\text{PaO}_2 <60$  mmHg).
  - Auscultatory and/or percussion findings consistent with pneumonia (e.g., crackles, egophony, dullness).
  - White blood cell (WBC) count  $>10,000$  cells/ $\text{mm}^3$  or  $<4500$  cells/ $\text{mm}^3$  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  $\geq$ III and require IV antibiotic therapy as initial treatment for the current episode of CABP.
8. If female, meets the following criteria:
  - Surgically sterile or  $\geq$ 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  $\geq$ 28 days after the last dose of study drug. If a male partner has been surgically sterile for  $\geq$ 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  $\geq$ 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  $\geq$ 28 days after the last dose of study drug. If surgically sterile for  $\geq$ 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 to fluoroquinolones and, in the case of methicillin-resistant *Staphylococcus aureus* (MRSA), oxazolidinones.
2. Require concomitant systemic antibacterial therapy potentially effective against CABP pathogens (See Section 6.8).
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., *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. Require mechanical ventilation.
8. 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).
9. Be receiving a strong p-glycoprotein inhibitor or a strong CYP3A inducer or inhibitor (See Appendix 4)
10. 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).
11. Have a history of any hypersensitivity or allergic reaction to any fluoroquinolone, or any drug in the pleuromutilin class (i.e., retapamulin).
12. Have severely impaired renal function, defined as creatinine clearance (CrCl)  $\leq 30$  mL/min as calculated by the Cockcroft-Gault formula.
13. 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) or total bilirubin  $>3$  times the ULN.
  - 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<sup>3</sup>).
  - Thrombocytopenia ( $<50,000$  platelets/mm<sup>3</sup>).
  - Known infection with human immunodeficiency virus and a CD4 count  $<200$ /mm<sup>3</sup>.
14. Have known or suspected severe immunosuppression, defined as receipt of corticosteroid therapy ( $\geq 20$  mg prednisone/day or equivalent for more than 4 weeks) within the previous 8 weeks; solid organ or bone marrow transplantation within the previous 12 months; or currently receiving cytotoxic chemotherapy.
15. Have a life expectancy of  $\leq 3$  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).
16. Have participated in any study involving administration of an investigational agent or device within 30 days or  $\leq 5$  terminal elimination half-lives of the previous investigational medicinal product, whichever is longer, before enrollment.
17. Have been previously treated with lefamulin or previously enrolled in this study.
18. Have any condition that, in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data.

**In addition, for subjects suspected to have MRSA for whom adjunctive linezolid or matching placebo will be added, each subject must NOT:**

19. Have received any of the following medications:
- Monoamine oxidase inhibitors (within 2 weeks of randomization).
  - Serotonergic agents (e.g., SSRI antidepressant medications) (within 5 weeks of randomization).
20. Have pheochromocytoma, carcinoid syndrome, uncontrolled hypertension, or thyrotoxicosis.
21. Have a history of any hypersensitivity or allergic reaction to linezolid or tedizolid.

**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	IV	150 mg of lefamulin in 15 mL of 0.9% saline, to be further diluted in 10mM citrate buffered 0.9% saline
	PO	600 mg of lefamulin as a yellow oval film coated immediate-release tablet
Moxifloxacin	IV	400 mg of moxifloxacin in a ready-to-use latex-free flexibag
	PO	400 mg of moxifloxacin as an over-encapsulated film-coated tablet
Linezolid	IV	600 mg of linezolid in a ready-to-use flexible plastic (latex-free) infusion bag
	PO	600 mg of linezolid as an over-encapsulated film-coated tablet

**Baseline Study Drug Assignment:** Subjects will be randomized in a 1:1 ratio to either IV lefamulin or IV moxifloxacin. Subjects randomized to IV lefamulin will receive 150 mg of lefamulin q12h. Subjects randomized to IV moxifloxacin will receive 400 mg of moxifloxacin q24h. In order to maintain the blind, subjects randomized to IV moxifloxacin will receive alternating doses of IV placebo administered q24h so that IV study drug is administered q12h.

As part of the screening evaluation, the Investigator will determine whether MRSA is a probable pathogen in the subject. MRSA should be considered a potential cause of CABP when a good quality sputum Gram's stain shows both polymorphonuclear leukocytes and abundant Gram-positive cocci in clusters, or if local epidemiology and recent clinical experience suggest it is prevalent in the community. Linezolid is provided as empiric therapy in subjects where MRSA is suspected as the pathogen until culture results are available. If MRSA is suspected, adjunctive linezolid therapy will be added to the moxifloxacin treatment group, while matching placebo will be added in the lefamulin group pending final culture results. Linezolid treatment or matching placebo will only be continued in the presence of a microbiological culture confirming the presence of MRSA. If cultures do not grow MRSA, linezolid (or matching placebo) will be discontinued and subjects will be continued on moxifloxacin (or lefamulin). Once culture results are available, study drug treatment will be modified as described below.

**Duration of Treatment:** It is estimated that the duration of blinded study drug administration for the majority (~90%) of subjects will be 7 days of active treatment as shown in Table 1 below. Subjects with CABP due to MRSA will receive 10 days of active treatment as shown in Table 2 below. Subjects with CABP due to MRSA, or those with confirmed *S. aureus* bacteremia will have their treatment adjusted as described below.

**Post-Baseline Treatment Modifications:** Following receipt of the screening microbiological results, the following treatment modifications will be made. The investigator (or designee) must communicate culture results in a timely manner to the unblinded pharmacist so that study treatment can be adjusted accordingly:

- Subjects who were suspected to have MRSA at Screening and whose microbiological results confirm MRSA as a causative pathogen during the IV treatment period will be managed as follows:

- Subjects randomized to receive moxifloxacin: IV moxifloxacin should be discontinued and linezolid will be continued for 10 days as shown in Table 2 below.
- Subjects randomized to receive lefamulin: IV linezolid placebo should be discontinued and lefamulin will be continued for 10 days as shown in Table 2 below.
- Subjects who were suspected to have MRSA at Screening and whose microbiological results confirm MRSA as a causative pathogen during the oral treatment period will be managed as follows:
  - Subjects randomized to receive moxifloxacin: Oral moxifloxacin should be discontinued. Subjects will continue to receive oral linezolid plus oral lefamulin placebo to complete 10 days of study drug therapy as shown in Table 2 below.
  - Subjects randomized to receive lefamulin: Oral moxifloxacin placebo should be discontinued. Subjects will continue to receive oral lefamulin plus oral linezolid placebo to complete 10 days of study drug therapy as shown in Table 2 below.
- Subjects who were suspected to have MRSA at Screening and whose microbiological results do NOT confirm MRSA will have linezolid or matching placebo discontinued and will continue treatment with study drug for 7 days as shown in Table 1 below.
- Subjects whose microbiological results confirm *S. aureus* bacteremia (either methicillin-susceptible or methicillin-resistant) will be discontinued from study drug and have appropriate alternate therapy initiated promptly. If possible, blood samples should be collected and sent for microbiological culture prior to switching to alternate therapy.

NOTE: If a subject is determined to have an infection caused by MRSA plus an organism known to be resistant to linezolid, the Sponsor's medical monitor should be contacted.

NOTE: If MRSA is not suspected at Screening, but subsequently confirmed as an etiological pathogen the Investigator should assess the subject's clinical status at the time the microbiological results become available. If at this time the subject is demonstrating clear and progressive clinical improvement (e.g., improving temperature, respiratory signs and symptoms, etc.), then the subject may remain on blinded study drug therapy (i.e., lefamulin or moxifloxacin) and receive a total of 10 days of treatment. If not, then the subject should be discontinued from study drug and appropriate alternative therapy initiated promptly. Linezolid or matching placebo cannot be added as study drug therapy subsequent to Day 1.

Similarly, if local laboratory susceptibility results from the screening cultures reveal resistance to a fluoroquinolone or linezolid, the Investigator should assess the subject's clinical status at the time the microbiological results become available. If at this time the subject is demonstrating clear and progressive clinical improvement (e.g., improving temperature, respiratory signs and symptoms, etc.), then the subject may remain on blinded study drug therapy. If not, then the subject should be discontinued from study drug and appropriate alternative therapy initiated promptly.

**IV to Oral Switch:** Subjects will be permitted to switch from IV to oral study drug if all of the following criteria have been met:

- Have received at least 6 doses of IV therapy;
- Are hemodynamically stable, as defined by a normalizing (including return to pre-pneumonia baseline) heart rate, respiratory rate, systolic blood pressure and oxygen saturation;
- Have a normalizing temperature curve with a maximum temperature in the previous 24 hours of < 38.0°C (<100.4°F);
- Have demonstrated improvement in at least 1 severity category (e.g., moderate to mild) in at least 2 of 4 cardinal symptoms of CABP
  - Dyspnea
  - Cough
  - Sputum production
  - Chest pain;
- Are able to swallow and absorb oral medications (i.e., normally functioning gastrointestinal tract).

The treatment scenarios for IV plus oral study drug are displayed in the tables below.

**Table 1. CABP (not caused by MRSA)**

Study Drug	Regimen	Duration/Additional Dosing Information
Lefamulin	150 mg IV q12h	Total duration of blinded study drug = 7 days of active treatment. Days 1-3 = IV; Days 4-7 = IV or PO If IV study drug administration is switched to oral, moxifloxacin placebo will be administered q24h through Day 7.
	600 mg PO q12h	
Moxifloxacin	400 mg IV q24h	Total duration of blinded study drug = 7 days of active treatment. Days 1-3 = IV; Days 4-7 = IV or PO Separate, alternating doses of IV placebo will be administered q24h such that IV study drug is administered q12h; If IV study drug administration is switched to oral, lefamulin placebo will be administered q12h through Day 7.
	400 mg PO q24h	

NOTE: Subjects with confirmed *Staphylococcus aureus* bacteremia should have study drug discontinued and appropriate alternate therapy should be initiated promptly. If possible, blood samples should be collected for microbiological culture prior to switching to alternate therapy.

**Table 2. CABP (MRSA suspected at Baseline and confirmed Post-baseline)**

Study Drug	Regimen	Duration/Additional Dosing Information
Lefamulin	150 mg IV q12h	Total duration of blinded study drug = 10 days of active treatment. Days 1-3 = IV; Days 4-10 = IV or PO If IV study drug administration is switched to oral, moxifloxacin placebo will be administered q24h until an etiologic pathogen is confirmed (see below). <b>Linezolid placebo q12h x 10 days (IV Days 1-3, IV or PO Days 4-10)</b>
	600 mg PO q12h	
Moxifloxacin	400 mg IV q24h	Total duration of blinded study drug = 10 days of active treatment. Days 1-3 = IV; Days 4-10 = IV or PO Separate, alternating doses of IV placebo will be administered q24h such that IV study drug is administered q12h. If IV study drug administration is switched to oral, lefamulin placebo will be administered q12h. <b>Linezolid 600 mg q12h x 10 days (IV Days 1-3; IV or PO Days 4-10)</b>
	400 mg PO q24h	

NOTE: If results of baseline respiratory tract cultures **do not confirm** MRSA as an etiological pathogen, then linezolid or matching placebo will be discontinued and the subject will complete 7 days of study drug as shown in Table 1 above.

NOTE: If results of baseline respiratory tract cultures **confirm** MRSA as an etiological pathogen during the IV treatment period, then IV moxifloxacin (for subjects in the moxifloxacin treatment arm) or IV linezolid placebo (for subjects in the lefamulin treatment arm) should be discontinued. If results of baseline respiratory tract cultures **confirm** MRSA as an etiological pathogen after a subject has switched to oral treatment, then oral moxifloxacin (for subjects in the moxifloxacin treatment arm) or oral moxifloxacin placebo (for subjects in the lefamulin treatment arm) should be discontinued.

NOTE: Subjects who are confirmed to have *Staphylococcus aureus* bacteremia should have study drug discontinued and appropriate alternate therapy should be initiated promptly. If possible, blood samples should be collected for microbiological culture prior to switching to alternate therapy.

