

# CLINICAL STUDY PROTOCOL

**IND 76,096**

**IND 62,772**

## **A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, COMPARATOR-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAVENOUS TO ORAL DELAFLOXACIN IN ADULT SUBJECTS WITH COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA**

**ML-3341-306**

**NCT02679573**

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### **CONFIDENTIAL**

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Melinta Therapeutics, Inc.

The study will be conducted according to the International Conference on Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice, FDA and EU clinical trial guidelines. (Sites in regions which have not yet implemented the E6(R2) addendum are subjecting themselves to it voluntarily.)

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### Protocol Approval


**Study Title** A Phase 3, Multicenter, Randomized, Double-Blind, Comparator-Controlled Study to Evaluate the Safety and Efficacy of Intravenous to Oral Delafloxacin in Adult Subjects with Community-Acquired Bacterial Pneumonia

**Protocol Number** ML-3341-306

**Protocol Date:** 04 December 2017

Protocol accepted and approved by:

**Sue Cammarata, MD**  
Chief Medical Officer  
Melinta Therapeutics, Inc.  
300 TriState International, Suite 272  
Lincolnshire, IL 60069, USA



Signature



Date



### **Study Acknowledgement**

I confirm that I have read protocol ML-3341-306, entitled “A Phase 3, Multicenter, Randomized, Double-Blind, Comparator-Controlled Study to Evaluate the Safety and Efficacy of Intravenous to Oral Delafloxacin in Adult Subjects with Community-Acquired Bacterial Pneumonia.” I understand the study protocol and will conduct the study according to the procedures therein and according to the principles of good clinical practice.

#### **Principal Investigator:**

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Signature

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Date

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Print Name

## Protocol Synopsis

|                     |  |
|---------------------|--|
| <b>Title:</b>       | A Phase 3, Multicenter, Randomized, Double-Blind, Comparator-Controlled Study to Evaluate the Safety and Efficacy of Intravenous to Oral Delafloxacin in Adult Subjects with Community-Acquired Bacterial Pneumonia  |
| <b>Sponsor:</b>     | Melinta Therapeutics, Inc.<br>300 George Street, Suite 301<br>New Haven, CT 06511  |
| <b>Study Phase:</b> | 3  |
| <b>Study Sites:</b> | Approximately 150 global study sites   |
| <b>Objectives:</b>  | <p><b><u>FOR FDA</u></b></p> <p><b><u>Primary Objective:</u></b></p> <ul style="list-style-type: none"><li>• To assess the clinical efficacy of intravenous (IV) to oral delafloxacin in adult subjects with community-acquired bacterial pneumonia (CABP) based on Early Clinical Response (ECR) defined as improvement at 96 hours (<math>\pm</math> 24 hours) after the first dose of study drug compared to IV to oral moxifloxacin in the Intent-to-Treat (ITT) population.</li></ul> <p><b><u>Secondary Objective(s):</u></b></p> <ul style="list-style-type: none"><li>• To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on Clinical Outcome at the Test of Cure (TOC) visit, 5 to 10 days after the last dose of study drug, compared to IV to oral comparator study drug arm in the CE and ITT populations.</li><li>• To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on ECR compared to IV to oral moxifloxacin in the microbiologic ITT (MITT) population.</li><li>• To assess the microbiologic response to delafloxacin in respiratory pathogens.</li><li>• To assess the safety and tolerability of IV to oral delafloxacin in adult subjects with CABP.</li><li>• To assess the all-cause mortality in adult subjects with CABP on Day 28.</li><li>• To assess delafloxacin pharmacokinetics (PK) in adult subjects with CABP.</li></ul> <p><b><u>FOR EMA</u></b></p> <p><b><u>Primary Objective:</u></b></p> <ul style="list-style-type: none"><li>• To assess the clinical efficacy of IV to oral delafloxacin in</li></ul> |

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|                            | <p>adult subjects with CABP at 5 to 10 days after the last dose of study drug (TOC) compared to IV to oral comparator study drug arm in the Modified ITT (ModITT) and Modified CE (ModCE) populations.</p> <p><b><u>Secondary Objective(s):</u></b></p> <ul style="list-style-type: none"> <li>• To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on ECR defined as improvement at 96 hours (<math>\pm</math> 24 hours) after the first dose of study drug compared to IV to oral moxifloxacin in the ModITT and ModCE populations.</li> <li>• To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at the TOC visit compared to IV to oral moxifloxacin in the Modified MITT (ModMITT) and Modified ME (ModME) populations.</li> <li>• To assess the microbiologic response to delafloxacin in respiratory pathogens in the ModMITT and ModME populations.</li> <li>• To assess the safety and tolerability of IV to oral delafloxacin in adult subjects with CABP in safety population.</li> <li>• To assess the all-cause mortality in adult subjects with CABP on Day 28 in ModITT.</li> <li>• To assess delafloxacin PK in adult subjects with CABP in PK population.</li> </ul> |
| <b>Study Population:</b>   | Adult male and female subjects 18 years of age or older with clinical and radiographic evidence of CABP and a Pneumonia Patient Outcomes Research Team (PORT) risk class of II, III, IV, or V (Pneumonia Severity Index [PSI] score > 50).  |
| <b>Inclusion Criteria:</b> | <ol style="list-style-type: none"> <li>1. Male and female subjects 18 years of age or older. <ul style="list-style-type: none"> <li>• Patients from a nursing home setting may be enrolled if they are normally ambulatory and are not on enteral feeding</li> </ul> </li> <li>2. Evidence of acute onset of CABP.<br/>Subjects must have at least 2 of the following clinical signs and symptoms (new or worsening): <ul style="list-style-type: none"> <li>• Cough</li> <li>• Production of purulent sputum consistent with a bacterial infection</li> <li>• Difficulty breathing (dyspnea)</li> <li>• Chest pain due to pneumonia</li> </ul> <p style="text-align: center;"><b>AND</b></p> </li> </ol>   |

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|  | <p>Subjects must also have at least 2 of the following findings:</p> <ul style="list-style-type: none"> <li>• Fever (oral temperature &gt; 38°C or equivalent) within 24 hours prior to randomization</li> <li>• Hypothermia (oral temperature &lt; 35°C or equivalent) within 24 hours prior to randomization</li> <li>• Tachycardia (&gt; 100 beats per minute)</li> <li>• Tachypnea (elevated respiratory rate &gt; 18 breaths per minute)</li> </ul> <p style="text-align: center;"><b>AND</b></p> <p>Subjects must also have at least 1 of the following findings:</p> <ul style="list-style-type: none"> <li>• Hypoxemia (oxygen saturation &lt; 90% or PaO<sub>2</sub> &lt; 60 mmHg) on room air or with subject's baseline (pre-CABP under study) supplemental oxygen flow rate</li> <li>• Clinical evidence of pulmonary consolidation and/or presence of pulmonary rales</li> <li>• An elevated white blood cell count (WBC) &gt; 10,000/mm<sup>3</sup> or 15% immature neutrophils (bands), regardless of total peripheral WBC count or leukopenia with WBC &lt; 4500/mm<sup>3</sup></li> </ul> <ol style="list-style-type: none"> <li>3. Presence of lobar, multilobar, or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia on a pulmonary imaging study (e.g., chest radiograph [CXR] [posteroanterior and lateral preferred; single view acceptable if conclusive] or computed tomography [CT] of thorax), as per local standard of care, within 48 hours before the first dose of study drug.</li> <li>4. PORT risk class of II, III, IV, or V (PSI score greater than 50). Subjects may be initially pre-screened based on meeting CURB-65 score of 2 to 4. PORT risk class II will be limited to no more than 25% of randomized subjects.</li> <li>5. In the opinion of the investigator, the subject must be a suitable candidate for possible IV to oral switch antibiotic therapy and must also be able to swallow large tablets/capsules intact without crushing.</li> <li>6. Females of childbearing potential (including females less than 2 years post-menopausal) must have a negative pregnancy test prior to enrollment. Sexually active women and men with partners of childbearing potential must agree to use an acceptable form of contraception, as determined by the investigator (e.g., abstinence, oral contraceptives, double barrier methods, hormonal injectable, transdermal, or implanted contraceptives, tubal ligation, or vasectomy) during participation in the study and through the Follow-up Visit (Day 28). Female partners of male subjects should also use an</li> </ol> |
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|                                   | <p>additional reliable method of contraception, such as spermicide with male or female condoms, cervical sponge, intrauterine device, cervical cap or diaphragm, or oral, implantable, transdermal, or injectable contraceptives during study and through the Follow-up Visit (Day 28).</p> <ol style="list-style-type: none"> <li>7. In the opinion of the investigator, the subject must be able and willing to comply with protocol requirements.</li> <li>8. A written, voluntarily signed informed consent must be obtained from the subject or, where allowed by local regulations, legally authorized representative, in accordance with local regulations, before the initiation of any study-related procedures. The subject or legally authorized representative must be able to read and/or understand the informed consent form as required by the legal jurisdiction and the institutional review board/independent ethics committee where the subject is treated.</li> </ol>  |
| <p><b>Exclusion Criteria:</b></p> | <ol style="list-style-type: none"> <li>1. Medical history of significant hypersensitivity or allergic reaction to antibiotics of the quinolone or oxazolidinone class or study drug excipients in the judgment of the investigator.</li> <li>2. Women who are pregnant or lactating.</li> <li>3. Any infection expected to require other systemic antibacterial agents in addition to study drug.</li> <li>4. Receipt of systemic antibiotic therapy in the 7 days before enrollment unless one or more of the following are documented: <ul style="list-style-type: none"> <li>• The subject received at least 48 hours of antibiotic therapy for CABP <b>and</b> the clinic notes document treatment failure (i.e., not by patient history or pulmonary imaging alone) with new or worsening symptoms while on pre-study therapy, or identification of a respiratory pathogen that is resistant to a pre-study antibiotic which would be susceptible to study drug (delafloxacin or moxifloxacin) in subjects with new or worsening signs and symptoms of CABP.</li> <li>• The subject received 1 dose of a single, potentially effective, short-acting antimicrobial drug or a short-acting antimicrobial drug regimen for treatment of the CABP under study within 24 hours of enrollment. (Note: 1 dose of a regimen is defined as the standard therapy for CABP at the study site.) Subjects who received prior antimicrobial drug under this criterion will be limited to no more than 25% of total randomized subjects.</li> </ul> </li> <li>5. Respiratory infection confirmed or suspected to be secondary to hospital-acquired or ventilator-associated pneumonia or that requires treatment in an intensive care setting (because they are</li> </ol> |

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|  | <p>hemodynamically unstable, and/or likely to need mechanical ventilation) at the time of informed consent.</p> <ol style="list-style-type: none"> <li>6. Intubated at the time of informed consent or clinical presentation with pneumonia that would require invasive mechanical ventilation.</li> <li>7. Current or suspected diagnosis of: <ul style="list-style-type: none"> <li>• Viral pneumonia, fungal pneumonia, including <i>Pneumocystis jiroveci</i> pneumonia</li> <li>• Aspiration pneumonia</li> <li>• Other noninfectious causes of pulmonary infiltrates (e.g., pulmonary embolism, hypersensitivity pneumonia, congestive heart failure)</li> <li>• Primary or metastatic lung cancer</li> <li>• Cystic fibrosis</li> <li>• Active or suspected tuberculosis</li> <li>• Empyema (not including sterile parapneumonic effusions)</li> </ul> </li> <li>8. Known anatomical or pathological bronchial obstruction, or a history of bronchiectasis, or documented Global initiative for chronic Obstructive Lung Disease (GOLD) Stage 4 chronic obstructive pulmonary disease, or a history of post obstructive pneumonia.</li> <li>9. Severely compromised immune system, e.g.: <ul style="list-style-type: none"> <li>• Known absolute neutropenia (absolute neutrophil count &lt; 500 cells/<math>\mu</math>L)</li> <li>• Known human immunodeficiency virus infection (HIV) with a CD4 count &lt; 350 cells/<math>\mu</math>L within the last 4 months</li> <li>• Cancer chemotherapy or radiation in the last 3 months</li> <li>• Hematological malignancy</li> <li>• Bone marrow transplantation</li> <li>• Chronic steroid use (&gt; 20 mg prednisone per day or equivalent) prior to enrollment</li> </ul> </li> <li>10. Known history of Child-Pugh Class B or C liver disease and/or presence or possible signs of significant hepatic disease, or alanine aminotransferase (ALT) &gt; 3<math>\times</math> the upper limit of normal (ULN).</li> <li>11. Severe renal disease, or creatinine clearance (CrCl) <math>\leq</math> 29 mL/min using Cockcroft-Gault formula, or need for hemodialysis or peritoneal dialysis.</li> <li>12. Uncorrected hypokalemia, or known uncorrected hypomagnesemia, at the time of enrollment. If treatment normalizes the serum potassium or magnesium, confirmed by retest during the screening period, the patient may then be enrolled.</li> </ol> |
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|                      | <ol style="list-style-type: none"> <li>13. Ongoing treatment for seizures or untreated history of seizures.</li> <li>14. History of peripheral neuropathy.</li> <li>15. History of tendon damage/disorders due to quinolone therapy.</li> <li>16. Known history of myasthenia gravis.</li> <li>17. History of post-antibiotic colitis within the last 3 months.</li> <li>18. Ventricular arrhythmia and /or ongoing proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia.</li> <li>19. History of prolonged QT syndrome, or mean QTcF (QT interval corrected with the Fridericia formula) greater than 450 msec for males and 470 msec for females on screening summary electrocardiogram (ECG).</li> <li>20. Concomitant use of drugs known to prolong the QT interval, including class IA (such as quinidine, procainamide, disopyramide) or Class III (such as amiodarone, sotalol, bretylium, ibutilide) antiarrhythmics.</li> <li>21. Concomitant use of monoamine oxidases (MAO) A or B inhibitor agents and adrenergic and serotonergic agents within 2 weeks of screening.</li> <li>22. Patients with known uncontrolled hypertension, pheochromocytoma, carcinoid thyrotoxicosis; and rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.</li> <li>23. Life expectancy of &lt; 3 months.</li> <li>24. Immediate life-threatening disease.</li> <li>25. Any underlying disease (e.g., severe cardiac disease, malignancy, or psychiatric disorder) that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study.</li> <li>26. Previous participation in any study of delafloxacin.</li> <li>27. Receipt of an investigational drug within 30 days of randomization.</li> <li>28. Subject should not participate in the study, in the opinion of the investigator.</li> </ol> <p>Laboratory tests with exclusionary results judged by the investigator as not compatible with the subject's clinical status may be repeated once for eligibility purposes.</p> |
| <b>Study Design:</b> | <p>This is a Phase 3, randomized, double-blind, comparator controlled, multicenter, global study. Subjects who consent to the study will have screening procedures performed. Subjects will be evaluated for baseline characteristics that include chest radiography within 48 hours before the first dose of study drug, and medical history, physical examination, clinical laboratory evaluation and blood cultures within 24 hours before the first dose</p>   |

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|  | <p>of study drug. Subjects may be initially pre-screened based on meeting CURB-65 score of 2 to 4, but will be eligible for enrollment only if classified as PORT Risk Class II, III, IV, or V. A pretreatment respiratory specimen will be collected for Gram stain and culture and susceptibility testing, if positive. Blood samples for procalcitonin and serology will be obtained at Day 1, as well as nasopharyngeal and oropharyngeal swabs for culture and/or polymerase chain reaction (PCR) testing, and urine samples for antigen testing. Subjects may be enrolled and may start study drug before results of the baseline pathogen identification are known.</p> <p>Subjects who meet the entry criteria will be randomly assigned in a 1:1 ratio to receive delafloxacin or moxifloxacin. Randomization will be stratified by PORT Class, medical history of chronic obstructive pulmonary disease (COPD)/asthma, and prior single-dose/regimen systemic antimicrobial use. Enrollment will be limited to no more than 25% PORT Class II and no more than 25% of subjects who received 1 dose of a single, potentially effective, short-acting antimicrobial drug or drug regimen for treatment of the CABP under study within 24 hours of enrollment.</p> <p>Subjects will be randomized to receive either IV delafloxacin 300 mg every 12 hours (BID) with an option to switch to oral delafloxacin 450 mg BID, or IV moxifloxacin 400 mg every 24 hours (QD) with an option to switch to oral moxifloxacin 400 mg QD for the remaining doses. Subjects randomized to receive IV moxifloxacin 400 mg QD will receive alternating IV placebo QD to preserve the double blind nature of the study, such that all randomized subjects will receive an IV infusion on a BID basis.</p> <p>The investigator may elect to switch subjects from moxifloxacin/moxifloxacin placebo to linezolid (600 mg IV BID)/linezolid placebo if methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) is confirmed (up to 10 days total moxifloxacin and linezolid duration of therapy). In this case of confirmed MRSA, subjects randomized to delafloxacin will continue to receive delafloxacin BID, discontinue moxifloxacin placebo QD, and start linezolid placebo BID.</p> <p>Subjects who meet suggested criteria can switch to oral treatment after a minimum of 6 IV delafloxacin/delafloxacin placebo doses, regardless of the treatment arm, to complete treatment. The total duration of treatment (IV and oral) is 5 days up to 10 days if clinically indicated (minimum 10 doses and up to 20 delafloxacin/delafloxacin placebo doses).</p> <p>Key visits will be ECR at 96 hours (<math>\pm</math> 24 hours) after the start of the first dose of study drug, End of Treatment (EOT), and TOC, 5-10 days after last dose. A Follow-up (FU) Visit or phone contact</p> |
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|  | will also be conducted at Day 28.  |
| <b>Efficacy Assessments:</b>                                       | Efficacy will be evaluated through assessment of clinical signs and symptoms of pneumonia and microbiological culture and susceptibility testing of bacterial isolates. Other measures of clinical efficacy as detailed in the protocol will be assessed at baseline and at multiple time points during the study.   |
| <b>Health-Related Quality-of-Life Assessments:</b>                 | Health-related quality of life will be assessed through administration of the SF-12v2 <sup>®</sup> Health Survey (acute) multipurpose short-form survey and quality-of-life questions.   |
| <b>Pharmacokinetic Assessments:</b>                                | Serial blood samples for PK analysis will be obtained at select investigative sites on Day 3 ( $\pm$ 1 day) of treatment within the 30 minutes before study drug administration and at 1.5 and 3 hours after the start of the infusion. All time points will have a $\pm$ 10-minute window. Subjects should have received a minimum of 3 consecutive doses of study drug prior to the start of PK blood collection. Subjects do not need to be fasted before dosing or during PK sample collections. |
| <b>Safety Assessments:</b>   | Safety will be assessed by monitoring of AEs (including serious AEs [SAEs]), vital sign measurements and body temperature, clinical laboratory tests, (including pregnancy testing), physical examination findings, electrocardiograms (ECGs) if clinically warranted, and concomitant medications.  |
| <b>Study Drug, Dosage, and Route of Administration:</b>            | Delafloxacin 300 mg will be administered as a 1-hour IV infusion every 12 hours ( $\pm$ 2 hours) for a minimum of 6 doses with an option to switch to delafloxacin 450 mg tablet administered orally every 12 hours ( $\pm$ 2 hours) for the remaining doses.  |
| <b>Comparator Study Drug, Dosage, and Route of Administration:</b> | Moxifloxacin 400 mg will be administered as a 1-hour IV infusion every 24 ( $\pm$ 2 hours) hours for a minimum of 3 active doses with an option to switch to moxifloxacin 400 mg (over-encapsulated tablet) administered orally every 24 hours ( $\pm$ 2 hours) for the remaining doses.   |
| <b>Comparator Study Drug, Dosage, or Route of Administration:</b>  | At local investigator discretion, subjects in the moxifloxacin arm with confirmed MRSA, in place of remaining moxifloxacin doses, can receive linezolid 600 mg administered as a 1-hour IV infusion every 12 hours ( $\pm$ 2 hours) for the remaining doses.   |
| <b>Placebo Study Drug , Dosage, and Route of Administration:</b>   | Each site will document a blinding plan prior to study start. All blinded IV dosing will be maintained with a 12-hour schedule. IV bags will be blinded.<br><br>Subjects in the moxifloxacin arm, when on IV therapy, will receive once-daily active therapy via alternating doses of IV moxifloxacin and IV placebo every 12 ( $\pm$ 2) hours.<br><br>Subjects in the delafloxacin arm, when on oral therapy, will receive oral placebo moxifloxacin QD or IV placebo linezolid BID                 |

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|                                    | <p>to maintain blinding.<br/>         Subjects in the moxifloxacin/linezolid arm, when on oral therapy or when meeting criteria for oral therapy, will receive placebo delafloxacin oral formulation to maintain blinding.</p>   |
| <p><b>Sample Size:</b></p>         | <p><b><u>FOR FDA PRIMARY ENDPOINT:</u></b> At least 860 adult male and female subjects (430 subjects per treatment group) will be randomized. Used on a normal approximation approach (Miettinen and Nurminen’s Likelihood Score Test), 860 subjects in ITT population will provide a 90% power to assess noninferiority of delafloxacin vs. moxifloxacin based on the following assumptions: (1) a rate of Early Clinical Response for the moxifloxacin therapy and delafloxacin of 77% and 74%, respectively; (2) 1-sided type I error (<math>\alpha</math>) of 0.025; (3) a noninferiority margin of 12.5%.</p> <p><b><u>FOR EMA PRIMARY ENDPOINT:</u></b> At least 860 adult male and female subjects (430 subjects per treatment group) will be randomized. Used on a normal approximation approach (Miettinen and Nurminen’s Likelihood Score Test), and assuming approximately 12% of patients will be in PORT Class II, and 80% of patients will be clinically evaluable, 755 subjects in the ModITT population and 604 subjects in the ModCE population will provide, respectively, a power of 91% and 83% to assess noninferiority of delafloxacin vs. moxifloxacin based on the following assumptions: (1) a rate of Clinical Outcome at the TOC visit for moxifloxacin and delafloxacin of 88% and 86%, respectively; (2) 1-sided type I error (<math>\alpha</math>) of 0.025; (3) a noninferiority margin of 10%.</p> |
| <p><b>Statistical Methods:</b></p> | <p>Continuous characteristics including baseline values will be summarized by treatment group using means, standard deviations, minimum, maximum, and median values. Categorical variables will be summarized by treatment group using frequency distributions. For the baseline characteristics, data will be presented overall as well. The differences in proportions for the responders from the 2 treatment groups will be tested for noninferiority using confidence intervals (CIs) generated by the Miettinen-Nurminen method, without stratification. Continuous secondary efficacy measures will be analyzed using an analysis of covariance (ANCOVA) model with treatment as the main effect and adjusted for PORT Class, medical history of COPD/asthma, and prior antimicrobial therapy, and the baseline measure as the covariate. All statistical analyses, unless otherwise specified, will be based on 2-sided 95% CIs around the difference in treatment outcomes.</p>   |
| <p><b>Efficacy Endpoints:</b></p>  | <p><b><u>FOR FDA</u></b><br/>         In order to control Type 1 error rate of 5%, a gate-keeping statistical method of a fixed sequence procedure will be used to</p>   |