NOTE: If a subject is determined to have an infection caused by MRSA plus an organism known to be resistant to linezolid, the Sponsor's medical monitor should be contacted.

**Study Drug Administration:** Blinded IV study drug will be administered approximately every 12 hours (q12h). Blinded lefamulin and moxifloxacin study drug doses will be infused over approximately 60 minutes. Blinded linezolid and matching placebo will also be infused over approximately 60 minutes. In subjects with suspected or confirmed MRSA, IV lefamulin and IV linezolid placebo or IV moxifloxacin and IV linezolid may be administered concurrently if two separate IV lines are used. If only one IV line is used, IV lefamulin and moxifloxacin should always be infused prior to linezolid or matching placebo.

Every attempt should be made to administer 2 doses of study drug on Study Day 1. On Study Day 1, if q12h dosing is not feasible, the 1<sup>st</sup> and 2<sup>nd</sup> 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. Despite this, there may still be instances where it is not possible to administer 2 doses on Day 1. Subjects who receive only a single dose of study drug on Day 1 will receive their final dose in the morning on either Day 8 (to complete a 7-day course) or on Day 11 (to complete a 10-day course).

As described above, subjects randomized to the moxifloxacin treatment arm will receive IV moxifloxacin alternating with IV placebo to maintain the blind. Subjects should always receive active IV moxifloxacin as the first dose on Day 1. Subjects who begin therapy in the evening on Study Day 1 and whose schedule does not permit a second dose on Day 1 should have their dosing schedule adjusted on Day 2, so that active IV moxifloxacin is given as part of the morning dosing on all subsequent days.

Example 1: If a subject begins therapy at 3pm on Day 1, a second dose may be given at 11pm on Day 1. The subject's dosing schedule may then be adjusted on Day 2 to a regular q12h schedule (e.g., 8am and 8pm dosing). In this scenario, subjects randomized to moxifloxacin will receive active IV moxifloxacin at 3pm and IV matching placebo at 11pm on Day 1.

Example 2: If a subject begins therapy at 5pm on Day 1, it is not possible to give a second dose on Day 1 within the 8 hour minimum between doses. Therefore, the subject will receive a single dose on Day 1, and then be adjusted on Day 2 to a regular q12h dosing schedule (e.g., 6am and 6pm dosing). In this scenario, subjects randomized to moxifloxacin will receive active IV moxifloxacin at 5pm on Day 1, active IV moxifloxacin again in the morning on Day 2 (e.g., 6am) and IV matching placebo in the evening on Day 2 (e.g., 6pm). Subjects who require a 7-day course of study drug and who receive only a single dose of study drug on Day 1 will receive their final dose on Day 8 (to complete a 7-day course). Subjects who require a 10-day course of study drug and who receive only a single dose of study drug on Day 1 will receive their final dose in the morning on Day 11 (to complete a 10-day course).

Blinded oral lefamulin, linezolid, or matching placebo will be administered q12h, while blinded oral moxifloxacin or matching placebo will be administered q24h. Oral moxifloxacin (or matching placebo for subjects in the lefamulin treatment arm) will always be given as part of the morning dosing.

NOTE: Every effort should be made to maintain a q12h dosing schedule. On days when this is not feasible doses should be given within 4 hours of the scheduled dosing time (i.e., a minimum of 8 hours between doses).

For oral dosing 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. Oral doses should be administered with approximately 240 mL (8 ounces) of water.

Subjects are not required to be hospitalized for entry into the protocol, however, while subjects are hospitalized, all doses of study drug will be administered by hospital staff or study personnel. Subjects may receive IV dosing as an outpatient; however, all IV dosing should be administered by hospital staff or study personnel (i.e., subjects are not permitted to self-administer IV study drug). In the event a subject is discharged from the hospital during

the oral study drug administration period, subjects may self-administer oral study drug at home. The site of care/site of study drug administration (e.g., emergency room, IV infusion center, subject's home, etc.) will be recorded for each IV dose.

**Blinding:** An unblinded pharmacist at the investigative site will prepare and blind all IV study drug infusions using an IV bag cover and IV tubing cover. Oral study drug will be blinded using a double-dummy technique. IV study drug will be administered by an unblinded designee(s) at the study site. Unblinded site personnel who administer study drug will not perform other study related procedures or evaluations. Only blinded study personnel will perform study related procedures and evaluations. Intravenous infusions should be administered at a controlled rate (over approximately 60 minutes). For blinding purposes, in subjects receiving linezolid/matching placebo, if an infusion pump with a digital display is used, then the unblinded site personnel administering study drug must remain with the subject for the duration of the IV linezolid/matching placebo infusion.

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. Sponsor representative(s) will be unblinded to treatment assignment in order to review drug accountability on an ongoing basis throughout the study. A Data Monitoring Committee (DMC) will review summary safety data by masked treatment group throughout the study. 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 clinical site staff 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 125 centers. The planned enrollment is 550 subjects with PORT Risk Class  $\geq$ III. However, if based upon regulatory requirements additional subjects exposed to lefamulin are needed, up to 626 subjects may be enrolled. Eligible subjects will be randomized 1:1 to lefamulin or the comparator, moxifloxacin, using an interactive response technology (IRT). Subject randomization will be stratified according to PORT Risk Class (Risk Class III vs. IV and V), 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):  $96 \pm 24$  hours after the first dose of study drug (i.e., after at least 6 doses of study drug have been given)
- 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): 30 days ( $\pm 3$  days) after the first dose of study drug

Assessment of the 4 cardinal symptoms of CABP (dyspnea, cough, purulent sputum production and chest pain) will be conducted daily; an assessment at  $96 \pm 24$  hours after the first dose of study drug will be used to 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. CABP signs and symptoms will be assessed in person while subjects are hospitalized. Outpatients may have signs and symptoms assessed daily by telephone; however, they must also have a study site visit  $96 \pm 24$  hours after the first dose of study drug to assess CABP signs and symptoms in person.

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 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.

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 every subject during administration of IV study drug, and in a subset of subjects who are switched from IV to oral study drug.

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 performed.

Overviews of study designs for subjects receiving 7 days of treatment and for subjects receiving 10 days of treatment are presented in Figure 1 and Figure 2, respectively. The schedule of assessments/procedures is presented in Table 3.

### **Statistical Considerations:**

Sample Size: Utilizing an anticipated ECR responder rate of 79% in the ITT Analysis Set, and a one-sided alpha of 0.025, a sample size of 550 subjects (275 in each treatment group) provides >90% power to establish the non-inferiority (NI) of lefamulin to moxifloxacin for ECR using a NI margin of 12.5% 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 80% power for demonstration of NI for IACR at the TOC Visit using a 10% NI

margin. However, if based upon regulatory requirements additional subjects exposed to lefamulin are needed, up to 626 subjects may be enrolled. This sample size provides >95% power for demonstration of NI for ECR and 85% power for demonstration of NI for IACR at the TOC Visit.

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

Interim Analysis: In order to ensure that the point estimate of the ECR responder and IACR success rates used in the estimation of the sample size are valid for this study, an interim analysis for sample size re-estimation will be performed when ECR data at  $96 \pm 24$  hours post first dose are available for approximately 60% of randomized subjects (330 subjects). An independent statistician will provide the Independent Interim Analysis Committee (IAC) with the results of the interim analysis; the IAC will make a recommendation regarding any potential increase to the planned sample size.

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 one baseline “typical” bacterial pathogen known to cause CABP, *Legionella pneumophila* from an appropriate microbiological specimen, or who have CABP caused by *Mycoplasma pneumoniae* or *Chlamydomphila 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 (other than adjunctive linezolid) 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 Set, 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  $96 \pm 24$  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 6.10) 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 (other than adjunctive linezolid) 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 (other than adjunctive linezolid) 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.
- 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 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 24 h AUC values from Day 1 obtained from the population PK model will be used for the PK/PD analysis focusing on efficacy. 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 (SF-12) will be performed.

### **Statistical Methods:**

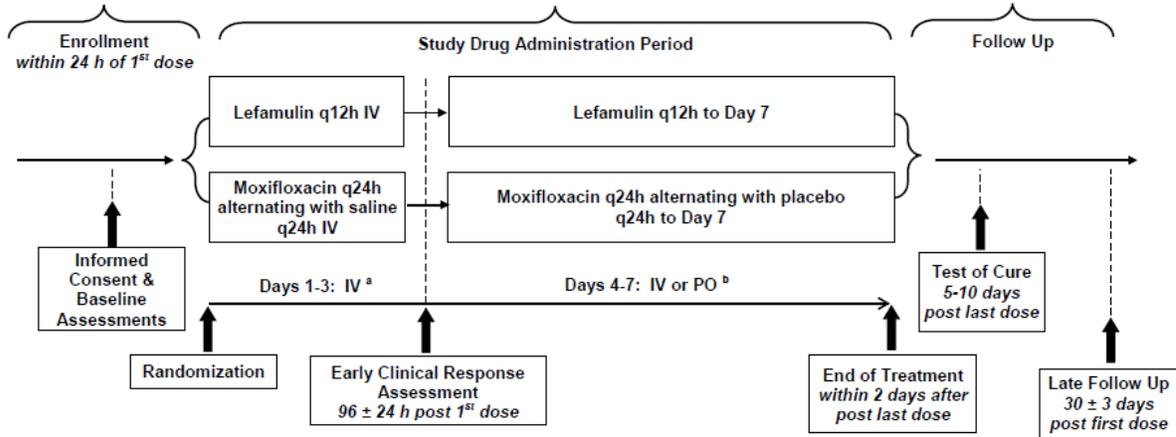
A 2-sided unstratified 95% confidence interval (CI) for the observed difference between treatment groups (lefamulin minus moxifloxacin) in ECR responder rates at  $96 \pm 24$  hours post first dose will be calculated using a continuity corrected Z-statistic. Non-inferiority for the primary efficacy analysis variable (FDA) will be concluded if the lower limit of the 2-sided 95% CI is greater than  $-12.5\%$  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% CI will be calculated using a continuity corrected Z-statistic (FDA secondary efficacy outcome). For the primary analysis for the EMA, a stratified 2-sided 95% CI 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  $96 \pm 24$  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.

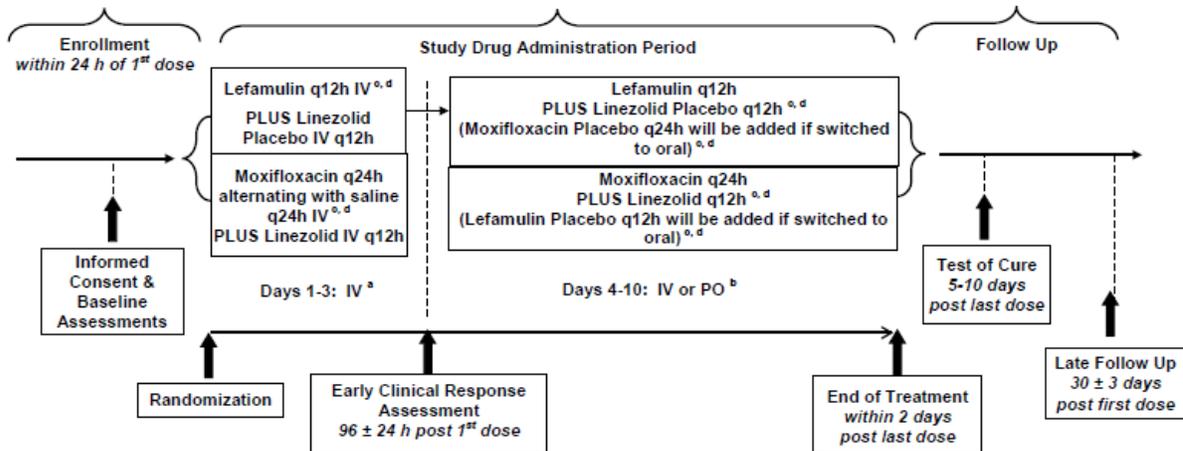
The incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), deaths, and discontinuations of study drug due to an AE or SAE will be summarized by System Organ Class (SOC) and Preferred Term according to the Medical Dictionary for Regulatory Activities (MedDRA), by relationship to study drug,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

**Figure 1. Study Design Overview – CABP not caused by MRSA**



- a: IV treatment will be initiated with 1 infusion q12h. All infusions will be blinded. While receiving IV treatment, subjects in the moxifloxacin treatment arm will receive moxifloxacin q24h alternating with saline placebo q24h to maintain the blind.
- b: All subjects will have IV treatment for a minimum of 3 days (6 doses) after which time IV treatment may be changed to oral if pre-defined criteria are met.