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|  | <p>test for the secondary efficacy endpoints once the primary efficacy endpoint is claimed to be successful. If the noninferiority of delafloxacin is declared in the primary analysis, the secondary endpoints will be tested for superiority in a sequential (hierarchical) fashion using a fixed sequential procedure. The difference (delafloxacin – moxifloxacin) and CIs for all secondary endpoints will be reported. The primary and secondary efficacy endpoints are presented in the following text.</p> <p><b>Primary Efficacy Endpoint:</b> The ECR defined as improvement at 96 hours (<math>\pm</math> 24 hours) after first dose of study drug in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum, and difficulty breathing, and no worsening in the other symptoms in the ITT population.</p> <p><b>Secondary Efficacy Endpoint(s):</b></p> <ul style="list-style-type: none"> <li>• ECR with the addition of improvement in vital signs and no worsening of the 4 symptoms required as Response in the ITT population</li> <li>• Clinical Outcome at TOC (Clinically Evaluable [CE] and ITT populations)</li> <li>• Clinical outcome at EOT</li> <li>• ECR in the MITT population</li> <li>• Microbiologic response (ME and MITT)</li> <li>• All-cause mortality (ITT)</li> </ul> <p><b><u>FOR EMA</u></b></p> <p>All the primary and secondary endpoints will be analyzed for noninferiority with the possibility to switch to superiority.</p> <p><b>Primary Efficacy Endpoint:</b> The Clinical Outcome responder rate at 5 to 10 days after the last dose of study drug (TOC) defined as resolution or near resolution of the symptoms of CABP present at study entry, and no use of additional antimicrobial therapy for the current infection, and no new symptoms associated with the current CABP infection (success) in the ModITT and ModCE populations.</p> <p><b>Secondary Efficacy Endpoint(s):</b></p> <ul style="list-style-type: none"> <li>• ECR defined as improvement at 96 hours (<math>\pm</math> 24 hours) after first dose of study drug in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum and difficulty breathing and no worsening of any of the other symptoms in the ModITT and ModCE populations</li> <li>• ECR with the addition of improvement in vital signs and no worsening of the 4 symptoms required as Response in the</li> </ul> |
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|  | <p>ModITT and ModCE populations</p> <ul style="list-style-type: none"> <li>• Clinical Outcome at EOT (ModITT and ModCE)</li> <li>• Clinical Outcome at TOC in the ModMITT and ModME populations</li> <li>• Microbiologic response (ModMITT and ModME)</li> <li>• All-cause mortality (ModITT)</li> </ul>   |
| <b>Health-Related Quality-of-Life Endpoints:</b> | <p>Health-related quality-of-life and Health Economics Outcomes Research (HEOR) endpoints include:</p> <ul style="list-style-type: none"> <li>• Compare SF-12v2<sup>®</sup> from baseline to EOT to TOC</li> <li>• Compare subject's ability to work and earn income from baseline to EOT and TOC</li> <li>• Compare time to oral switch</li> <li>• Compare time to hospital discharge</li> </ul>  |
| <b>Pharmacokinetic Endpoints:</b>                | <p>The time course of delafloxacin plasma concentrations will be assessed.</p>   |
| <b>Safety Endpoints:</b>                         | <ul style="list-style-type: none"> <li>• AEs, including SAEs</li> <li>• Vital sign measurements and body temperature</li> <li>• Clinical laboratory test results</li> <li>• Physical examination findings</li> <li>• Concomitant medications</li> <li>• ECGs (obtained after baseline only if clinically indicated)</li> </ul>   |
| <b>Analysis Populations:</b>                     | <p>The following analysis populations will be analyzed:</p> <p><b>Safety:</b> All randomized subjects who receive at least 1 dose of study drug, analyzed according to the treatment they received.</p> <p><b>Intent-to-Treat (ITT):</b> All randomized subjects analyzed according to the treatment arm to which they were randomized.</p> <p><b>Modified ITT (ModITT):</b> All randomized subjects who received at least one dose of study medication, classified as PORT Class III-V, analyzed according to the treatment arm to which they were randomized.</p> <p><b>Microbiological ITT (MITT):</b> All subjects in the ITT population who had a baseline bacterial pathogen identified on culture of a respiratory or blood specimen, or a nonculture method of detection of bacterial pathogens (i.e., urinary antigen test, PCR, and serologic testing) that is known to cause CABP against which the study drug has antibacterial activity.</p> <p><b>Modified MITT (ModMITT):</b> All subjects in the MITT population classified as PORT Class III-V.</p> <p><b>Clinically Evaluable (CE):</b> All subjects in the ITT population</p> |

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|  | <p>who met the following criteria:</p> <ul style="list-style-type: none"> <li>• Evidence of acute onset of community-acquired bacterial pneumonia (CABP).</li> <li>• Received the correct study drug based on the randomization assignment.</li> <li>• Received 80% of the expected doses of study drug in the treatment period (e.g., at least 11 doses of delafloxacin for a 7-day treatment period).</li> <li>• Did not receive any concomitant, systemic antibacterial therapy except for lack of efficacy.</li> <li>• Had no protocol deviations that would affect assessment of efficacy.</li> </ul> <p><b>Modified CE (ModCE):</b> All subjects in the CE population classified as PORT Class III-V.</p> <p><b>Microbiologically Evaluable (ME):</b> All subjects in the MITT population who also met the criteria for the CE population.</p> <p><b>Modified ME (ModME):</b> All subjects in the ME population classified as PORT Class III-V.</p> <p><b>Pharmacokinetic (PK):</b> All subjects who receive at least 3 consecutive IV doses of study drug prior to the start of the blood sample collections on Day 3 (<math>\pm</math> 1 Day), and have at least one delafloxacin plasma concentration data available. The PK population will be used for PK analyses.</p>  |
| <p><b>Criteria for Evaluation - Definitions:</b></p> | <p><b>For Early Clinical Response:</b></p> <p><b>Responders:</b> Improvement at 96 hours (<math>\pm</math> 24 hours) after first dose of study drug in at least 2 of the following symptoms: pleuritic chest pain, frequency or severity of cough, amount and quality of productive sputum, and dyspnea (difficulty breathing), and no worsening of the other symptoms.</p> <p><b>Non-responders:</b> Improvement is not achieved at 96 hours (<math>\pm</math> 24 hours) after first dose of study drug in at least 2 of the following symptoms: pleuritic chest pain, frequency or severity of cough, amount and quality of productive sputum, and dyspnea (difficulty breathing); or there is use of additional non-study antimicrobial therapy for treatment of the current CABP infection due to lack of efficacy; or the subject died from the current CABP infection. Indeterminate/missing assessments will be mapped to Non-responders in the statistical analysis of the ITT population.</p> <p>Symptoms for the Early Clinical Response will be evaluated on a 4-point scale (absent, mild, moderate, severe) with improvement defined as at least a 1-point improvement (decrease) from baseline to the assessment at 96 hours (<math>\pm</math>24 hours) after the first dose of study drug (e.g., from severe to moderate, from moderate to mild,</p> |

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|                                       | <p>or from mild to absent).</p> <p><b>For Clinical Outcome at EOT and TOC:</b></p> <p><b>Success:</b> Resolution or near resolution of the symptoms of CABP present at study entry, and no use of additional antimicrobial therapy for the current infection, and no new symptoms associated with the current CABP infection.</p> <p><b>Failure:</b> Symptoms of CABP present at study entry have not resolved, or new symptoms of CABP have developed, or the subject died from pneumonia, or use of additional non-study antimicrobial therapy for treatment of the current CABP infection due to lack of efficacy. Subjects must receive at least 4 doses of study drug by the end of Day 3 to be called a Failure.</p> <p><b>Indeterminate/Missing:</b> A response cannot be determined because an efficacy assessment was not completed at the visit, or subject did not complete the planned course of study therapy for reasons other than lack of efficacy. Indeterminate/missing responses will be considered failures for purposes of the primary ITT/ModITT analyses and will be excluded from the CE and ME populations.</p> <p><b>For Microbiologic Response</b></p> <p><b>Eradication:</b> The respiratory and/or blood specimen at the TOC Visit shows all causative pathogen(s) at enrollment eradicated and no use of additional antimicrobial therapy for the current infection.</p> <p><b>Presumed Eradication:</b> No respiratory and/or blood specimen was available at TOC with a clinical assessment of Success.</p> <p><b>Persistence:</b> The respiratory and/or blood specimen at the TOC visit shows appearance of causative pathogen(s) present at enrollment.</p> <p><b>Presumed Persistence:</b> No respiratory and/or blood specimen was available for a case classified as clinical failure.</p> <p><b>Superinfection:</b> A culture taken during treatment shows appearance of a new pathogen causing respiratory infection associated with clinical failure.</p> <p><b>Colonization/Contamination:</b> A culture taken post-baseline through the TOC visit shows appearance of a new pathogen(s), with a clinical assessment of Success and no use of additional antimicrobial therapy for the current infection.</p> |
| <p><b>Microbiologic Measures:</b></p> | <p>The following pathogens are examples of primary pathogens that will be used to determine the microbiological responses in the study: the typical bacterial pathogens include but may not be limited to <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, <i>S. aureus</i>, <i>Klebsiella pneumoniae</i>, and <i>Moraxella catarrhalis</i>, and the atypical bacterial pathogens <i>Chlamydomphila pneumoniae</i>, <i>Mycoplasma pneumoniae</i>, and <i>Legionella pneumophila</i>. The causative pathogen will be identified by isolation from a baseline</p>  |

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|                                | culture specimen (either a respiratory specimen or blood), by urinary antigen, by serology, and/or by PCR. |
| <b>Date of Final Protocol:</b> | 04 December 2017   |