**Figure 2. Study Design Overview – MRSA Suspected at Baseline and Confirmed Post-baseline**



- a: IV treatment will be initiated with 2 infusions q12h (lefamulin plus linezolid placebo OR moxifloxacin plus linezolid). All infusions will be blinded. While receiving IV treatment, subjects in the moxifloxacin treatment arm will receive moxifloxacin q24h alternating with saline placebo q24h to maintain the blind.
- b: All subjects will have IV treatment for a minimum of 3 days (6 doses) after which time IV treatment may be changed to oral if pre-defined criteria are met.
- c: If results of baseline respiratory tract cultures confirm MRSA as an etiological pathogen during the IV treatment period, then IV moxifloxacin (for subjects in the moxifloxacin treatment arm) or IV linezolid placebo (for subjects in the lefamulin treatment arm) should be discontinued. If results of baseline respiratory tract cultures confirm MRSA as an etiological pathogen after a subject is switched to oral treatment, then oral moxifloxacin (for subjects in the moxifloxacin treatment arm) or oral moxifloxacin placebo (for subjects in the lefamulin treatment arm) should be discontinued.
- d: If results of baseline respiratory tract cultures do NOT confirm MRSA as an etiological pathogen, then linezolid or matching placebo will be discontinued and the subjects will complete 7 days of study drug as shown in Figure 1.

**Table 3. Schedule of Assessments and Procedures**

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

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

- a: Perform Screening/Baseline assessments within 24 hours before first dose of IV study drug. Administration of study drug should begin as soon as possible after the diagnosis of CABP. Assessments performed as part of routine standard of care prior to consent (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.
- c: Days 4 to 7: Subjects receiving 7 days of randomized study drug.
- d: [Days 4 to 10: Subjects receiving 10 days of randomized study drug.]
- e: Perform EOT assessments at the study site within 2 days (1 day preferred) after the last dose of study drug or at the time of premature discontinuation of study drug or early withdrawal from study. EOT assessments resulting from premature discontinuation of study drug should be done in place of the regular study visit on Days 1 to 7 (or Days 1 to 10, as applicable).
- f: Perform TOC assessments at the study site 5–10 days after the last dose of study drug. All subjects will have a TOC Visit irrespective of early clinical failure or receipt of an alternative antibiotic.
- g: Perform LFU assessments at the study site on Day 30 ± 3 days. All subjects will have a LFU Visit irrespective of early clinical failure or receipt of an alternative antibiotic.
- h: Obtain informed consent before initiating any study assessments or procedures.
- i: Randomization may occur at either Screening or on Day 1 prior to receipt of the first dose of study drug.
- j: Record vital signs (heart rate, blood pressure, respiratory rate, body temperature), O<sub>2</sub> saturation, and supplemental oxygen usage daily on days the subject is seen in person (i.e., at baseline, daily while the subject is hospitalized [record vital signs associated with highest temperature], daily while the subject is on IV therapy, at in-person visits while the subject is taking oral study drug as an outpatient), and at EOT and TOC. Record vital signs, O<sub>2</sub> saturation, and supplemental oxygen usage at LFU if medically indicated. If Screening and Day 1 occur on the same day, vital signs should be obtained as part of the Screening evaluation (prior to administration of any study drug) and repeated as part of the Day 1 assessment (record the vital signs associated with the highest temperature post dosing). If EOT and the last day of study drug are the same day, vital signs do not need to be repeated, they may be recorded once on that day (i.e., as part of the EOT assessment).
- k: Evaluate signs and symptoms of CABP at baseline, daily while receiving study drug and at EOT, TOC, and LFU. Signs and symptoms are not obtained at TOC or LFU if the subject was previously deemed to have an IACR of Failure. Subjects who are receiving medication at home may be contacted by phone to track signs and symptoms of CABP if an in-person assessment is not required or planned for that day. **EXCEPTION: Subjects must have a visit at the study site that is 96 ± 24 hours after the first dose of study drug to assess CABP signs and symptoms for calculation of ECR.** Study personnel will inform subjects as to the timing of this visit. If Screening and Day 1 are the same day, signs and symptoms of CABP do not need to be repeated on Day 1. If EOT and the last day of study drug are the same day, signs and symptoms of CABP should be done only once on that day (i.e., as part of the EOT assessment).
- l: Record AEs from the signing of the ICF through TOC and SAEs from signing of the ICF through LFU. Study personnel will follow unresolved AEs and SAEs present at LFU until resolution or stabilization.
- m: **At each required time point, ECGs should be recorded in triplicate within a 5-minute interval.** The subject should be stabilized in a supine position for 5 min before recording the ECG. Record ECGs at Screening. On Day 1 and Day 3 record ECGs prior to the first infusion of study drug on that day and within 15 minutes after the end of the first infusion on that day. If Screening and Day 1 are on the same day, the Screening ECG can serve as the Day 1 ECG prior to the first infusion of study drug. Additional ECG's may be performed if clinically indicated. If at any time the subject demonstrates an average QTcF value >500 ms (mean of 3 ECG's at any time point), or an average QTcF value >480ms with a concurrent increase in average QTcF value of > 60 ms (mean of 3 post-dose ECGs compared to mean pre-dose ECG's taken on that day) study drug will be discontinued.
- n: A complete physical examination is performed at baseline and directed physical examinations are performed on Day 4 (Day 3 is acceptable for outpatients who are not able to return on Day 4) and at EOT and TOC.
- o: For all subjects, collect blood and urine at Screening, Day 4 (Day 3 is acceptable for outpatients who are not able to return on Day 4), EOT, and TOC. In addition, for subjects receiving 10 days of study drug, collect blood and urine on Day 7 (Day 8 is acceptable for outpatients who are not able to return on Day 7). Subjects treated as outpatients must agree to return to the site for blood draws. Collect blood and/or urine at LFU only if subject had an abnormal (high/low flag) result at TOC. Blood samples sent to the local laboratory for the purposes of determining study eligibility must be repeated and sent to the central laboratory following enrollment.
- p: A pregnancy test will be performed on all females unless surgically sterile or at least 2 years post-menopausal. A negative urine pregnancy test is required prior to randomization and must be confirmed as soon as possible using a serum pregnancy test.
- q: Blood to be collected and sent to central laboratory for serologic tests for *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila* at Screening and LFU.
- r: Record arterial blood gas and blood pH data if available. Study sites are not required to measure arterial blood gas or blood pH.
- s: Collect blood samples (2 sets via peripheral venipuncture) for microbiologic culture and susceptibility testing at the local/regional lab at Screening and as clinically indicated during the study. Repeat blood cultures after a positive result until sterilization is documented. If possible, subjects who are discontinued from study drug due to confirmed MRSA or MSSA bacteremia should have blood samples collected for microbiologic culture prior to switching to alternate appropriate therapy. All organisms isolated from blood cultures which are not considered contaminants will be sent to the central laboratory for confirmatory identification and susceptibility testing.

- t: All lower respiratory tract and expectorated sputum samples (including the Screening sample) should be sent to the local/regional laboratory for Gram's stain, culture and susceptibility testing. If a subject is unable to produce an adequate (> 25 polymorphonuclear [PMN] cells **AND** < 10 squamous epithelial cells per LPF) sputum sample at Screening, a specimen should be obtained, if possible, within 24 hours after the first dose of study drug. Gram's stain and culture results from the local/regional laboratory will be recorded in the eCRF. Slides (stained and unstained) will also be sent to the central laboratory for a confirmatory reading of the Gram's stain. If possible, subjects who are discontinued from study drug due to clinical failure should have repeat cultures collected for microbiologic culture prior to switching to alternate appropriate therapy. All organisms isolated from sputum samples, which are not considered contaminants, will be sent to the central laboratory for confirmatory identification and susceptibility testing. In addition, a portion of all sputum samples must be frozen until sent to the central laboratory for PCR. Subjects with a positive urinary antigen will also have isolation of *L. pneumophila* performed at the central laboratory on the frozen sputum.
- u: An oropharyngeal specimen (2 swabs) will be collected and frozen until sent to the central laboratory. The oropharyngeal specimen will be used for culture of *M. pneumoniae* and identification by PCR.
- v: A nasopharyngeal specimen will be collected and frozen until sent to the central laboratory. The nasopharyngeal specimen will be used for culture of *S. pneumoniae* and identification by PCR.
- w: Study drug should be administered approximately the same time each day. On days when this is not feasible, doses should be given within 4 hours of the scheduled dosing time (i.e., a minimum of 8 hours between doses). Subjects who receive only a single dose of study drug on Day 1 will receive their final dose in the morning on either Day 8 (to complete a 7-day course) or on Day 11 (to complete a 10-day course). Administration of study drug may occur on the same calendar day as EOT, and if so will be completed before EOT assessments begin.
- x: Collect blood for PK analysis in association with the morning dose of IV study drug on Day 3. Collect blood for PK samples within 1 h before administration of IV study drug, within 10 minutes following completion of the infusion, at 2–4 h after infusion, and at 8–12 h after the infusion. In subjects who agree via written consent, and for whom collection is logistically feasible, blood for PK analysis will be collected in association with the first morning dose of oral study drug. Blood will be collected within 1 h prior to dose, 1–3 h after dose, and 4–8 h after dose. Since blood collection is required both before and after the first morning oral dose, outpatients should be instructed to not take their first morning dose of oral study drug at home, rather to bring all blister packs (used and unused) to the study site. Following collection of the pre-dose blood sample, subjects will take their dose of study drug under supervision of study personnel, and subsequent PK blood samples will be collected.
- y: Investigator to determine IACR - Success, Failure or Indeterminate (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.
- z: Collect pleural fluid samples and/or BAL only if medically indicated. Gram's stain samples, culture, and test the isolated pathogens for susceptibility. Pathogens isolated from pleural fluid and/or BAL samples will be sent to the central laboratory for confirmatory identification and susceptibility testing. If possible, pleural fluid samples should be incubated in blood culture bottles for optimal pathogen recovery.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
24 h AUC/MIC	24 h area under the drug concentration–time curve over the MIC
ABG	Arterial blood gas
ACM	All-cause mortality
ABPI	Association of British Pharmaceutical Industry
ABSSSI	Acute bacterial skin and skin structure infection
ADME	Absorption, Distribution, Metabolism, and Elimination
AE	Adverse event
AGP	$\alpha$ 1-acid glycoprotein
ALT	Alanine aminotransferase
APAC	Asia Pacific
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the drug concentration–time curve
AUC <sub>0–12h</sub>	AUC from time zero to 12 h
AUC <sub>0–24h</sub>	AUC from time zero to 24 h
AUC <sub>0–inf</sub>	AUC from time zero to infinity
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-TOC	Clinically Evaluable at Test-of-Cure
CFR	Code of Federal Regulation
CFU	Colony Forming Unit
CI	Confidence interval
C <sub>max</sub>	Maximum observed plasma concentration
C <sub>min</sub>	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

<b>Abbreviation</b>	<b>Definition</b>
DMC	Data Monitoring Committee
ECA	Early Clinical Assessment
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 $\beta$ -lactamase
EU	European Union
F	Fahrenheit
$fAUC$	Area under the concentration-time curve of the unbound fraction of the drug
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
hERG	Human ether a go go related Gene
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
IAC	Interim Analysis Committee
IACR	Investigator's Assessment of Clinical Response
IC <sub>50</sub>	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
JP	Japanese Pharmacopoeia
K <sub>3</sub> EDTA	Tripotassium ethylene diamine tetraacetic acid
LFU	Late Follow-up
LLQ	Lower limit of quantification
LPF	Low power field
MAA	Marketing Authorization Application
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
ME-EOT	Microbiologically Evaluable at End-of-Treatment

<b>Abbreviation</b>	<b>Definition</b>
ME-TOC	Microbiologically Evaluable at Test-of-Cure
Mg	Milligram
MIC	Minimum inhibitory concentration
MIC <sub>90</sub>	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 <i>Staphylococcus aureus</i>
Ms	Millisecond
MSSA	Methicillin-susceptible <i>Staphylococcus aureus</i>
N	Group size, number of replicates
NaCl	Sodium chloride
NCS	Not clinically significant
NI	Non-inferiority
NOAEL	No Adverse Effect Level
O <sub>2</sub>	Oxygen
Pa O <sub>2</sub>	Partial Pressure of Arterial Oxygen
PCR	Polymerase Chain Reaction
PCS	Potentially clinically significant
PD	Pharmacodynamic
p-gp	p-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PO	By mouth (oral)
PORT	Pneumonia Outcomes Research Team
PRO	Patient-reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
PVG	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
rRNA	Ribosomal ribonucleic acid
RTI	Respiratory tract infection
SAE	Serious Adverse Event

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<b>Abbreviation</b>	<b>Definition</b>
SAP	Statistical Analysis Plan
SENTRY	SENTRY Antimicrobial Surveillance Program
SPC	Summary of Product Characteristics
SSRI	Selective Serotonin Re-uptake Inhibitor
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

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

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# 1 INTRODUCTION

## 1.1 Background of the Disease and Treatment Options

Community-acquired bacterial pneumonia (CABP) is a commonly occurring serious infection that requires systemic antibiotic therapy and is associated with substantial morbidity, mortality, and considerable healthcare costs. It is the leading cause of death from infectious diseases in the United States (US) and, when combined with influenza, remains the eighth leading cause of death in the US (CDC, 2013). In Europe, there are 44 cases of CABP for every 1000 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 3329 *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. Both the intravenous (IV) and oral dosage forms of lefamulin are 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<sup>®</sup>) for the topical treatment of impetigo and in Europe (Altargo<sup>®</sup>) for the topical short-term treatment of impetigo and infected small lacerations, abrasions or sutured wounds. Tiamulin (Denagard<sup>®</sup>) and valnemulin (Econor<sup>®</sup>), 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 respiratory tract infection (RTI), acute bacterial skin and skin structure infection (ABSSSI) and sexually transmitted diseases (STD). The antibacterial spectrum comprises *S. aureus* including MRSA and CA-MRSA,  $\beta$ -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,  $\beta$ -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  $>1 \mu\text{g/mL}$  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  $\mu\text{g/mL}$ ), *H. influenzae* (2  $\mu\text{g/mL}$ ), *M. catarrhalis* (0.25  $\mu\text{g/mL}$ ), *L. pneumophila* (0.5  $\mu\text{g/mL}$ ), *M. pneumoniae* (0.006  $\mu\text{g/mL}$ ), and *C. pneumoniae* (0.04  $\mu\text{g/mL}$ ). When compared with other antibiotics used to treat bacterial pneumonia such as macrolides,  $\beta$ -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*.

Lefamulin was shown to have no interaction – neither antagonism nor synergy – when combined with other antibiotics against Gram-positive or Gram-negative organisms, including those with important resistance phenotypes (e.g., MRSA and extended-spectrum  $\beta$ -lactamase [ESBL]), suggesting that there is no potential issue for combination therapy, if necessary.

Lefamulin accumulated 30- to 50-fold in murine macrophages at clinically relevant concentrations of 1 and 5  $\mu\text{g/mL}$ . 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  $fAUC/MIC$  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  $\alpha$ 1-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.

*In vitro* drug transporter studies showed that lefamulin is not a substrate of efflux transporters BCRP, BSEP or uptake transporters OATP1B1 and OATP1B3, and is a substrate of the uptake transporter OCT1. Only a weak inhibition was shown with BSEP ( $IC_{50} = 24.5 \mu M$ ) and OCT1 ( $IC_{50} = 20.3 \mu M$ ), while very poor or no inhibition was seen with OATP1B1 and OATP1B3. For BCRP in the GI tract, inhibition cannot be excluded ( $IC_{50} = 42.2 \mu M$ ,  $[I]_2/IC_{50} = 112 > 10$ ). With regard to the renal uptake transporters, inhibition potential of lefamulin towards PAH uptake by OAT1, furosemide uptake by OAT3, and MPP<sup>+</sup> uptake by OCT2 was not considered significant.

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<sub>Kr</sub> (hERG) assays and a study using rabbit Purkinje fibers showed a potential for QT/QTc prolongation, but — importantly — 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 4200 mg daily in 60 kg humans and exceeds the maximum intended daily dose of 1200 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 major 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 major 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 safe and well tolerated at the doses to be used in the current study (150 mg IV over 60 minutes and 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  $\geq 65$  years of age. In the Phase 2 study, 141 subjects (95 male, 46 female) were exposed to lefamulin, 7 of whom were  $\geq 65$  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).

Lefamulin PK is characterized by rapid absorption after oral administration. Steady-state is achieved after 2 days of q12h dosing, irrespective of the route of administration. After oral administration of an immediate-release tablet containing 600 mg of lefamulin, exposure — as measured by AUC (the driver of efficacy) — was similar to a 150 mg IV dose, the higher dose used in the Phase 2 study in ABSSSI (NAB-BC-3781-2001) (Wicha et al., 2013).

### 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 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, 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.

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 parent drug 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. 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.

### 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 ( $\geq 1000$  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 and 150 mg demonstrated consistently high clinical and microbiological success rates at several time points including the 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). The early clinical responder rate (Day 3) for lefamulin was also high and comparable to that of 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 criteria. The stopping criteria were not reached in any of the studies.

In the Phase 2 study in subjects with ABSSSI, lefamulin (100 mg and 150 mg) administered intravenously over 5 to 14 days was safe and well tolerated. The incidence of treatment-emergent adverse events (TEAEs) considered related to study drug was numerically lower for subjects treated with lefamulin (34% and 39% in the 100 and 150 mg groups, respectively) than for 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  $\Delta QTcF > 60$  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/pharmacodynamics 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 with no signs or symptoms of clinical concern.

This is the first Phase 3 study to be conducted in subjects with a systemically-administered pleuromutilin antibiotic. The population in this study will be subjects with CABP and they

will receive treatment with either lefamulin or moxifloxacin (with or without adjunctive linezolid), a standard treatment for this condition.

## 2 STUDY OBJECTIVES

### 2.1 Primary Objectives

- Demonstrate the non-inferiority (NI) of lefamulin versus comparator with respect to the Early Clinical Response ( $96 \pm 24$  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 Early Clinical Response PLUS improvement in vital signs in the ITT Analysis Set.
- Evaluate the Investigator's Assessment of Clinical Response at TOC in the microITT and Microbiologically Evaluable at TOC (ME-TOC) Analysis Sets.
- 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-EOT 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-TOC Analysis Sets (ME-TOC for IACR at TOC and ME-LFU for IACR at LFU).
- Evaluate the By-Subject Microbiologic Response at TOC in the microITT and ME-TOC Analysis Sets.
- Evaluate the plasma pharmacokinetics (PK) of lefamulin in the PK Analysis Set.

- Explore a variety of health utilization variables and an investigational patient reported outcome (PRO) measure (SF-12) 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 community-acquired bacterial pneumonia (CABP) will be conducted at approximately 125 centers. The planned enrollment is 550 subjects with Pneumonia Outcomes Research Team (PORT) Risk Class  $\geq$ III. However, if based upon regulatory requirements additional subjects exposed to lefamulin are needed, up to 626 subjects may be enrolled. Eligible subjects will be randomized 1:1 to lefamulin or the comparator, moxifloxacin, using interactive response technology (IRT). Subject randomization will be stratified according to PORT Risk Class (Risk Class III vs. IV and V), 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 the first dose of study drug.

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

- Early Clinical Assessment (ECA):  $96 \pm 24$  hours after the first dose of study drug (i.e., after at least 6 doses of study drug have been given)
- 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):  $30 \pm 3$  days after the first dose of study drug

Assessment of the 4 cardinal symptoms of CABP (dyspnea, cough, purulent sputum production and chest pain) will be conducted daily (see Section 6.10); an assessment at  $96 \pm 24$  hours after the first dose of study drug will be used to determine Early Clinical Response (ECR) (as defined in the Primary Objective - FDA) (Section 9.4.1). 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. CABP signs and symptoms will be assessed in person while subjects are hospitalized. Outpatients may have signs and symptoms assessed daily by telephone; however, they must also have a study site visit  $96 \pm 24$  hours after the first dose of study drug to assess CABP signs and symptoms in person.

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 throughout the study as clinically indicated (see Section 6.14). Samples will be taken for Gram's staining, for diagnostic tests (serology, urine antigen tests, and molecular tests) and for culture and antimicrobial susceptibility testing.

Safety will be assessed by monitoring vital signs, ECG measurements, safety laboratory parameters, and recording of adverse events (AEs) (see Sections 6.1, 6.4, 6.12, and 7). Safety procedures will be performed by the Investigator or suitably qualified individuals designated by the Investigator. A Data Monitoring Committee (DMC) will review the safety data throughout the study (Section 10.2).

Blood samples for PK analyses will be collected from every subject during administration of IV study drug, and in a subset of subjects who are switched from IV to oral study drug (Section 6.13).

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 performed (Section 6.15).

Overviews of study designs for subjects receiving 7 days of treatment and for subjects receiving 10 days of treatment are presented in Figure 1 and Figure 2, respectively. The schedule of assessments/procedures is presented in Table 3.

### 3.1 Study Rationale

Lefamulin (BC-3781), a semi-synthetic pleuromutilin, represents a new class of antibiotics for 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 and other infections. 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. Lefamulin is therefore being examined further in subjects with other infections including CABP.

This study will examine whether lefamulin is non-inferior to moxifloxacin (with or without adjunctive linezolid), for the treatment of CABP in adults  $\geq 18$  years of age. All subjects will initially receive a minimum of 6 doses of IV study medication, after which they may be switched to oral study medication if they meet pre-specified clinical criteria (Section 5.5.3).

The comparison between lefamulin and comparator will be made with respect to the following assessments: ECR ( $96 \pm 24$ h 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  $\geq 18$  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 ( $\leq 7$  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  $>38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) measured orally or equivalent temperature from an alternate body site) or hypothermia (body temperature  $<35.0^{\circ}\text{C}$  ( $95.0^{\circ}\text{F}$ ) 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.,  $\text{O}_2$  saturation  $<90\%$  on room air or while receiving supplemental oxygen at subject's baseline requirement or  $\text{PaO}_2 <60$  mmHg).

- Auscultatory and/or percussion findings consistent with pneumonia (e.g., crackles, egophony, dullness).
  - White blood cell (WBC) count  $>10,000$  cells/mm<sup>3</sup> or  $<4500$  cells/mm<sup>3</sup> 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  $\geq$ III and require IV antibiotic therapy as initial treatment for the current episode of CABP.
  8. If female, meets the following criteria:
    - Surgically sterile or  $\geq 2$  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  $\geq 28$  days after the last dose of study drug. If a male partner has been surgically sterile for  $\geq 1$  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  $\geq 28$  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  $\geq 28$  days after the last dose of study drug. If surgically sterile for  $\geq 1$  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 and, in the case of methicillin-resistant *Staphylococcus aureus* (MRSA), oxazolidinones.
2. Require concomitant systemic antibacterial therapy potentially effective against CABP pathogens (See Section 6.8).