## List of Abbreviations

| Abbreviation        | Definition  |
|---------------------|---|
| ABG                 | Arterial blood gas  |
| ABSSI               | Acute bacterial skin and skin structure infection   |
| AE                  | Adverse event   |
| ALT                 | Alanine aminotransferase  |
| ANCOVA              | Analysis of covariance  |
| AUC <sub>0-24</sub> | Area under the concentration versus time curve from time 0 to 24 hours  |
| AUC <sub>0-t</sub>  | Area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration |
| AUC <sub>inf</sub>  | Area under the concentration versus time curve from time 0 extrapolated to infinity                           |
| BAL                 | Bronchoalveolar lavage  |
| BCRP                | Breast cancer-resistant protein   |
| BID                 | Bis in die (twice daily)  |
| BMI                 | Body mass index   |
| CABP                | Community-acquired bacterial pneumonia  |
| CAP                 | Community-acquired pneumonia  |
| CE                  | Clinically evaluable  |
| CFR                 | Code of Federal Regulations   |
| cfu                 | Colony-forming units  |
| CI                  | Confidence interval   |
| CLSI                | Clinical Laboratory Standards Institute   |
| C <sub>max</sub>    | Maximum concentration   |
| COPD                | Chronic obstructive pulmonary disease   |
| CrCl                | Creatinine clearance  |
| CRO                 | Contract research organization  |
| CT                  | Computerized tomography   |
| CURB-65             | Confusion, urea, respiratory rate, blood pressure, age 65 or older  |
| CV                  | Coefficient of variation  |
| CXR                 | Chest radiograph  |
| CYP                 | Cytochrome  |
| D <sub>5</sub> W    | Dextrose 5% in water  |
| DNA                 | Deoxyribonucleic acid   |
| ECG                 | Electrocardiogram   |
| ECR                 | Early clinical response   |



| <b>Abbreviation</b> | <b>Definition</b>   |
|---------------------|---|
| eCRF                | Electronic case report form   |
| EDTA                | Ethylenediaminetetraacetic acid   |
| EMA                 | European Medicines Agency   |
| EOT                 | End of Treatment  |
| ESRD                | Erythrocyte sedimentation rate  |
| EUCAST              | European Committee on Antimicrobial Susceptibility Testing                          |
| FDA                 | Food and Drug Administration  |
| GOLD                | Global initiative for chronic Obstructive Lung Disease                              |
| HIV                 | Human immunodeficiency virus  |
| HEOR                | Health economics outcomes research  |
| HRQoL               | Health-related quality of life  |
| ICF                 | Informed consent form   |
| ICH                 | International Conference on Harmonisation   |
| IEC                 | Independent ethics committee  |
| IRB                 | Institutional review board  |
| ITT                 | Intent-to-treat   |
| IV                  | Intravenous   |
| IXRS                | Interactive voice and web response system   |
| LOE                 | Lack of efficacy  |
| MAOI                | Monoamine oxidase inhibitor   |
| MCS                 | Mental component summary  |
| ME                  | Microbiologically evaluable   |
| MIC                 | Minimum inhibitory concentration  |
| MIC <sub>50</sub>   | Minimum inhibitory concentration required to inhibit the growth of 50% of organisms |
| MIC <sub>90</sub>   | Minimum inhibitory concentration required to inhibit the growth of 90% of organisms |
| MITT                | Microbiological intent-to-treat   |
| ModCE               | Modified clinically evaluable   |
| ModITT              | Modified intent-to-treat  |
| ModME               | Modified microbiologically evaluable  |
| ModMITT             | Modified microbiological intent-to-treat  |
| MRSA                | Methicillin-resistant <i>Staphylococcus aureus</i>                                  |
| MSSA                | Methicillin-susceptible <i>Staphylococcus aureus</i>                                |
| MTD                 | Maximum tolerated dose  |
| PA                  | Posteroanterior   |

| <b>Abbreviation</b> | <b>Definition</b>                                     |
|---------------------|---|
| PCR                 | Polymerase chain reaction                             |
| PD                  | Pharmacodynamics                                      |
| PD <sub>50</sub>    | Dose of vaccine required to protect 50%               |
| PK                  | Pharmacokinetic                                       |
| PORT                | Pneumonia Patient Outcomes Research Team              |
| P-gp                | P-glycoprotein  |
| PSB                 | Protected specimen brush                              |
| PSC                 | Physical component summary                            |
| PSI                 | Pneumonia severity index                              |
| QD                  | Quaque die (once daily)                               |
| QoL                 | Quality of life                                       |
| QSSP                | Quinolone-susceptible <i>Streptococcus pneumoniae</i> |
| RBC                 | Red blood cell  |
| SAE                 | Serious adverse event                                 |
| SAP                 | Statistical analysis plan                             |
| SCr                 | Serum creatinine                                      |
| SD                  | Standard deviation                                    |
| SF                  | Short form  |
| SmPC                | Summary of Product Characteristics                    |
| TEAE                | Treatment-emergent adverse event                      |
| TOC                 | Test of Cure  |
| ULN                 | Upper limit of normal                                 |

## 1. Introduction

Delafloxacin is an investigational broad spectrum fluoroquinolone antibiotic. Throughout the world, the incidence of antimicrobial resistance has increased for bacterial infections in hospital and community settings. Delafloxacin is active against an array of bacteria, including Gram-positive organisms (methicillin-susceptible *Staphylococcus aureus* [MSSA], methicillin-resistant *S. aureus* [MRSA], *Streptococcus pyogenes*, enterococci), Gram-negative organisms (*Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*), atypical organisms and anaerobes (*Bacteroides fragilis* and *Clostridium* spp.). Delafloxacin provides antimicrobial coverage of prevalent MRSA and methicillin-resistant coagulase-negative staphylococci. Delafloxacin is more active than levofloxacin against most Gram-positive pathogens, and notably has been shown to have a minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC<sub>90</sub>) of at least 32-fold more active than levofloxacin against MRSA isolates. Delafloxacin has good activity against Gram-negative organisms that are susceptible to levofloxacin, including species responsible for surgical site infections, community and nosocomial respiratory tract infections, urinary tract infections, bloodstream infections, skin and skin structure infections, and anaerobic infections.

Delafloxacin is being developed as a sterile 300-mg lyophilized formulation for intravenous (IV) administration as well as an oral 450-mg tablet formulation.

Delafloxacin has been generally well tolerated, with mild to moderate gastrointestinal adverse events (AEs) being most common. Refer to the Investigator's Brochure ([Melinta 2016](#)) for a more complete discussion of these studies, the safety and tolerability profile to date, and for detailed information presented in the section.

### 1.1 Microbiology

#### 1.1.1 Mechanism of Action Pharmacology

Fluoroquinolones act on DNA gyrase and topoisomerase IV, the 2 bacterial type-II topoisomerases involved in maintaining appropriate DNA supercoiling and chromosome segregation, respectively. Data suggest that delafloxacin is dual-targeting by inhibiting both DNA gyrase and topoisomerase IV in both Gram-positive and Gram-negative bacteria to a similar extent, unlike most other fluoroquinolones. Delafloxacin has slightly increased inhibitory activity against Gram-positive DNA gyrase and nearly equivalent activity against Gram-negative DNA gyrase compared to its activity against topoisomerase IV in enzymatic assays.

### 1.1.2 In Vitro Studies

#### **Comparative Antibacterial Activity**

In a recent survey of 2014 US and European isolates, delafloxacin's MIC<sub>50</sub> and MIC<sub>90</sub> were 0.008 µg/mL and 0.015 µg/mL, respectively for *Streptococcus pneumoniae*. Delafloxacin was 128 times more active than levofloxacin in this study. Against levofloxacin-resistant *S. pneumoniae*, delafloxacin had MIC<sub>50</sub> and MIC<sub>90</sub> of 0.12 µg/mL and 0.5 µg/mL, respectively. Delafloxacin is highly active against *Moraxella catarrhalis*; and delafloxacin has MIC<sub>50</sub> and MIC<sub>90</sub> of ≤ 0.001 µg/mL and 0.004 µg/mL, respectively, against *Haemophilus influenzae*. MIC<sub>90</sub>s of 0.12 µg/mL and 0.5 µg/mL have been reported for delafloxacin against MSSA and MRSA, respectively.

#### **Time-Kill Analysis**

The rate of bacterial killing was determined for *S. pneumoniae* 2486; delafloxacin was bactericidal at as low as 4 times the MIC against *S. pneumoniae* 2486. Delafloxacin demonstrated bactericidal activity against a quinolone-resistant isolate of *S. aureus* at 4 and 8 times the MIC, similar to ciprofloxacin and moxifloxacin.

### 1.1.3 In Vivo Studies

Delafloxacin was evaluated for *in vivo* activity against clinical isolates of *S. pneumoniae*, including strains bearing macrolide- and penicillin-resistance mechanisms, and *H. influenzae* in a series of rat lung-infection studies. Against quinolone-susceptible *S. pneumoniae* (QSSP) 6303, oral delafloxacin was 3-fold more efficacious than trovafloxacin and 10-fold more efficacious than levofloxacin. Against *S. pneumoniae* 5649, a multidrug-resistant strain, delafloxacin demonstrated a dose required to protect 50% (ED<sub>50</sub>) of < 5.0 mg/kg/day, whereas levofloxacin and trovafloxacin resulted in ED<sub>50</sub>s of 12.9 and 10.2 mg/kg/day, respectively. Against *H. influenzae*, all compounds were highly efficacious in this rat lung-infection model, with delafloxacin, levofloxacin, and trovafloxacin demonstrating ED<sub>50</sub>s of 2.1, 6.9, and 5.9 mg/kg/day, respectively.

#### **Evaluation of Delafloxacin in the Mouse Lung-Infection Model**

Delafloxacin was evaluated for its ability to both reduce lung bacterial burdens and protect mice from lethal infection by *S. pneumoniae* D39. The untreated control group had an increase in lung bacterial burden of 1.63 log<sub>10</sub> colony-forming units (cfu) from the start of therapy to the end of the study at 40 hours, whereas delafloxacin dosed at 50, 25, 10, 5, and 1 mg/kg/dose was efficacious, demonstrating reductions in lung bacterial burdens of 4.70, 4.76 (limit of detection), 3.33, 3.11, and 0.12 log<sub>10</sub> cfu, respectively, compared to untreated controls at the start of therapy. Seven-day survival was also monitored; for delafloxacin

dosed at 50, 25, 10, 5, and 1 mg/kg/dose, 100, 60, 0, 0, and 0% survival was observed, respectively.

## 1.2 Pharmacokinetics, Safety, and Efficacy of Delafloxacin

### 1.2.1 Pharmacokinetics, Safety, and Tolerability of IV and Oral Delafloxacin

Single doses ranging from 50 to 1200 mg were assessed for safety, tolerability, and pharmacokinetics (PK) in 5 Phase 1 studies with 4 different IV formulations. In the RX-3341-108 study ([Rib-X 2011](#)), a maximum tolerated dose (MTD) for single IV administration was 900 mg given over 1 hour. Delafloxacin was given to subjects in daily doses ranging from 50 to 1600 mg as either single dose or multiple oral doses for up to 5 consecutive days in 8 Phase 1 studies. The aggregate data suggested a dose relationship for the frequency and severity of diarrhea. The primary dose-limiting AEs were gastrointestinal in nature.

Delafloxacin is rapidly absorbed orally, reaching peak concentrations in 0.8 hour. The absolute bioavailability of delafloxacin after oral administration is 58.8%. After IV and oral administration, delafloxacin has a mean half-life of 10.9 and 14.1 hours, respectively. There is minimal accumulation ( $Rac = 1.09$ ) of delafloxacin upon twice-daily IV (300 mg) or twice-daily oral (450 mg) administration. Delafloxacin is renally excreted primarily as the parent compound, metabolism by glucuronidation represents  $\leq 20\%$  of an administered dose. The 450-mg commercial tablet and 300-mg IV Captisol® lyophilized formulations are bioequivalent with regard to total exposure (AUC). The administration of delafloxacin with food delays absorption and reduces maximum concentration ( $C_{max}$ ), but does not alter total absorption (AUC). Plasma protein binding is approximately 84%.

Delafloxacin does not inhibit cytochrome P450 enzymes or transporters to any significant degree. In vitro, delafloxacin has been shown to be a mild inducer of CYP3A4. Hence, clinically significant drug-drug interactions due to inhibition of CYP-mediated biotransformation of co-administered drugs by delafloxacin are unlikely in humans.

Delafloxacin is a substrate of breast cancer-resistant protein (BCRP) and a possible substrate of P-glycoprotein (P-gp). Delafloxacin is well absorbed ( $BA = 58.8\%$ ), so any interaction with inhibitors of BCRP or P-gp at the enterocyte is not expected to increase peak exposures beyond those exposures already shown to be tolerable at doses higher than a 450-mg oral dose.

The pharmacokinetics of delafloxacin has been studied in subjects with mild, moderate, and severe renal disease, including subjects with end-stage renal disease (ESRD) on dialysis. Patients with severe renal impairment should receive delafloxacin 200 mg IV BID. Dosing recommendations are not available for patients with ESRD with or without dialysis.

Two dedicated QT studies have been conducted with the oral and IV formulations with no evidence of delafloxacin impact on QT interval. The effect of delafloxacin on cardiac repolarization using the QTcF interval showed no signal. A phototoxicity study has been performed with oral delafloxacin with no evidence of phototoxic effects.

### 1.2.2 Phase 2 Study for Community-Acquired Pneumonia: Study M01-344

Study M01-344, a double-blind, randomized, parallel-group, Phase 2 study, was conducted to determine the safety and efficacy of a 7-day oral course of delafloxacin in subjects with community-acquired pneumonia (Abbott 2003). Three hundred and nine subjects were randomized to 1 of 3 dosing groups: 100, 200, or 400 mg delafloxacin once daily for 7 days. The Test of Cure (TOC) was on study Day 16-21. The primary endpoint of this trial was the investigators' assessment of clinical response rate at the TOC time point in the Clinically Evaluable (CE) group. All doses tested showed similar excellent response rates in all of the analysis groups. All pathogens in this study had a delafloxacin MIC  $\leq$  0.015  $\mu$ g/mL.

**Table 1-1 Proportion of Patients Achieving Endpoints (Study M01-344)**

| Outcome at Test of Cure<br>Proportion of Patients With: | Delafloxacin<br>100 mg | Delafloxacin<br>200 mg | Delafloxacin<br>400 mg |
|---|------------------------|------------------------|------------------------|
| Investigator Assessment of Clinical Response (CE)       | 90% (83/92)            | 95% (79/83)            | 93% (90/97)            |
| Investigator Assessment of Clinical Response (ITT)      | 80% (83/104)           | 87% (79/91)            | 87% (90/104)           |
| Microbiologic response (ME)                             | 90% (54/60)            | 96% (48/50)            | 94% (47/50)            |

Among subjects who were microbiologically evaluable, at TOC, 91% of pathogens in the 100-mg group, 95% of pathogens in the 200-mg group, and 97% of pathogens in the 400-mg group were eradicated. Eradication rates are shown in the table below. All pathogens had a delafloxacin MIC of 0.015  $\mu$ g/mL or lower.

**Table 1-2 Target Pathogen Eradication Rates at the TOC Visit (Study M01-344)**

| Pathogen                        | Delafloxacin<br>100 mg QD | Delafloxacin<br>200 mg QD | Delafloxacin<br>400 mg QD |
|---------------------------------|---------------------------|---------------------------|---------------------------|
| <i>Streptococcus pneumoniae</i> | 14/16 (88%)               | 12/14 (86%)               | 16/16 (100%)              |
| <i>Moraxella catarrhalis</i>    | 6/6 (100%)                | 4/4 (100%)                | 0/0                       |
| <i>Haemophilus influenzae</i>   | 14/15 (93%)               | 13/13 (100%)              | 15/16 (94%)               |
| <i>H. parainfluenzae</i>        | 18/20 (90%)               | 14/15 (93%)               | 15/15 (100%)              |
| <i>Staphylococcus aureus</i>    | 8/8 (100%)                | 7/7 (100%)                | 2/2 (100%)                |
| <i>Legionella pneumophila</i>   | 0/0                       | 1/1 (100%)                | 1/1 (100%)                |
| <i>Mycoplasma pneumoniae</i>    | 7/8 (88%)                 | 6/6 (100%)                | 8/8 (100%)                |
| <i>Chlamydophila pneumoniae</i> | 3/4 (75%)                 | 3/3 (100%)                | 1/2 (50%)                 |

The common AEs in this trial were nausea, diarrhea, and headache. No subjects died during the study.

### 1.2.3 Treatment of Acute Bacterial Skin and Skin Structure Infections: Study RX-3341-302

Study RX-3341-302 was a randomized, double-blind, Phase 3 study comparing the efficacy of IV delafloxacin 300 mg to IV vancomycin (15 mg/kg) with aztreonam (1-2 g) for the treatment of ABSSSI including infections caused by MRSA (Rib-X 2015). All patients were randomized and dosed twice daily for 5-14 days in a double-blind fashion. The study enrolled 660 patients at 34 sites in the United States and Europe.

The primary outcome measure for the FDA was a comparison of the proportion of patients who achieved an objective response at 48 to 72 hours following initiation of treatment, based on at least 20% decrease in lesion size. The trial protocol also had secondary and exploratory endpoints including a secondary outcome measure of noninferiority of the proportion of patients with a clinical response at the follow-up visit based on the investigator's assessment of cure (total resolution of all signs and symptoms); "improved" outcome was grouped with failure in the primary analysis.

Delafloxacin achieved its primary FDA efficacy endpoint of noninferiority for objective response at 48 to 72 hours after initiation of therapy as determined by at least 20% decrease in lesion size in the Intent-to-Treat (ITT) population. Delafloxacin also met the primary endpoint for the European Medicine Agency (EMA), the investigator assessment of cure defined as complete resolution of signs and symptoms at the Follow-up visit. Delafloxacin's outcome was sustained with clinical outcomes comparable to vancomycin at the Late Follow-up visit. Delafloxacin also demonstrated clinical activity against MRSA with comparable eradication rates to vancomycin in patients with MRSA infections in the microbiologically evaluable (ME) population.

**Table 1-3 Proportion of Patients Achieving Endpoints (Study RX-3341-302)**

| Key Endpoints   | Delafloxacin    | Vancomycin (+aztreonam) | Difference (V-D) (95% CI) |
|---|-----------------|-------------------------|---------------------------|
| <b>Objective response at 48-72 hours (ITT) (FDA primary)</b>  | 259/331 (78.2%) | 266/329 (80.9%)         | 2.60 (-3.57, 8.78)        |
| <b>Investigator assessment of cure at Follow-up visit (ITT) (EMA Primary)</b>   | 172/331 (52.0%) | 166/329 (50.5%)         | -1.51 (-9.11, 6.11)       |
| <b>Investigator assessment of cure at Late Follow up (ITT) (Secondary)</b>  | 233/331 (70.4%) | 219/329 (66.6%)         | -3.83 (-10.89, 3.27)      |
| <b>Microbiological response of eradicated at the Follow-up Visit in patients (ME) with MRSA infections (ME) (Secondary)</b> | 58/58 (100%)    | 65/66 (98.5%)           | -1.52 (-8.14, 4.79)       |

Abbreviations: BID = 2 times a day; BMI = body mass index; CI = confidence interval; EMA = European Medicine Agency; FDA = US Food and Drug Administration; ITT = intent-to-treat population; IV = intravenous; ME = microbiologically evaluable population; MRSA = methicillin-resistant *Staphylococcus aureus*; V-D = difference between vancomycin and delafloxacin.

Safety data from this trial shows that delafloxacin is well tolerated and has a favorable safety profile compared to vancomycin. The most common AEs related to delafloxacin treatment, reported in at least 2% of patients, were nausea, vomiting, diarrhea, and headache, which are events typically reported for other antibiotics. There were more reports of diarrhea for delafloxacin compared to vancomycin (8.3% vs 3.1%, respectively). None of these events caused patients to stop delafloxacin treatment, and there were no reports of *Clostridium difficile* diarrhea. There were fewer reports of pruritus (0.9% vs 4.6% respectively) and infusion site extravasation (8.6% vs 13.5% respectively) for delafloxacin compared to vancomycin.

### 1.3 Dose Selection of Delafloxacin for This Study

Delafloxacin will be administered as 300 mg IV every 12 hours with an option to switch to 450 mg orally every 12 hours in this study. This dosage regimen is currently being used in the ABSSSI program and was selected based on MIC<sub>90</sub> data against MRSA, Phase 1 PK data, PK/pharmacodynamics (PD) data in murine models of thigh infection, clinical PK/PD modeling, and previous clinical experience. The IV dose of 300 mg, as demonstrated by animal PK/PD and human clinical trial ABSSSI data, is expected to provide an adequate free-drug AUC<sub>0-24</sub>: MIC ratio to cover primary pathogens implicated in ABSSSI.

In treatment of patients with community-acquired bacterial pneumonia (CABP), the same dosage regimen is planned based on MIC<sub>90</sub> data against *S. pneumoniae* and other respiratory pathogens, *in vivo* models of infection, Phase 1 PK data, PK/PD data in murine models of thigh infection as well as preliminary PK/PD data in murine model of lung infection, and previous clinical experience. The following information, provided in more detail in the Investigator's Brochure ([Melinta 2016](#)), is supportive of this dosing regimen:

- Based on MIC<sub>50</sub> and MIC<sub>90</sub>, delafloxacin was several-fold more potent than levofloxacin against evaluated Gram-positive organisms. In a recent study against bacterial isolates associated with respiratory infections collected from the US, delafloxacin was determined to be the most active agent against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, with MIC<sub>90</sub> values that were 64 to 128 times lower than levofloxacin against *S. pneumoniae* and 8 times lower against *H. influenzae* and *M. catarrhalis*. In that same study, delafloxacin was found to be active against subsets of *S. pneumoniae* that were penicillin-resistant, ceftriaxone non-susceptible, and levofloxacin-resistant.
- Delafloxacin is active in animal models against key respiratory pathogens, primarily *S. pneumoniae*, including data from a mouse protection model, mouse lung infection model, rat lung infection model, rat neutropenic thigh model, mouse neutropenic thigh



model, and mouse neutropenic lung model. In these models, delafloxacin is multi-fold more active than other quinolones tested.

- In human subjects, delafloxacin 300 mg IV BID delivers a total  $AUC_{0-24}$  of approximately  $50 \mu\text{g}\cdot\text{h}/\text{mL}$ . Based on preliminary PK/PD assessments of the free  $AUC_{0-24}/\text{MIC}$  ratio which predicts response in animal models, the 300 mg IV/450 mg oral twice-daily dose is predicted to provide adequate coverage for most MIC values observed in CABP.
- Delafloxacin has shown evidence of efficacy in a completed phase 2 community-acquired pneumonia (CAP) trial (M01-344 [Abbott 2003]). In addition, a phase 2 trial in acute bacterial exacerbation of chronic bronchitis (M01-298 [Abbott 2003]) and 2 phase 2 ABSSSI trials (studies RX-3341-201 [Rib-X 2009] and RX-3341-202 [Rib-X 2014]) provide evidence of efficacy of delafloxacin in these indications.
- Delafloxacin has shown evidence of efficacy in a completed Phase 3 ABSSSI trial (RX-3341-302 [Melinta 2015]) using the intended 300 mg IV BID dose.
- Delafloxacin has been well tolerated at the 300 mg IV BID dose used in 2 phase 2 ABSSSI trials (studies RX-3341-201 [Rib-X 2009] and -202 [Rib-X 2014]) and 1 Phase 3 ABSSSI trial (study RX-3341-302).

#### 1.4 Comparator Selections for This Study

Moxifloxacin is the comparator for this study. Moxifloxacin 400 mg IV or oral once daily is the recommended dosage in treatment of patients with CABP. As a fluoroquinolone used in CABP, moxifloxacin has the antibacterial coverage to treat the range of Gram-positive and Gram-negative pathogens seen in CABP such as *S. pneumoniae* and *H. influenzae* as well as atypical pathogens. In vitro, moxifloxacin is active against both extracellular and intracellular community acquired-MRSA (CA-MRSA) if the MIC is low (does not exceed 0.125 mg/L) (Lemaire 2011).

At the investigator's discretion in patients with confirmed infection due to MRSA, linezolid may be substituted for moxifloxacin. Linezolid is approved for treatment of CABP at dose of 600 mg BID. Linezolid is one of the currently recommended treatments for patients with confirmed MRSA infections (Mandell 2007).