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., *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. Require mechanical ventilation.
8. 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).
9. Be receiving a strong p-glycoprotein inhibitor or a strong CYP3A inducer or inhibitor (see Appendix 4)
10. 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).
11. Have a history of any hypersensitivity or allergic reaction to any fluoroquinolone or any drug in the pleuromutilin class (i.e., retapamulin).
12. Have severely impaired renal function, defined as creatinine clearance (CrCl)  $\leq 30$  mL/min as calculated by the Cockcroft-Gault formula.

13. Have evidence of significant hepatic, hematologic, or immunologic disease including any of the following:
  - Known acute hepatitis, including active viral hepatitis.
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level >5 times the upper limit of normal (ULN) or total bilirubin >3 times the ULN.
  - 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<sup>3</sup>).
  - Thrombocytopenia (<50,000 platelets/mm<sup>3</sup>).
  - Known infection with human immunodeficiency virus and a CD4 count <200/mm<sup>3</sup>.
14. Have known or suspected severe immunosuppression, defined as receipt of corticosteroid therapy ( $\geq 20$  mg prednisone/day or equivalent for more than 4 weeks) within the previous 8 weeks; solid organ or bone marrow transplantation within the previous 12 months; or currently receiving cytotoxic chemotherapy.
15. Have a life expectancy of  $\leq 3$  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).
16. Have participated in any study involving administration of an investigational agent or device within 30 days or  $\leq 5$  terminal elimination half-lives of the previous investigational medicinal product, whichever is longer, before enrollment.
17. Have been previously treated with lefamulin or previously enrolled in this study.
18. Have any condition that, in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data.

**In addition, for subjects suspected to have MRSA for whom adjunctive linezolid or matching placebo will be added, each subject must NOT:**

19. Have received any of the following medications:
  - Monoamine oxidase inhibitors (within 2 weeks of randomization).
  - Serotonergic agents (e.g., SSRI antidepressant medications) (within 5 weeks of randomization).
20. Have pheochromocytoma, carcinoid syndrome, uncontrolled hypertension, or thyrotoxicosis.
21. Have a history of any hypersensitivity or allergic reaction to linezolid or tedizolid.

## 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 with 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 150 mg IV q12h for the treatment of subjects with CABP caused by *S. pneumoniae* or *S. aureus* (the dosing regimen being utilized in this Phase 3 study). 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 this Phase 3 study) 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<sub>ELF</sub>/MIC ratio targets for *S. pneumoniae* and *S. aureus* associated with a 1-log<sub>10</sub> CFU reduction from baseline as it has been demonstrated that patients with CABP who attain a 1-log<sub>10</sub> 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 fAUC/MIC ratio targets for a 1-log<sub>10</sub> 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.

Percent probabilities of attaining the median  $AUC_{ELF}/MIC$  ratio targets associated with a  $1\text{-log}_{10}$  CFU reduction from baseline by MIC were 97.0 % at a MIC of 0.5  $\mu\text{g}/\text{mL}$  for *S. pneumoniae* and 99.4 % at a MIC of 0.25  $\mu\text{g}/\text{mL}$  for *S. aureus* (thus, covering  $\geq 99.5$  % of Northern America and EU or worldwide isolates for either pathogen).

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 the lefamulin 150 mg IV q12h/ 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

For hospitalized patients with CABP admitted to a general ward, the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) treatment guidelines recommend the use of an antipneumococcal fluoroquinolone. In addition, if MRSA is suspected, the IDSA/ATS recommend the use of linezolid (Mandell et al., 2007). Consistent with these expert, consensus guidelines, the comparator chosen for this study is moxifloxacin (with or without adjunctive linezolid; see Section 5.3). Moxifloxacin (IV/PO) is indicated for the treatment of CABP caused by *S. pneumoniae* (including multi-drug resistant isolates), *H. influenzae*, *M. catarrhalis*, methicillin-susceptible *S. aureus*, *Klebsiella pneumoniae*, *M. pneumoniae*, or *C. pneumoniae*. Moxifloxacin will be administered at a dose of 400 mg every 24 hours for 7 -10 days as recommended in the prescribing information (Moxifloxacin SPC [solution], 2012; Moxifloxacin SPC [tablet], 2014). No dose adjustment of moxifloxacin will be permitted in this study. Subjects may be switched to oral moxifloxacin 400 mg once daily if, after receiving a minimum of 6 IV doses (3 IV moxifloxacin and 3 IV placebo), it is deemed clinically appropriate (see Section 5.5.3).

## 5.3 Adjunctive Treatment with Linezolid

As part of the Screening evaluation, the Investigator will determine whether MRSA is a probable pathogen in the subject. MRSA should be considered a potential cause of CABP when a good quality sputum Gram's stain shows both polymorphonuclear leukocytes and abundant Gram-positive cocci in clusters, or if local epidemiology and recent clinical experience suggest it is prevalent in the community. Linezolid is provided as empiric therapy in subjects where MRSA is suspected as the pathogen until culture results are available. If MRSA is suspected, adjunctive linezolid therapy will be added to the moxifloxacin treatment group, while matching placebo will be added in the lefamulin group pending final culture results. Linezolid treatment or matching placebo will only be continued in the presence of a microbiological culture confirming the presence of MRSA. If cultures do not grow MRSA, linezolid (or matching placebo) will be discontinued and subjects will be continued on moxifloxacin (or lefamulin).

Overall, it is anticipated that the proportion of subjects receiving adjunctive linezolid therapy would constitute the minority of enrolled subjects (e.g., <10%). Following receipt of

screening microbiological results, study drug therapy will be adjusted as described in Section 5.5.2.

Subjects for whom adjunctive therapy with linezolid is required will receive 600 mg IV q12h with potential switch to oral linezolid 600 mg q12h (see Section 5.5.3) (Linezolid SPC [solution], 2014; Linezolid SPC [tablet], 2014).

## 5.4 Randomization

Qualified subjects will be randomized to receive lefamulin or moxifloxacin in a 1:1 allocation ratio. Randomization may occur at either Screening or on Day 1 prior to receipt of the first dose of study drug. Subjects randomized to IV lefamulin will receive 150 mg of lefamulin q12h and subjects randomized to IV moxifloxacin will receive 400 mg of moxifloxacin q24h. In order to maintain the blind, subjects randomized to IV moxifloxacin will receive alternating doses of IV placebo administered q24h so that IV study drug is administered q12h.

Randomization will be stratified by PORT Risk Class (Risk Class III vs. IV and V; see Section 6.2), 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 25% of the total number of subjects randomized will have a PORT risk class of IV or V.

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.

## 5.5 Study Drug Treatment

### 5.5.1 Duration of Treatment

It is estimated that the duration of blinded study drug administration for the majority (~90%) of subjects will be 7 days of active treatment as shown in Table 4 (Section 5.5.4). Subjects with CABP due to MRSA will receive 10 days of active treatment as shown in Table 5 (Section 5.5.4). Subjects with CABP due to MRSA, or those with confirmed *S. aureus* bacteremia will have their treatment adjusted as described below

### 5.5.2 Post-Baseline Treatment Modifications

Following receipt of the screening microbiological results, the following treatment modifications will be made. The investigator (or designee) must communicate culture results

in a timely manner to the unblinded pharmacist so that study treatment can be adjusted accordingly:

- Subjects who were suspected to have MRSA at Screening, and whose microbiological results confirm MRSA as a causative pathogen during the IV treatment period will be managed as follows:
  - Subjects randomized to receive moxifloxacin: IV moxifloxacin should be discontinued and linezolid will be continued for 10 days as shown in Table 5 below.
  - Subjects randomized to receive lefamulin: IV linezolid placebo should be discontinued and lefamulin will be continued for 10 days as shown in Table 5 below.
- Subjects who were suspected to have MRSA at Screening and whose microbiological results confirm MRSA as a causative pathogen during the oral treatment period will be managed as follows:
  - Subjects randomized to receive moxifloxacin: Oral moxifloxacin should be discontinued. Subjects will continue to receive oral linezolid plus oral lefamulin placebo to complete 10 days of study drug therapy as shown in Table 5 below.
  - Subjects randomized to receive lefamulin: Oral moxifloxacin placebo should be discontinued. Subjects will continue to receive oral lefamulin plus oral linezolid placebo to complete 10 days of study drug therapy as shown in Table 5 below.
- Subjects who were suspected to have MRSA at Screening and whose microbiological results do NOT confirm MRSA will have linezolid or matching placebo discontinued and will continue treatment with study drug for 7 days as shown in Table 4 below.
- Subjects whose microbiological results confirm *S. aureus* bacteremia (either methicillin-susceptible or methicillin-resistant) will be discontinued from study drug and have appropriate alternate therapy initiated promptly. If possible, blood samples should be collected and sent for microbiological culture prior to switching to alternate therapy.

NOTE: If a subject is determined to have an infection caused by MRSA plus an organism known to be resistant to linezolid, the Sponsor's medical monitor should be contacted.

If MRSA is confirmed as an etiological pathogen, but the subject was not prescribed adjunctive linezolid at Screening, the Investigator should assess the subject's clinical status at the time the microbiological results become available. If at this time the subject is demonstrating clear and progressive clinical improvement (e.g., improving temperature, respiratory signs and symptoms, etc.), then the subject may remain on blinded study drug therapy (i.e., lefamulin or moxifloxacin) and receive a total of 10 days of treatment. If not, then the subject should be discontinued from study drug therapy and appropriate alternative therapy initiated promptly. Linezolid or matching placebo cannot be added as study drug therapy subsequent to Day 1.

Similarly, if local laboratory susceptibility results from the screening cultures reveal resistance to a fluoroquinolone or linezolid, the Investigator should assess the subject's clinical status at the time the microbiological results become available. If at this time the subject is demonstrating clear and progressive clinical improvement (e.g., improving

temperature, respiratory signs and symptoms, etc.), then the subject may remain on blinded study drug therapy. If not, then the subject should be discontinued from study drug therapy and appropriate alternative therapy initiated promptly.

### 5.5.3 Optional Switch to Oral Study Drug

Subjects will be permitted to switch from IV to oral study drug (i.e., lefamulin or moxifloxacin ± linezolid or matching placebo) if all of the following criteria are met:

- Have received at least 6 doses of IV therapy;
- Are hemodynamically stable, as defined by a normalizing (including return to pre-pneumonia baseline) heart rate, respiratory rate, systolic blood pressure and oxygen saturation;
- Have a normalizing temperature curve with a maximum temperature in the previous 24 hours of <math><38.0^{\circ}\text{C}</math> (<math><100.4^{\circ}\text{F}</math>);
- Have demonstrated improvement in at least 1 severity category (e.g., moderate to mild) in at least 2 of 4 cardinal symptoms of CABP
  - Dyspnea
  - Cough
  - Sputum production
  - Chest pain;
- Are able to swallow and absorb oral medications (i.e., normally functioning gastrointestinal tract).

### 5.5.4 Treatment Scenarios

The treatment scenarios for IV plus oral study drug are outlined in the tables below.

**Table 4. CABP (not caused by MRSA)**

Study Drug	Regimen	Duration/Additional Dosing Information
Lefamulin	150 mg IV q12h	Total duration of blinded study drug = 7 days of active treatment. Days 1-3 = IV; Days 4-7 = IV or PO If IV study drug administration is switched to oral, moxifloxacin placebo will be administered q24h through Day 7.
	600 mg PO q12h	
Moxifloxacin	400 mg IV q24h	Total duration of blinded study drug = 7 days of active treatment. Days 1-3 = IV; Days 4-7 = IV or PO Separate, alternating doses of IV placebo will be administered q24h such that IV study drug is administered q12h; If IV study drug administration is switched to oral, lefamulin placebo will be administered q12h through Day 7.
	400 mg PO q24h	

NOTE: Subjects with confirmed *Staphylococcus aureus* bacteremia should have study drug discontinued and appropriate alternate therapy should be initiated promptly. If possible, blood samples should be collected for microbiological culture prior to switching to alternate therapy.