The treatment duration in this study is 5 to 10 days. Treatment guidelines recommend at least 5 days of therapy, noting that in clinical trials, 5 days appears to be the minimal overall duration of therapy documented to be effective in usual forms of CAP (Mandell 2007).

## 2. Study Objectives

### 2.1 Primary Objective

The primary objective is:

| FDA  | EMA   |
|--|---|
| To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on Early Clinical Response (ECR) defined as improvement at 96 hours ( $\pm$ 24 hours) after the first dose of study drug compared to IV to oral moxifloxacin in the ITT population. | To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at 5 to 10 days after the last dose of study drug (TOC) compared to IV to oral comparator study drug arm in the Modified ITT (ModITT) and Modified CE (ModCE) populations. |

### 2.2 Secondary Objective(s)

The secondary objectives are:

| FDA   | EMA  |
|---|--|
| To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on clinical outcome at the TOC visit, 5 to 10 days after the last dose of study drug compared to IV to oral comparator study drug arm in the CE and ITT populations. | To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on ECR defined as improvement at 96 hours ( $\pm$ 24 hours) after the first dose of study drug compared to IV to oral moxifloxacin in the ModITT and ModCE populations. |
| To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on ECR compared to IV to oral moxifloxacin in the Microbiological ITT (MITT) population  | To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at the TOC visit compared to IV to oral moxifloxacin in the Modified MITT (ModMITT) and Modified ME (ModME) populations.  |
| To assess the microbiologic response to delafloxacin in respiratory pathogens.  | To assess the microbiologic response to delafloxacin in respiratory pathogens in the ModMITT and ModME populations.  |

| <b>FDA</b>   | <b>EMA</b>   |
|--|--|
| To assess the safety and tolerability of IV to oral delafloxacin in adult subjects with CABP | To assess the safety and tolerability of IV to oral delafloxacin in adult subjects with CABP in safety population. |
| To assess the all-cause mortality in adult subjects with CABP on Day 28                      | To assess the all-cause mortality in adult subjects with CABP on Day 28 in ModITT.                                 |
| To assess delafloxacin PK in adult subjects with CABP  | To assess delafloxacin PK in adult subjects with CABP in PK population.  |

### 3. Investigational Plan

#### 3.1 Study Design

This is a Phase 3, randomized, double-blind, comparator-controlled, multicenter, global study. Subjects who consent to the study will have screening procedures performed. Subjects will be evaluated for baseline characteristics that include chest radiography within 48 hours before the first dose of study drug, and medical history, physical examination, clinical laboratory evaluation, and blood cultures within 24 hours before the first dose of study drug. Subjects may be initially pre-screened based on meeting CURB-65 score of 2 to 4, but will be eligible for enrollment only if classified as Pneumonia Patient Outcomes Research Team (PORT) Risk Class II, III, IV or V. A pretreatment respiratory specimen will be collected for Gram stain and culture, and susceptibility testing, if positive. Blood samples for procalcitonin and serology will be obtained at Day 1, as well as nasopharyngeal and oropharyngeal swabs for culture and/or polymerase chain reaction (PCR) testing, and urine samples for antigen testing. Subjects may be enrolled and may start study drug before results of the baseline pathogen identification are known.

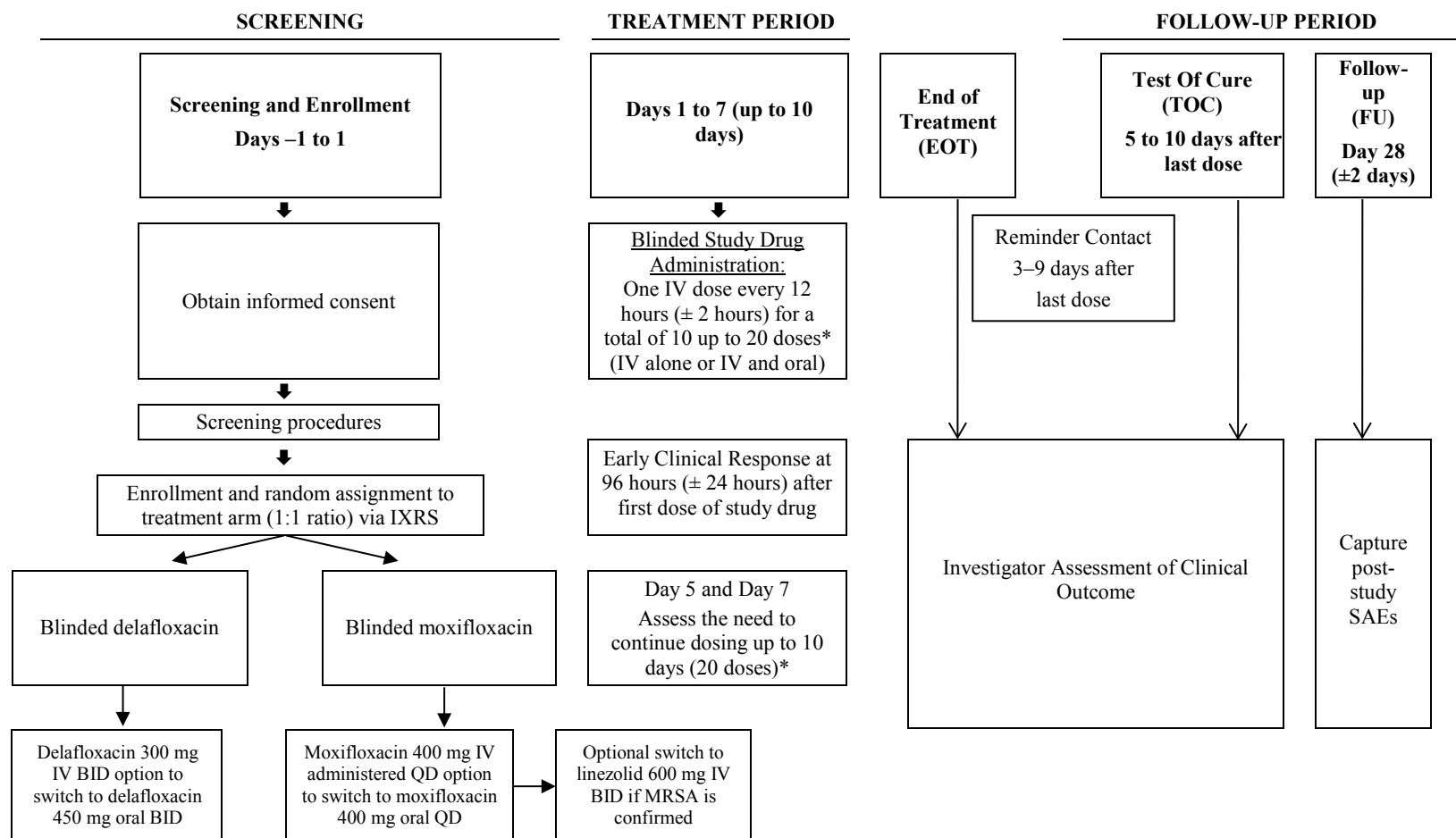
Subjects who meet the entry criteria will be randomly assigned in a 1:1 ratio to receive delafloxacin or moxifloxacin. Randomization will be stratified by PORT Class, medical history of COPD/asthma, and prior single-dose/regimen systemic antimicrobial use. Enrollment will be limited to no more than 25% PORT Class II and no more than 25% of subjects who received 1 dose of a single, potentially effective, short-acting antimicrobial drug or drug regimen for treatment of the CABP under study within 24 hours of enrollment. Subjects will be randomized to receive either IV delafloxacin 300 mg every 12 hours (BID) with an option to switch to oral delafloxacin 450 mg BID, or IV moxifloxacin 400 mg every 24 hours (QD) with an option to switch to oral moxifloxacin 400 mg QD for the remaining doses. Subjects randomized to receive IV moxifloxacin 400 mg QD will receive alternating IV placebo QD to preserve the double blind nature of the study, such that all randomized subjects will receive an IV infusion on a BID basis.

The investigator may elect to switch subjects from moxifloxacin/moxifloxacin placebo to linezolid (600 mg IV BID)/ linezolid placebo if MRSA is confirmed (up to 10 days total moxifloxacin and linezolid duration of therapy). In this case of confirmed MRSA, subjects randomized to delafloxacin will continue to receive delafloxacin BID, discontinue moxifloxacin placebo QD, and start linezolid placebo BID.

Subjects who meet suggested criteria can switch to oral treatment after a minimum of 6 IV delafloxacin/delafloxacin placebo doses, regardless of the treatment arm, to complete treatment. The total duration of treatment (IV and oral) is 5 days up to 10 days if clinically

indicated (minimum 10 doses and up to 20 delafloxacin/delafloxacin placebo doses). Key visits will be ECR at 96 hours ( $\pm$  24 hours) after the start of the first dose of study drug, End of Treatment (EOT), and Test of Cure (TOC), 5-10 days after last dose. A Follow-up (FU) Visit or phone contact will also be conducted at Day 28. A schematic of the study design is provided in [Figure 3-1](#).

**Figure 3-1 Schematic of Study Design**



\* delafloxacin/delafloxacin placebo doses

Abbreviations: EOT = End of Treatment; TOC = Test of Cure; FU = Follow-up; IXRS = interactive voice and web response system; IV = intravenous; BID = every 12 hours; QD = every 24 hours; MRSA = methicillin-resistance *Staphylococcus aureus*

## 3.2 Selection of Study Sample

At least 860 male and female subjects, 18 years of age or older, with clinical and radiographic evidence of CABP and a pneumonia Patient Outcomes Research Team (PORT) Risk Class of II, III, IV, or V (pneumonia severity index score [PSI] greater than 50) will be enrolled in the study.

### 3.2.1 Inclusion Criteria

To be enrolled in this study, subjects must meet the following criteria at Screening:

1. Male and female subjects 18 years of age or older.
  - Patients from a nursing home setting may be enrolled if they are normally ambulatory and are not on enteral feeding.
2. Evidence of acute onset of CABP.

Subjects must have at least 2 of the following clinical signs and symptoms (new or worsening):

- Cough
- Production of purulent sputum consistent with a bacterial infection
- Difficulty breathing (dyspnea)
- Chest pain due to pneumonia

#### AND

Subjects must also have at least 2 of the following findings:

- Fever (oral temperature  $> 38^{\circ}\text{C}$  or equivalent ) within 24 hours prior to randomization
- Hypothermia (oral temperature  $< 35^{\circ}\text{C}$  or equivalent) within 24 hours prior to randomization
- Tachycardia ( $> 100$  beats per minute)
- Tachypnea (elevated respiratory rate  $> 18$  breaths per minute)

#### AND

Subjects must also have at least 1 of the following findings:

- Hypoxemia (oxygen saturation  $< 90\%$  or  $\text{PaO}_2 < 60$  mmHg) on room air or with subject's baseline (pre-CABP under study) supplemental oxygen flow rate

- Clinical evidence of pulmonary consolidation and/or presence of pulmonary rales
  - An elevated white blood cell count (WBC)  $> 10,000/\text{mm}^3$  or 15% immature neutrophils (bands), regardless of total peripheral WBC count or leukopenia with  $\text{WBC} < 4500/\text{mm}^3$
3. Presence of lobar, multilobar, or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia on a pulmonary imaging study (e.g., chest radiograph [CXR] [posteroanterior and lateral preferred; single view acceptable if conclusive] or computed tomography [CT] of thorax), as per local standard of care, within 48 hours before the first dose of study drug.
  4. PORT Risk Class of II, III, IV, or V (PSI Score greater than 50) ([Fine 1997](#)) ([Appendix 7.2](#)). Subjects may be initially pre-screened based on meeting CURB-65 Score ([Appendix 7.3](#)) of 2 to 4. PORT Risk Class II will be limited to no more than 25% of randomized subjects.
  5. In the opinion of the investigator, the subject must be a suitable candidate for possible IV to oral switch antibiotic therapy and must also be able to swallow large tablets/capsules intact without crushing.
  6. Females of childbearing potential (including females less than 2 years post-menopausal) must have a negative pregnancy test prior to enrollment. Sexually active women and men with partners of childbearing potential must agree to use an acceptable form of contraception, as determined by the investigator (e.g., abstinence, oral contraceptives, double-barrier methods, hormonal injectable, transdermal, or implanted contraceptives, tubal ligation, or vasectomy) during participation in the study through the Follow-up Visit (Day 28). Female partners of male subjects should also use an additional reliable method of contraception, such as spermicide with male or female condoms, cervical sponge, intrauterine device, cervical cap or diaphragm, or oral, implantable, transdermal, or injectable contraceptives during study and through the Follow-up Visit (Day 28).
  7. In the opinion of the investigator, the subject must be able and willing to comply with protocol requirements.
  8. A written, voluntarily signed informed consent must be obtained from the subject or, where allowed by local regulations, legally authorized representative, in accordance with local regulations, before the initiation of any study-related procedures. The subject or legally authorized representative must be able to read and/or understand the informed consent form as required by the legal jurisdiction and the institutional review board/independent ethics committee where the subject is treated.



### 3.2.2 Exclusion Criteria

Potential subjects who meet any of the following criteria at Screening will be excluded from the study:

1. Medical history of significant hypersensitivity or allergic reaction to antibiotics of the quinolone or oxazolidinone class or study drug excipients in the judgment of the investigator.
2. Women who are pregnant or lactating.
3. Any infection expected to require other systemic antibacterial agents in addition to study drug.
4. Receipt of systemic antibiotic therapy in the 7 days before enrollment unless one or more of the following are documented:
  - The subject received at least 48 hours of antibiotic therapy for CABP **and** the clinic notes document treatment failure (i.e., not by patient history or pulmonary imaging alone) with new or worsening symptoms while on pre-study therapy, or identification of a respiratory pathogen that is resistant to a pre-study antibiotic which would be susceptible to study drug (delafloxacin or moxifloxacin) in subjects with new or worsening signs and symptoms of CABP.
  - The subject received 1 dose of a single, potentially effective, short-acting antimicrobial drug or a short-acting antimicrobial drug regimen for treatment of the CABP under study within 24 hours of enrollment. (Note: 1 dose of a regimen is defined as the standard therapy for CABP at the study site.) Subjects who received prior antimicrobial drug under this criterion will be limited to no more than 25% of total randomized subjects.
5. Respiratory infection confirmed or suspected to be secondary to hospital-acquired or ventilator-associated pneumonia or that requires treatment in an intensive care setting (because they are hemodynamically unstable, and/or likely to need mechanical ventilation) at the time of informed consent.
6. Intubated at the time of informed consent or clinical presentation with pneumonia that would require invasive mechanical ventilation.
7. Current or suspected diagnosis of:
  - Viral pneumonia, fungal pneumonia, including *Pneumocystis jiroveci* pneumonia
  - Aspiration pneumonia

- Other noninfectious causes of pulmonary infiltrates (e.g., pulmonary embolism, hypersensitivity pneumonia, congestive heart failure)
  - Primary or metastatic lung cancer
  - Cystic fibrosis
  - Active or suspected tuberculosis
  - Empyema (not including sterile parapneumonic effusions)
8. Known anatomical or pathological bronchial obstruction, or a history of bronchiectasis, or documented Global initiative for chronic Obstructive Lung Disease (GOLD) Stage 4 chronic obstructive pulmonary disease, or a history of post obstructive pneumonia.
9. Severely compromised immune system, e.g.:
- Known absolute neutropenia (absolute neutrophil count < 500 cells/ $\mu$ L)
  - Known human immunodeficiency virus infection (HIV) with a CD4 count < 350 cells/ $\mu$ L within the last 4 months
  - Cancer chemotherapy or radiation in the last 3 months
  - Hematological malignancy
  - Bone marrow transplantation
  - Chronic steroid use (> 20 mg prednisone per day or equivalent) prior to enrollment
10. Known history of Child-Pugh Class B or C liver disease ([Appendix 7.4](#)) and/or presence or possible signs of significant hepatic disease, or alanine aminotransferase (ALT) > 3 $\times$  the upper limit of normal (ULN).
11. Severe renal disease, or creatinine clearance (CrCl)  $\leq$  29 mL/min using Cockcroft-Gault formula ([Appendix 7.5](#)), or need for hemodialysis or peritoneal dialysis.
12. Uncorrected hypokalemia, or known uncorrected hypomagnesemia, at the time of enrollment. If treatment normalizes the serum potassium or magnesium, confirmed by retest during the screening period, the patient may then be enrolled.
13. Ongoing treatment for seizures or untreated history of seizures.
14. History of peripheral neuropathy.
15. History of tendon damage/disorders due to quinolone therapy.

16. Known history of myasthenia gravis.
17. History of post-antibiotic colitis within the last 3 months.
18. Ventricular arrhythmia and/or ongoing proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia.
19. History of prolonged QT syndrome, or mean QTcF (QT interval corrected with the Fridericia formula) greater than 450 msec for males and 470 msec for females on screening summary electrocardiogram (ECG).
20. Concomitant use of drugs known to prolong the QT interval, including class IA (such as quinidine, procainamide, disopyramide) or Class III (such as amiodarone, sotalol, bretylium, ibutilide) antiarrhythmics.
21. Concomitant use of monoamine oxidases (MAO) A or B inhibitor agents and adrenergic and serotonergic agents within 2 weeks of screening.
22. Patients with known uncontrolled hypertension, pheochromocytoma, carcinoid thyrotoxicosis; and rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
23. Life expectancy of < 3 months.
24. Immediate life-threatening disease.
25. Any underlying disease (e.g., severe cardiac disease, malignancy, or psychiatric disorder) that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study.
26. Previous participation in any study of delafloxacin.
27. Receipt of an investigational drug within 30 days of randomization.
28. Subject should not participate in the study, in the opinion of the investigator.

Laboratory tests with exclusionary results judged by the investigator as not compatible with the subject's clinical status may be repeated once for eligibility purposes.

### **3.3 Patient Withdrawal from Treatment or Study**

#### **3.3.1 Reasons for Withdrawal**

Subjects will be informed that they are free to withdraw from the study drug treatment or study at any time and for any reason. Any subject may withdraw his or her consent at any time.

Subjects will be discontinued from the study drug if any of the following occur:

- The subject requires other systemic antibacterial agents to treat the primary CABP in addition to study drug.
- In the opinion of the investigator, it is not in the best interest of the subject to continue.
- There is a change in compliance with an inclusion or exclusion criterion that is clinically relevant and affects subject safety.
- The subject takes a concomitant medication that might affect patient safety or study assessments/objectives.
- The subject experiences (a) serious or intolerable AE(s).
- The subject has ALT or AST of  $> 5 \times$  ULN or total bilirubin  $> 3 \times$  ULN.

Upon occurrence of a serious or intolerable AE, the principal investigator will confer with the Medical Monitor. If a subject is discontinued from the study drug because of an AE, the event will be followed to a satisfactory resolution or until the principal investigator deems the event to be chronic or the subject to be stable.

### **3.3.2 Handling of Withdrawals**

Subjects who discontinue study drug and receive a non-study antibiotic for CABP will have EOT visit procedures performed with clinical assessment, but will not return for further on-site visits. Additional specimens for microbiological cultures and CXR should be collected before initiation of any rescue therapy and/or if the subject is a clinical failure, if possible. These subjects should be contacted by phone for the FU visit.

Subjects who discontinue study drug and do not receive additional non-study antibiotic for CABP will have EOT visit procedures performed and should return to the site for the TOC and FU visits.

Should a subject's study participation be discontinued after receiving study drug, efforts must be made to perform all required EOT procedures with corresponding data recorded in the electronic case report form (eCRF). Subjects who prematurely discontinue study treatment should be encouraged to return to the study site for these safety evaluations.

Every attempt will be made to contact all subjects who received at least 1 dose of study drug to collect all-cause mortality data on Day 28 (FU visit). Subjects who withdraw consent will not be contacted after withdrawal.

Subjects who fail to return for a study visit will be contacted directly by the study site personnel. A minimum of 2 documented phone calls should be made over the course of at

least 2 weeks. If the study site personnel receive no response, and if the local government or regulatory agency permits, they should send a certified letter requesting that the subject contact the study site regarding his or her status in the study. If a subject does not return for the final visit, and the appropriate permission has been obtained, the investigator may obtain a verbal report on the subject's health status from the subject's local health care provider.

It is vital to obtain follow-up data on any subject withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified safety and follow-up procedures.

### **3.3.3 Replacements**

Subjects who prematurely discontinue after randomization will not be replaced.

## **3.4 Study Procedures**

Before performing any study procedures, all potential subjects will sign an informed consent form (ICF). Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator or subinvestigator must address all questions raised by the subject. The investigator or subinvestigator will also sign the ICF.

### **3.4.1 Study Visits**

Subjects enrolled in the study will have signs and symptoms consistent with CABP which are moderate to severe enough to warrant initial IV therapy. Subjects may be treated as hospitalized inpatients or outpatients in accordance with local treatment guidelines for moderate to severe CABP, provided that all study-drug infusions are administered by study-site personnel or hospital staff who have been trained on protocol specifics and the Sponsor-approved study drug-blinding plan. Hospital discharge will be at the discretion of the investigator. The date of hospital discharge will be recorded in the eCRF.

#### **3.4.1.1 Screening**

Screening procedures will occur in the 24 hours prior to the first dose of study drug. The following will be performed after the subject or, where allowed by local regulations, their legally authorized representative provides informed consent:

- Access interactive voice and web response system (IXRS) to register screening.
- Record demographic data and medical, pulmonary, surgical, alcohol, and smoking history.
- Record medications taken once or more in the 14 days before Screening, including nonprescription medications and dietary supplements. In addition, prior antibacterial treatments up to 30 days before first dose of study drug will be collected.

- Assess clinical signs/symptoms of CABP.
- Record vital signs, body temperature and pulse oximetry (or arterial blood gases [ABGs], if clinically warranted).
- Perform 12-lead electrocardiogram (ECG).
- Conduct complete physical examination with height and weight.
- Obtain posteroanterior (PA) and lateral CXR. A CT scan of the thorax is an acceptable alternative, if available per local standard of care. The CXR or CT scan obtained per local standard of care will not be repeated if obtained within 48 hours before the first dose of study drug.
- Perform urine or serum pregnancy test for women of childbearing potential.
- Obtain blood samples for hematology, serum chemistry, and coagulation profile and urine sample for urinalysis. The results of any of these tests obtained within 24 hours before enrollment may be used for screening purposes and to verify entry criteria by the local laboratory; however, blood and urine samples must be obtained at Screening (prior to the first dose of study drug) and sent to the central laboratory for analysis to serve as baseline values.
- Obtain 2 sets of blood specimens for culture from 2 separate venipuncture sites.
- Collect deep cough sputum specimen for Gram stain and culture, if possible. Additionally, other respiratory sources are acceptable if available (refer to [Section 3.4.3.2.1](#)).
- Obtain blood samples for hepatitis serology.
- Determine PORT Risk Class and CURB-65 score.
- Collect and assess any AEs that have occurred since informed consent was signed.
- Verify entry criteria.
- Access the IXRS to randomize (or screen fail) subject.