**Table 5. CABP (MRSA suspected at Baseline and confirmed Post-baseline)**

Study Drug	Regimen	Duration/Additional Dosing Information
Lefamulin	150 mg IV q12h	Total duration of blinded study drug = 10 days of active treatment. Days 1-3 = IV; Days 4-10 = IV or PO If IV study drug administration is switched to oral, moxifloxacin placebo will be administered q24h until an etiologic pathogen is confirmed (see below). <b>Linezolid placebo q12h x 10 days (IV Days 1-3, IV or PO Days 4-10)</b>
	600 mg PO q12h	
Moxifloxacin	400 mg IV q24h	Total duration of blinded study drug = 10 days of active treatment. Days 1-3 = IV; Days 4-10 = IV or PO Separate, alternating doses of IV placebo will be administered q24h such that IV study drug is administered q12h; If IV study drug administration is switched to oral, lefamulin placebo will be administered q12h <b>Linezolid 600 mg q12h x 10 days (IV Days 1-3; IV or PO Days 4-10)</b>
	400 mg PO q24h	

NOTE: If results of baseline respiratory tract cultures **do not confirm** MRSA as an etiological pathogen, then linezolid or matching placebo will be discontinued and the subject will complete 7 days of study drug as shown in Table 4 above.

NOTE: If results of baseline respiratory tract cultures **confirm** MRSA as an etiological pathogen **during the IV treatment period**, then IV moxifloxacin (for subjects in the moxifloxacin treatment arm) or IV linezolid placebo (for subjects in the lefamulin treatment arm) should be discontinued. If results of baseline respiratory tract cultures **confirm** MRSA as an etiological pathogen **after a subject has switched to oral treatment**, then oral moxifloxacin (for subjects in the moxifloxacin treatment arm) or oral moxifloxacin placebo (for subjects in the lefamulin treatment arm) should be discontinued.

NOTE: Subjects who are confirmed to have *Staphylococcus aureus* bacteremia should have study drug discontinued and appropriate alternate therapy should be initiated promptly. If possible, blood samples should be collected for microbiological culture prior to switching to alternate therapy.

NOTE: If a subject is determined to have an infection caused by MRSA **plus** an organism known to be resistant to linezolid, the Sponsor's medical monitor should be contacted.

## 5.6 Timing of Dosing and Dose Administration

Blinded IV study drug (lefamulin, moxifloxacin, linezolid, and matching placebo) will be administered approximately every 12 hours. Blinded IV lefamulin and moxifloxacin study drug doses will be infused over approximately 60 minutes. Blinded IV linezolid and matching placebo will also be infused over approximately 60 minutes. In subjects with suspected or confirmed MRSA, IV lefamulin and IV linezolid placebo or IV moxifloxacin and IV linezolid may be administered concurrently if two separate IV lines are used. If only one IV line is used, IV lefamulin and moxifloxacin should always be infused prior to linezolid or matching placebo.

The first dose of study drug will be administered on Day 1, as soon as possible after the diagnosis of CABP and completion of all required Day 1 procedures as outlined in Table 3; subsequent study days are consecutive calendar days. Every attempt should be made to administer 2 doses of study drug on Study Day 1. On Day 1, if q12h dosing is not feasible, the 1<sup>st</sup> and 2<sup>nd</sup> 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. Despite this, there may still be instances where it is not possible to administer 2 doses on Day 1. Subjects who receive only a single dose of study drug on Day 1 will receive their final dose in the morning on either Day 8 (to complete a 7-day course) or on Day 11 (to complete a 10-day course).

As described above, subjects randomized to the moxifloxacin treatment arm will receive IV moxifloxacin alternating with IV placebo to maintain the blind. Subjects should always receive active IV moxifloxacin as the first dose on Day 1. Subjects who begin therapy in the evening on Study Day 1 and whose schedule does not permit a second dose on Day 1 should have their dosing schedule adjusted on Day 2, so that active IV moxifloxacin is given as part of the morning dosing on all subsequent days.

Example 1: If a subject begins therapy at 3pm on Day 1, a second dose may be given at 11pm on Day 1. The subject's dosing schedule may then be adjusted on Day 2 to a regular q12h schedule (e.g., 8am and 8pm dosing). In this scenario, subjects randomized to moxifloxacin will receive active IV moxifloxacin at 3pm and IV matching placebo at 11pm on Day 1.

Example 2: If a subject begins therapy at 5pm on Day 1, it is not possible to give a second dose on Day 1 within the 8 hour minimum between doses. Therefore, the subject will receive a single dose on Day 1, and then be adjusted on Day 2 to a regular q12h dosing schedule (e.g., 6am and 6pm dosing). In this scenario, subjects randomized to moxifloxacin will receive active IV moxifloxacin at 5pm on Day 1, active IV moxifloxacin again in the morning on Day 2 (e.g., 6am) and IV matching placebo in the evening on Day 2 (e.g., 6pm). Subjects who require a 7-day course of study drug and who receive only a single dose of study drug on Day 1 will receive their final dose in the morning on Day 8 (to complete a 7-day course). Subjects who require a 10-day course of study drug and who receive only a single dose of study drug on Day 1 will receive their final dose on Day 11 (to complete a 10-day course).

Oral study drug doses of lefamulin, linezolid or matching placebo are to be administered approximately q12h. Oral moxifloxacin (or matching placebo) should be administered approximately q24h. Oral moxifloxacin (or matching placebo for subjects in the lefamulin treatment arm) will always be given as part of the morning dosing.

Every effort should be made to maintain a q12h dosing schedule, about the same time each day. On days when this is not feasible, doses should be given within 4 hours of the scheduled dosing time (i.e., a minimum of 8 hours between doses).

Oral 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. Oral 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.

Infusions will be administered via an infusion set and IV catheter at a controlled rate over approximately 60 minutes.

Subjects are not required to be hospitalized for entry into the protocol; however, while subjects are hospitalized, all doses of study drug will be administered by hospital staff or study personnel. Subjects may receive IV dosing as an outpatient; however, all IV dosing should be administered by hospital staff or study personnel (i.e., subjects are not permitted to self-administer IV study drug). In the event the subject is discharged from the hospital during the oral study drug administration period, subjects may self-administer oral study drug at home (see Section 5.10).

## **5.7 Preparation of Infusions**

A Pharmacy Manual will be provided to investigative sites with additional details on preparation of study drug material.

### **Lefamulin**

For IV administration of lefamulin, the concentrate will be diluted into 250 mL of 10 mM citrate buffered 0.9% saline provided by the Sponsor (PVC-free, latex-free 250 mL infusion bag).

### **Moxifloxacin**

Moxifloxacin is provided as ready-to-use 250 mL latex-free flexibag as a sterile preservative-free, 0.8 % NaCl aqueous solution of moxifloxacin hydrochloride (containing 400 mg moxifloxacin). Moxifloxacin should only be mixed with water for injections, Sodium chloride 0.9%, Sodium chloride 1 molar, Glucose 5%/10%/40%, Xylitol 20%, Ringer's solution, Compound Sodium Lactate Solution (Hartmann's Solution, Ringer-Lactate Solution).

### **Linezolid**

Linezolid is provided as ready-to-use 300 ml flexible plastic (latex-free) infusion bag (containing 600 mg linezolid). If linezolid is to be given concomitantly with another drug IV, each drug should be given separately in accordance with the recommended dosage and route of administration for each product.

If the same IV line is used for sequential infusion, the line should be flushed before and after infusion of linezolid with an infusion solution that is compatible with linezolid and with any other drug(s) administered.

### **Placebo**

A 250 mL bag of 0.9% NaCl for injection will be provided by the sponsor to be utilized as placebo for lefamulin IV injection, moxifloxacin IV injection and linezolid IV injection.

## **5.8 Blinding**

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

All IV infusions will be prepared by an unblinded pharmacist. Blinding of IV lefamulin, moxifloxacin, linezolid and matching placebo will be achieved using a bag cover and IV tubing cover. IV study drug will be administered by an unblinded designee(s) at the study site. The Investigator, study personnel not performing study drug administrations, the Sponsor, and the subject will not know what study drug is being administered. Unblinded site personnel who administer study drug will not perform other study related procedures or evaluations. Only blinded study personnel will perform other study related procedures and evaluations. Intravenous infusions should be administered at a controlled rate (over approximately 60 minutes). For blinding purposes, in subjects receiving linezolid/matching placebo, if an infusion pump with a digital display is used, then the unblinded site personnel administering study drug must remain with the subject for the duration of the IV linezolid/matching placebo infusion. Oral formulations will be provided in blister packs and all oral study medication administration will utilize a “double-dummy” technique. Lefamulin or matching placebo tablets will be provided by the Sponsor. Moxifloxacin and linezolid will be over encapsulated; matching placebo capsules will also be provided by the Sponsor.

A member of the Sponsor’s drug metabolism and pharmacokinetics group (or his/her designee) will be unblinded to therapy assignment in order to perform PK assessments. Sponsor representatives will be unblinded in order to perform monitoring of study drug accountability on an ongoing basis throughout the study. A DMC will review summary safety data by masked treatment group throughout the study. 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 the clinical site staff will be unblinded to treatment status.

## 5.9 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 the primary analysis 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.

## 5.10 Adherence

While subjects are inpatients, hospital staff or study personnel will administer all doses of study drug. The date, start and stop time of each IV dose, the date and time of the first oral dose, the date of the last oral dose, and the number of tablets/capsules taken for the oral dose will be recorded in the eCRF. Subjects may receive IV dosing as an outpatient; however, all IV dosing should be administered by designated unblinded hospital staff or study personnel (i.e., subjects are not permitted to self-administer IV study drug).

If subjects are discharged from the hospital during the study drug administration period, subjects may self-administer oral study drug at home. An adequate supply of oral study drug will be dispensed for home use. Prior to discharge, subjects will be provided instructions regarding the dosing schedule.

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.

The site of care/site of IV study drug administration (e.g., emergency room, IV infusion center, subject's home, etc.) will be recorded on each study day.

## 5.11 Occupational Safety

Lefamulin, moxifloxacin, and linezolid being used in this study are not expected to pose a significant occupational safety risk to site staff 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.

In line with good handling of chemical products, precautions are to be taken to avoid eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure, any signs or symptoms should be treated appropriately and the Sponsor notified.

## 6 STUDY ASSESSMENTS AND PROCEDURES

The schedule of study procedures is presented in Table 3. 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 start of the first study drug infusion is counted as 0 h 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.

**NOTE:** All subjects **must have an in person 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.** Subjects who are receiving oral medication at home will be informed as to the timing of this visit by study personnel.

### 6.1 Medical/Surgical History and Physical Examination

A medical and surgical history will be taken at Screening. All medical history findings that have been present/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 3, 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.

### 6.2 PORT Risk Class Assessment

Study personnel will determine the subject's PORT Score (Table 6) and subsequent PORT Risk Class (Table 7) at Screening only.

**Table 6. 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 $\geq 30$ breaths/min	+20 if yes
Systolic blood pressure $< 90$ mmHg	+20 if yes
Temperature $< 35^{\circ}\text{C}$ ( $95^{\circ}\text{F}$ ) or $\geq 40^{\circ}\text{C}$ ( $104^{\circ}\text{F}$ )	+15 if yes
Pulse $\geq 125$ 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 $\geq 250$ mg/dL ( $\geq 14$ mmol/L)	+10 if yes
Hematocrit $< 30\%$	+10 if yes
Partial pressure of arterial $\text{O}_2$ $< 60$ mmHg (from ABG if medically indicated) or $\text{O}_2$ saturation $< 90\%$ (by pulse oximetry)	+10 if yes
Pleural effusion on radiograph	+10 if yes
<b>PORT SCORE</b>	<b>Sum of Applicable Numbers Above</b>

**Table 7. PORT Risk Class Determination**

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

### 6.3 Electrocardiograms

Triplicate 12-lead ECGs will be performed within a 5-minute interval at time points specified in Table 3. The subject should be stabilized in a supine position for 5 minutes before recording the ECG at Screening. 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.

## 6.4 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 3. Blood pressure and heart rate assessments will be performed according to standard practice at the clinical sites. Study personnel will record the highest daily temperature measured, the anatomical site where temperature was measured and the accompanying vital sign measurements in the eCRF. If Screening and Day 1 occur on the same day, vital signs should be obtained as part of the Screening evaluation (prior to administration of any study drug) and repeated as part of the Day 1 assessment (record the vital signs associated with the highest temperature post dosing). If EOT and the last day of study drug are the same day, vital signs do not need to be repeated, they may be recorded once on that day (i.e., as part of the EOT assessment).

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

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.

## 6.5 Chest X-Ray or CT Scan

Chest x-ray or CT scan will be performed at the time points specified in Table 3 and evaluated by the Investigator (or designee) to qualify a patient for enrollment; however, the imaging study must also be interpreted by a radiologist. The test date and the radiologist's reading/interpretation will be recorded in the eCRF.

## 6.6 Arterial Blood Gases

Study sites are not required to measure arterial blood gases (PaO<sub>2</sub>, PaCO<sub>2</sub>) or pH. However, if these data are available, they should be recorded in the eCRF

## 6.7 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.

### 6.7.1 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.

### 6.7.2 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 6.17.1.

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.

## 6.8 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 24 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, providing the organism is not resistant to fluoroquinolones and, in the case of MRSA, oxazolidinones.
- Agents that prolong the QT interval (see Appendix 5)

- Other systemic antibacterial agents that are potentially effective against pathogens associated with CABP except in the case of treatment failure or when medically necessary for treatment of a concomitant infection.

**NOTE:** The following antibacterial agents are permitted:

- Anti-tuberculosis drugs (exception: Rifampin)
  - Cinoxacin
  - Dapsone
  - Enoxacin
  - Fidaxomicin
  - Methenamine Mandelate
  - Metronidazole
  - Naladixic Acid
  - Nitrofurantoin
  - Norfloxacin
  - Oral Vancomycin
- Systemic corticosteroids at a dose  $\geq 20$  mg per day (prednisone equivalent)
  - Anti-epilepsy or seizure medication
  - Strong p-glycoprotein inhibitors and strong CYP3A inhibitors or inducers (see Appendix 4). [NOTE: The use of contraceptives containing progesterone is not permitted.]
  - Monoamine oxidase inhibitors, serotonergic agents or adrenergic agents (dobutamine, dopamine, epinephrine, norepinephrine, phenylpropanolamine, pseudoephedrine) (only for subjects in whom linezolid is added for MRSA).

## 6.9 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.

## 6.10 Assessment of Clinical Signs and Symptoms of CABP

Clinical signs and symptoms of CABP will be assessed at the time points specified in Table 3. 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 8 below. Subjects who are discharged to home will be contacted by phone to assess signs and symptoms of CABP daily while on study drug.

**NOTE: All subjects must have a face-to-face assessment of CABP signs and symptoms 96 ± 24 hours after the first dose of study drug. Subjects who are receiving outpatient study drug (IV or oral) during this timeframe MUST have a visit at the study site for this assessment.** Study personnel will inform outpatients as to the timing of this required study site visit.

**Table 8. 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 (other than adjunctive linezolid) for the treatment of CABP up through 120 hours after the first dose of study drug.

- 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 (other than adjunctive linezolid) 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.

## 6.11 Investigator's Assessment of Clinical Response (IACR)

The Investigator will assess Clinical Response at time points specified in Table 3.

### 6.11.1 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.

### 6.11.2 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.

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

## 6.12 Clinical Laboratory Tests (Safety)

Safety laboratory tests will be performed at the time points specified in Table 3 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. Collect blood and/or urine 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.

A full list of the clinical laboratory tests that will be performed and analyzed can be found in Appendix 1. A pregnancy test will be performed on all females who are not surgically sterile

or post-menopausal for at least 2 years. A negative urine pregnancy test is required prior to randomization and must be confirmed as soon as possible using a serum pregnancy test.

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.

### 6.13 Sample Collection for Pharmacokinetic Analysis

Blood samples for PK analysis of lefamulin and its main metabolite, BC-8041, in plasma following IV dosing will be collected in association with the morning dose of study drug on Study Day 3 as specified in Table 9 below.

**Table 9. Sample Collection Time Points for the Determination of Lefamulin Plasma Concentrations following IV Infusion**

Sample Time	Day 3 (morning dose)
Within 1 h prior to the morning infusion of study drug	X
Within 10 minutes following the end of infusion	X
2-4 h following the end of infusion	X
8-12 h following the end of infusion	X

In a subset of subjects, after switching from IV to oral treatment, blood samples for PK analysis will be collected relative to the first morning dose of **oral** drug as specified in Table 10 below. Blood sampling for PK analysis following oral dosing will be optional, and will be limited to subjects who agree via written consent, and for whom the additional blood collection is logistically feasible.

Outpatients who have consented for oral drug PK samples will return to the clinical site for PK blood collection relative to the first morning dose of oral drug. These subjects should be instructed to not take their first morning 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 10. Sample Collection Time Points for the Determination of Lefamulin Plasma Concentrations after Switch to Oral Treatment**

Sample Time	1 <sup>st</sup> oral morning dose after switch
Within 1 h prior to 1 <sup>st</sup> morning dose of oral study drug ( $C_{min}$ )	X
1-3 h after oral drug administration	X
4-8 h after oral drug administration	X

NOTE: For all subjects it is essential to record the exact date and actual time of each study drug administration for all IV doses as well as for the 1<sup>st</sup> oral dose. Additionally, for subjects who have blood collected for PK in association with the first morning oral dose, it is essential to record the exact date and actual time of all oral doses up to and including the PK sampling dose. Documentation of the exact blood sampling time points for population PK analysis is also essential (see Section 5.10 – Adherence).

### 6.13.1 Sample Collection Methodology

Blood samples for PK analysis will be collected from a vein in the opposite arm from the arm in which infusion is given into tubes containing K<sub>3</sub>EDTA, immediately chilled on crushed ice, and then centrifuged to separate plasma. Promptly following centrifugation, plasma specimens will be immediately deep frozen and stored at -20°C or cooler until transported. The total time period from blood withdrawal to storage of plasma at -20°C should not exceed 60 minutes.

Additional information and instructions for blood sample collection is provided in the investigative site study manual.

### 6.13.2 Assay Methodology

Plasma samples from subjects who received lefamulin will be analyzed for the concentration of lefamulin and its major metabolite, BC-8041, using a validated liquid chromatography-tandem mass spectrometry method at the bioanalytical laboratory. 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.

## 6.14 Microbiological Assessment

The following microbiological assessments will be performed at the time points described in Table 3. Details regarding storage of samples and shipment to the central laboratory can be found in the Laboratory Manual.

### 6.14.1 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 sputum sample at Screening, a specimen may be obtained 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.
- To be adequate, Gram's stains of sputum samples should have >25 polymorphonuclear (PMN) cells **AND** <10 squamous epithelial cells per LPF. A repeat sample may be taken

if these criteria are not met. 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 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.

#### 6.14.2 Bronchoalveolar Lavage Samples (BAL)

A BAL sample will be collected only if clinically indicated and sent to the local/regional laboratory for Gram's staining, culture and susceptibility testing. Repeat BAL samples will not be required. However, if the subject undergoes a repeat bronchoscopy as clinically warranted, 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.

#### 6.14.3 Pleural Fluid Samples

A pleural fluid sample will be collected only if clinically indicated and sent to the local/regional laboratory for Gram's staining, culture and susceptibility testing. Repeat pleural fluid samples will not be required. However, if the subject undergoes a repeat thoracentesis as clinically warranted, 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.

#### 6.14.4 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. If possible, subjects who have confirmed *S. aureus* bacteremia should have blood samples collected for microbiologic culture prior to switch to alternate appropriate therapy. Culture results from the local/regional laboratory will be recorded in the eCRF.

#### 6.14.5 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*.

#### 6.14.6 Urine Antigen Test

A urine sample will be taken at Screening and tested at the clinical site for *L. pneumophila* and *S. pneumoniae* antigen testing. Results will be recorded in the eCRF. Subjects who have urinary antigen test positive for *Legionella sp.* at Screening will have a portion of the sputum sample collected at Screening sent to the central laboratory for *L. pneumophila* testing as described above (Section 6.14.1). Clinical sites that are unable to perform urinary antigen testing will send urine to the central laboratory for testing.

#### 6.14.7 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.

#### 6.14.8 Nasopharyngeal Specimen

A nasopharyngeal specimen 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. Nasopharyngeal specimens must be frozen until shipment to the central laboratory.

### 6.15 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 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.

### 6.16 Food and Beverage Restrictions

Subjects must comply with the following restrictions during their participation in the study:

- Subjects who are suspected to have MRSA as a pathogen and receive adjunctive (active or placebo) linezolid therapy should not be on a high tyramine diet. Large quantities of

foods or beverages with high tyramine content should be avoided while taking linezolid. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses, fermented or air-dried meats, sauerkraut, soy sauce, tap beers and red wines. The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated. Further details regarding a high tyramine diet are provided in Appendix 6.

- Subjects should refrain from drinking alcohol throughout receipt of study drug.

In addition, as discussed in Section 5.6, doses of oral 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.

## 6.17 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.

### 6.17.1 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 visit. 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.

#### 6.17.2 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.

#### 6.17.3 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 visit. 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.

#### 6.17.4 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. 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 for subjects occurring from the time of informed consent through the LFU visit must be reported to Nabriva Therapeutics AG or their representative within 24 hours of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria). Reporting is done by completing the SAE form electronically in the Electronic Data Capture (EDC) system for the study. When the form is completed, PPD Pharmacovigilance (PVG) will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the system, site must fax the completed paper SAE report form to PPD PVG within 24 hours of awareness or call the PPD PVG SAE hotline. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available. PPD PVG personnel are available for SAE reporting on a 24 hour basis. Reports are reviewed during normal business hours. EDC and/or report forms should be completed in as much detail as possible but lack of complete information should not delay the reporting of the SAE.

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 5.9).

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.

### **Safety Contact Information**

Americas	Phone:	1-866-267-0754
	Fax:	1-866-676-6944
EU/APAC	Phone:	+44 1223 374 240
	Fax:	+44 1223 374 102

## **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 patient 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.

#### Lefamulin IV Formulation

The drug product for IV administration is supplied by the Sponsor in 15 mL sterile concentrate vials as a concentrate of 150 mg of lefamulin in 15 mL of 0.9% saline (Ph. Eur./USP/JP) for dilution into 250 mL 0.9% saline buffered with 10 mM citrate to pH 5. The citrate buffered saline bags (PVC-free, latex-free) are also supplied by the Sponsor. Each concentrate vial has a minimum extractable volume of 15 mL. A description of the unit formula of the concentrate vial is provided in the Lefamulin Investigator's Brochure.

#### Lefamulin Oral Formulation

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

#### Moxifloxacin IV Formulation

Moxifloxacin will be supplied by the Sponsor in ready-to-use 250 mL latex-free flexibags as a sterile, preservative free, 0.8% sodium chloride aqueous solution of moxifloxacin hydrochloride (containing 400 mg moxifloxacin) with pH ranging from 4.1 to 4.6. Moxifloxacin is presented as a yellow intravenous solution.

### Moxifloxacin Oral Formulation

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 Linezolid**

### Linezolid IV Formulation

Linezolid IV injection is provided by the Sponsor as a single-use, ready-to-use flexible plastic (latex-free) infusion bag containing 600 mg in 300 mL aqueous sodium citrate / dextrose solution.

### Linezolid Oral Formulation

The oral formulation of linezolid 600 mg is supplied by the Sponsor as an over-capsulated film-coated tablet.

Additional details regarding linezolid are found in the product monograph.

## **8.4 Placebo**

The following IV placebos will be supplied by the Sponsor and utilized to maintain the blind. Further details are found in the Study Pharmacy Manual.

<b>Drug Product</b>	<b>Route</b>	<b>Dosage Form/Strength</b>
Moxifloxacin placebo	IV	0.9% NaCl for Injection (Given as alternating doses with IV moxifloxacin)
Linezolid matching placebo	IV	0.9% NaCl for Injection

The following oral placebo tablets/capsules will be supplied by the Sponsor: lefamulin placebo tablet, moxifloxacin placebo capsule, linezolid placebo capsule.

Further details may be found in the Study Pharmacy Manual.

## **8.5 Packaging and Labeling**

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

## **8.6 Storage of Study Drugs**

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

Lefamulin concentrate vials and citrate buffered saline bags for dilution of lefamulin concentrate prior to administration will be provided in kits which will be stored between

+2°C and +8°C in a temperature monitored refrigerator. Intravenous bags containing moxifloxacin and linezolid must be stored at controlled room temperature (15 to 25°C).

Saline placebo must be stored at controlled room temperature (15 to 25°C).

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

- Lefamulin tablets and moxifloxacin placebo capsules
- Over-encapsulated moxifloxacin tablets and lefamulin placebo tablets
- Over-encapsulated linezolid tablets
- Linezolid placebo capsules

All blister packs containing oral study drug must be stored at controlled room temperature (15 to 25°C).

## 8.7 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 site 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.

All unused study drug provided by the Sponsor will be retained for purposes of drug accountability. In addition, empty and partially used vials of lefamulin will be retained by the pharmacy for the purposes of drug accountability.

An unblinded member of the Sponsor's clinical operations staff (or designee) will check the supplies storage, dispensing procedures and records at regular intervals throughout the study.

## 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 (SF-12) 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 ± linezolid).

## 9.2 Sample Size Determination

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

Retrospective analyses of clinical study data for patients with CABP of varying severity indicate the point estimates for an ECR responder at Days 3-5 range from 72%-81% (FDA, 2011). Thus, it is reasonable to assume that in a prospective study of subjects with CABP, the proportion of subjects who are responders for ECR at  $96 \pm 24$  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%-87% depending on the antibiotics under study and the severity of the CABP. The IACR success rate for subjects receiving moxifloxacin is 86% as reported in the prescribing information (AVELOX® [moxifloxacin] PI, 2013). Based on these data, an 85% IACR success rate in the CE-TOC Analysis Set was chosen for determination of the sample size. The success rate is expected to be about 5% lower in the mITT Analysis set. It is expected that <1% of subjects will be excluded from the mITT Analysis Set and thus, the sample size determination assumes the same number of subjects in the ITT and mITT Analysis Sets.

Utilizing an anticipated ECR responder rate of 79% in the ITT Analysis Set, and a one-sided alpha of 0.025, a sample size of 550 subjects (275 in each treatment group) provides >90% power to establish the NI of lefamulin to moxifloxacin for ECR using a NI margin of 12.5% 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 80% power for demonstration of NI for IACR at the TOC Visit using a 10% NI margin. If the sample size is

increased to 626 subjects, it will provide >95% power for demonstration of NI for ECR and 85% power for demonstration of NI for IACR at the TOC Visit.

The calculated power in each analysis set for the primary and secondary outcomes is provided in Table 11 below.

**Table 11. Power Calculations for the Primary and Secondary Efficacy Outcomes**

Analysis Set	Primary Outcome (FDA) (ECR 96 ± 24 h After the First Infusion of Study Drug)	Secondary Outcome (Investigator's Assessment of Clinical Response at TOC- Primary for EMA)	
	ITT	mITT	CE-TOC
N	550	550	440
Outcome Rate	79%	80%	85%
Evaluability Rate	NA	NA	80%
Power	93.8%	80.6%	80%

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 one 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 (other than adjunctive linezolid) 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 Set (ME-EOT, ME-TOC, and ME-LFU) will include all subjects who meet the criteria for inclusion both the microITT and CE-EOT (ME-EOT) Analysis Set, 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  $96 \pm 24$  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 6.10), 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 (other than adjunctive linezolid) 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 6.11). 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 6.11. ECR will be evaluated in the microITT Analysis Set. All-cause mortality will be evaluated in the ITT Analysis Set.

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 degrees Celsius (100.4 degrees Fahrenheit) measured orally, >38.5 degrees Celsius (101.3 degrees Fahrenheit) measured tympanically, or >39.0 degrees Celsius (102.2 degrees Fahrenheit) measured rectally]
- Hypothermia: [defined as body temperature <35.0 degrees Celsius (95.0 degrees Fahrenheit) measured orally, <35.5 degrees Celsius (95.9 degrees Fahrenheit) measured tympanically, or <36.0 degrees Celsius (96.8 degrees Fahrenheit) 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

### 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.

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 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 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 ( $\geq 4x$ ) or  $\geq 6$  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.

#### 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. Individual 24h AUC values from Day 1 obtained from the population PK model will be used for the PK/PD analysis focusing on efficacy. The PK based on population PK as well as a PK/PD analysis will be reported separately.

#### 9.4.5 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 (SF-12) 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  $96 \pm 24$  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. 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

$\Delta$  = 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 -12.5%, the null hypothesis will be rejected and the NI of lefamulin to moxifloxacin will be concluded.

Additional analyses of the primary efficacy analysis 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 an adjusted 95% CI (adjusted for the randomization stratification factors) and considering all subjects with missing data (i.e., Indeterminates) at  $96 \pm 24$  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 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 Sets. 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 adjusted (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 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 categorized as Responder, Non-responder and Indeterminate for ECR plus improvement in vital signs will also be presented for the ITT Analysis Set and a 2-sided unstratified 95% CI for the difference in responder rate will be calculated using a continuity-corrected Z-statistic.

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 failures (i.e., 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 success at LFU will be presented by baseline pathogen in the microITT, 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 Analysis Sets) 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 at LFU 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.

## 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<sup>®</sup>). 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 statistical analysis plan.

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. 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 Interim Analysis and Independent Interim Analysis Committee (IAC)**

In order to ensure that the point estimate of the ECR responder and IACR success rates used in the estimation of the sample size is valid for this study, an interim analysis for sample size re-estimation will be performed when ECR data at  $96 \pm 24$  h post first dose are available for approximately 60% of randomized subjects (330 subjects) (see Section 9.4.1). The draft FDA Guidance “Non-inferiority Clinical Trials” notes that such a sample size re-estimation if based on the blinded overall response rates is not only acceptable but is advisable. The interim analysis will involve a sample size re-estimation to either confirm the initial sample size estimate is adequate or increase the sample size (number of randomized subjects) to ensure the study has adequate power for determining whether lefamulin is non-inferior to moxifloxacin for the primary outcome measures for the FDA and EMA. The sample size re-estimation will be based on the blinded overall (not by treatment group) ECR responder rate and will be conducted by an independent, blinded statistician.

An Independent Interim Analysis Committee (IAC) will be provided the results of the interim analysis by the independent, blinded statistician and make a recommendation regarding any increase to the sample size. The IAC will consist of 3 members who will be selected by the Sponsor but will be independent from the Sponsor, 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 IAC members receive no financial incentives for their participation, but are reimbursed only for customary consultative and administrative support fees. A detailed IAC charter outlines the analyses to be completed, statistical rules, the potential increase to the sample size and the recommendations that can be made to the Sponsor.

The members of the IAC will not participate in the ongoing assessment of the important aspects of study conduct, including the assessment of safety data. This will be conducted by a separate Data Monitoring Committee (DMC) as outlined in Section 10.2.

## 9.10 Pharmacokinetic Analyses

Measured plasma concentrations of lefamulin and BC-8041 will be summarized descriptively by treatment group and 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 at least for Day 1 (PK/PD analysis). Additionally, plasma concentration time curves will be generated for day of IV/PO switch and PO treatment only. 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.

## 9.11 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 (SF-12) 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

# 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.

The members of the DMC will not participate in the interim analysis and re-assessment of the sample size for this trial. This will be conducted by a separate Interim Analysis Committee as outlined in Section 9.9.

## **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. The copy will be retained by the subject (or their legally authorized representative) and the original will be retained on file by the Investigator.

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/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, and information in the informed consent documentation of this study.

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 site 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 site 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

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

## **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

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

**Appendix 3 Closely Monitored CYP3A4 Substrates and P-Glycoprotein Substrates (excluding strong CYP3A inducers and inhibitors and excluding strong P-glycoprotein inhibitors)**

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

<b>Closely Monitored P-Glycoprotein Substrates</b>		
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

<b>Prohibited Strong P-Glycoprotein Inhibitors</b>		
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	

<b>Prohibited Strong CYP3A Inhibitors</b>	<b>Prohibited Strong CYP3A Inducers</b>
Indinavir	Carbamazepine
Nelfinavir	Phenobarbital
Ritonavir	Phenytoin
Itraconazole	Pioglitazone
Ketoconazole	Rifabutin
Nefazodone	Rifampin
Saquinavir	St. John's Wort
Suboxone	Troglitazone

## Appendix 5      Drugs That Prolong QT

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

Note: List not exhaustive.

## Appendix 6: High Tyramine Diet

Food	Allowed	Limit	Avoid
<b>Beverages</b>	Milk Decaf coffee and tea Carbonated drinks	Chocolate drinks Coffee, tea, and other caffeinated drinks White wine and clear spirits (limit two 8 oz. servings)	Alcoholic drinks, especially beer, ale, wine (Chianti, burgundy, sherry, vermouth, sauterne), and nonalcoholic beer and wine Acidophilus milk
<b>Bread</b>	Whole-wheat enriched white breads, rolls, crackers, and quick breads	None	Cheese breads Crackers Sourdough and fresh, homemade, yeast-leavened breads
<b>Cereals</b>	Cooked and dry cereals	None	None
<b>Cheese and Dairy Products</b>	Cottage cheese, farmer or pot cheese, cream cheese, ricotta cheese, and processed cheese	Buttermilk (limit to 4 oz.), sour cream, yogurt (national brands only-limit to 4 oz. per day)	All other cheese: aged cheese, Camembert, cheddar, Gouda, Gruyere, mozzarella, Parmesan, provolone, Roquefort, and Stilton
<b>Desserts</b>	Cakes and cookies Gelatins Ice cream and sherbets Pastries Puddings	Chocolate desserts	Cheese-filled desserts and cheesecake
<b>Eggs</b>	All	None	Quiche with cheese
<b>Fats</b>	All	None	None
<b>Fruits</b>	Fresh, frozen, or canned fruits and juices	None	Banana peel extract Overripe and spoiled fruits
<b>Meats, Fish, and Poultry</b>	All fresh or frozen meats, fish, or poultry	Aged meats and frankfurters Fresh sausage and pepperoni Canned sardines Canned meats	Caviar (more than 1 oz.) Chicken and beef liver Dried, salted, and pickled fish Fermented and dry sausages Salami

<b>Food</b>	<b>Allowed</b>	<b>Limit</b>	<b>Avoid</b>
		Fish roe (caviar) and paté (limit to 1 oz.)	Dried meats and meat extracts
<b>Potatoes and Substitutes</b>	White and sweet potatoes Grits, pasta, and rice	None	None
<b>Soups</b>	All cream and broth soups, except those on the "Avoid" list	None	Soups from Italian broad beans and fava beans Cheese soup Soup made with beer or wine Any soup cubes or meat extract Packet soups and packaged soups Miso soup
<b>Sweets</b>	Sugars, hard candies, honey, molasses, and syrups	Chocolate candies and chocolate syrups	Imported chocolate
<b>Vegetables</b>	All fresh, frozen, canned or dried vegetables and vegetable juices, except those on the "Avoid" list	None	Chinese pea pods Fava beans and Italian broad beans Sauerkraut Fermented soybean products miso and some tofu products)
<b>Miscellaneous</b>	Salt Nuts and peanut butter Spices, herbs, and flavorings	Soy sauce (limit to 1/4 cup) and teriyaki sauce (limit to 1/4 cup) Brewer's yeast	Marmite (vegetable extracts) Yeast concentrates Vitamin supplements with brewer's yeast Monosodium glutamate (MSG) All aged products