#### **3.4.1.2 Day 1**

Treatment may begin immediately after enrolling the subject via the IXRS. Subjects must begin study drug within 24 hours after the start of Screening procedures. If the first dose is administered the same day as Screening, then assessments that are required on Day 1, but already completed for Screening, will not be repeated unless otherwise specified below (assessments should be recorded in the Screening eCRF and NOT duplicated in the Day 1

eCRF). If not already performed on that day as part of the Screening visit, the following procedures will be performed on Day 1:

- Record concomitant medications (update from screening, if applicable).
- Assess clinical signs/symptoms of CABP.
- Administer SF-12v2<sup>®</sup> Health Survey and Quality-of-Life (QoL) assessment questions.
- Record vital signs, body temperature, and pulse oximetry around the time of the first dose.
- Collect deep cough sputum specimen for Gram stain and culture prior to dosing if not collected or determined to be not acceptable at Screening (if possible). Additionally, other respiratory sources are acceptable if available (refer to [Section 3.4.3.2.1](#)).
- Obtain urine sample for urinary antigen tests for *S. pneumoniae* and *Legionella pneumophila*.
- Obtain blood samples for procalcitonin and *Chlamydia pneumoniae*, *M. pneumoniae* and *L. pneumophila* serology.
- Obtain nasopharyngeal and oropharyngeal swabs prior to dosing.
- Administer first dose of study drug.
- Assess for AEs.
- Administer second dose of study drug after 12 hours ( $\pm 2$  hours). If the first dose is started late in the day because of screening and eligibility verifications, a 1-time adjustment is allowed for a more customary dosing schedule that is within  $\pm 4$  hours of the normally scheduled second dose. The every-12-hour ( $\pm 2$  hour) dosing schedule is set after the first dose (or dose adjustment).

#### **3.4.1.3 Daily While on IV Therapy**

The following procedures will be performed daily only while on IV therapy:

- Assess clinical signs and symptoms of CABP.
- Record vital signs, body temperature, and pulse oximetry at a consistent time each day.
- Collect blood cultures if clinically indicated.
- Record concomitant medications.
- Assess for AEs.
- Administer study drug every 12 hours ( $\pm 2$  hours).

- For sites participating in PK assessments, blood samples for PK analysis will be obtained on Day 3 ( $\pm 1$  day) of treatment within the 30 minutes before study drug administration, and at 1.5 and 3 hours after the start of the infusion. All time points have a  $\pm 10$ -minute window. Subjects should have received a minimum of 3 consecutive doses of study drug prior to the start of PK blood sample collections. Subjects do not need to be fasted before dosing or during PK sample collections. Refer to [Section 3.4.3.6 Pharmacokinetic Blood Sample Collections](#) for details.

#### **3.4.1.4 Early Clinical Response at 96 Hours ( $\pm 24$ hours)**

The following procedures will be performed on all subjects at 96 hours ( $\pm 24$  hours) after the start of the first dose of study drug. Procedures already completed as specified in [Sections 3.4.1.3](#) or [3.4.1.5](#) do not need to be repeated unless they occurred prior to the ECR 96 hour ( $\pm 24$  hours) window. If not already performed within the ECR window, the following procedures will be performed:

- Assess clinical signs and symptoms of CABP.
- Perform targeted physical examination.
- Record vital signs, body temperature, and pulse oximetry.
- Collect blood cultures if clinically indicated.
- Obtain hematology and serum chemistry.
- Record concomitant medications.
- Assess for AEs.
- Administer study drug every 12 hours ( $\pm 2$  hours).
- Subjects who continue oral treatment as an outpatient will be dispensed/administered study drug and instructed to return to the clinic on Day 5 (if applicable) with their study drug container(s).

#### **3.4.1.5 Day 5 (+ 1 Day)**

The assessments that are required on Day 5, but already completed as specified in [Section 3.4.1.3](#) or [3.4.1.4](#) do not need to be repeated. If not already performed on that day, the following procedures will be performed:

- Assess clinical signs and symptoms of CABP.
- Record vital signs and body temperature for all subjects, and pulse oximetry if clinically indicated and/or for subjects on supplemental oxygen.



- Collect blood cultures if clinically indicated.
- Record concomitant medications.
- Assess for AEs.
- Administer study drug every 12 hours ( $\pm$  2 hours).
- Perform study drug accountability on returned oral drug (outpatient subjects).
- Study drug may be stopped at the discretion of the investigator after completing a minimum of 10 delafloxacin/delafloxacin placebo doses. Determination of appropriate treatment duration is described in [Section 3.4.1.8.1](#).
- Access the IXRS to register completion or continued treatment.
- Subjects who continue oral treatment as an outpatient will be dispensed/administered study drug and instructed to return to the clinic on Day 7 with their study drug container(s).

#### **3.4.1.6 Day 7 (+ 1 Day)**

The assessments that are required on Day 7 but already completed as specified in [Section 3.4.1.3](#) do not need to be repeated. If not already performed on that day, the following procedures will be performed:

- Perform study drug accountability on returned oral drug (outpatient subjects).
- Assess clinical signs and symptoms of CABP.
- Record vital signs and body temperature for all subjects, and pulse oximetry if clinically indicated and/or for subjects on supplemental oxygen.
- Collect blood cultures if clinically indicated.
- Record concomitant medications.
- Assess for AEs.
- Study drug may be stopped at the discretion of the investigator. Subjects may be evaluated and study drug may be administered/dispensed as described above until the subject completes the investigator's planned course of therapy, up to a maximum 10 days of treatment (20 doses delafloxacin/delafloxacin placebo). Criteria for determination of appropriate treatment duration are described in [Section 3.4.1.8.1](#).
- Access the IXRS to register completion or continued treatment.

- Subjects who continue on treatment will be dispensed/administered sufficient quantity of study drug to complete treatment and will be instructed to return to the clinic (outpatient subjects) for the EOT visit with their study drug container(s).

#### **3.4.1.7 End of IV Treatment**

After a minimum of 6 delafloxacin/delafloxacin placebo doses, subjects can switch to oral treatment if, in the past 24 hours, the subject meets the following suggested criteria for switch to oral treatment:

- Is able to ingest intact large tablets/capsules,
- Has a normally functioning gastrointestinal tract, and
- Is clinically stable and has improved stability of vital sign indices, such as, no worsening from entry vital signs.

Register the IV to oral switch in the IXRS. For subjects completing treatment as an outpatient, dispense oral study drug. Outpatient subjects will be instructed to return to the clinic on Day 5 (+ 1 day), Day 7 (+ 1 day) as applicable, and at EOT with their study drug container(s). Refer to [Section 3.6.6](#).

#### **3.4.1.8 End of Treatment (EOT) or Early Termination**

##### **3.4.1.8.1 Criteria for Determining Treatment Duration**

After completing 5 days of treatment (minimum of 10 doses of delafloxacin/delafloxacin placebo), the investigator will assess the subject for clinical response to treatment to determine adequate treatment duration. The following suggested criteria can be used to assess clinical response; however, the duration of therapy should be individualized based upon the subject's clinical response to treatment and comorbidities up to a maximum treatment of 10 days (20 delafloxacin/delafloxacin placebo doses).

- Afebrile for 48 to 72 hours,
- Breathing without supplemental oxygen (unless required for preexisting disease),

**AND**

- Have no more than 1 clinical instability factor (defined as heart rate > 100 beats per minute, respiratory rate > 24 breaths per minute, and systolic blood pressure  $\leq$  90 mmHg) ([Mandell 2007](#)).

##### **3.4.1.8.2 End of Treatment or Early Termination Procedures**

Subjects who prematurely discontinue study drug or are completing treatment will have EOT procedures performed that same day or up to 24 hours (+ 4 hours) after the last dose of study

drug. Assessments already completed on the same day as the last dose of study drug can serve as EOT procedures, and do not need to be repeated. Assessments should be recorded in the EOT eCRF and not duplicated in other eCRF visits. Laboratory tests completed for a routine visit will not be repeated at EOT, if collected within 24 hours of the EOT visit.

- Assess clinical signs and symptoms of CABP.
- Investigator assessment of clinical response.
- **ONLY FOR LACK OF EFFICACY**, collect deep cough sputum specimen for Gram stain and culture, if possible. Additionally, other respiratory sources are acceptable if available (refer to [Section 3.4.3.2.1](#)).
- **ONLY FOR LACK OF EFFICACY**, obtain a repeat CXR.
- Administer SF-12v2® Health Survey and QoL questions.
- Targeted physical examination.
- Record vital signs and body temperature for all subjects, and pulse oximetry for subjects on supplemental oxygen.
- Collect blood cultures if clinically indicated.
- Perform urine or serum pregnancy test for women of childbearing potential.
- Obtain hematology and serum chemistry.
- Record concomitant medications.
- Assess for AEs.
- Perform study drug accountability on returned drug (outpatient subjects).
- Contact the IXRS to register treatment completion status.

#### **3.4.1.9 Reminder Contact (3-9 Days After Last Dose)**

Subjects will receive a telephone call or contact via other interactive method, e.g., text or email as allowed by local regulations, to remind the subject about the upcoming TOC Visit.

#### **3.4.1.10 Test of Cure (TOC Visit, 5-10 Days After Last Dose of Study Drug)**

The following procedures will be performed 5 to 10 days after the last dose of study drug:

- Assess clinical signs and symptoms of CABP.
- Investigator assessment of clinical response.
- Administer SF-12v2® Health Survey and QoL questions.

- Targeted physical examination.
- Record vital signs and body temperature on all subjects, and pulse oximetry for subjects on supplemental oxygen.
- Collect deep cough sputum specimen for culture, if possible. Additionally, other respiratory sources are acceptable if available (refer to [Section 3.4.3.2.1](#)).
- **ONLY FOR LACK OF EFFICACY**, obtain a repeat CXR.
- Perform urine or serum pregnancy test for women of childbearing potential.
- Obtain hematology and serum chemistry.
- Obtain blood samples for *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* serology and procalcitonin.
- Record post-treatment medications.
- Assess for AEs.

#### **3.4.1.11 Follow-up Visit (FU, Day 28 ± 2 Days)**

All efforts will be made to have subjects return to the clinic for a FU visit. Telephone contact is permissible for subjects unable, unwilling or not required (see [Section 3.3.2](#)) to return to the clinic. The following procedures will be performed at the FU Visit on Day 28 (± 2 days).

- Urine or serum pregnancy test in female subjects of childbearing potential (for subjects who return to the clinic).
- Obtain blood sample for *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* serology (for subjects who return to the clinic).
- Assess for AEs and record AEs in the subject's source (only SAEs will be collected in the eCRF) for all-cause mortality assessment.
- Record post-treatment medications in the subject's source, particularly any antibiotics taken after EOT.
- Administer SF-12v2® Health Survey and QoL questions (may be completed by interview for subjects contacted by phone).

#### **3.4.1.12 Early Withdrawal Procedures**

If a subject withdraws from study participation early, EOT procedures will be performed at the time of early withdrawal. Refer to [Section 3.3](#) for further instructions on early withdrawal.

### **3.4.2 Efficacy Assessments**

Efficacy will be evaluated through assessment of clinical signs and symptoms of pneumonia and microbiological culture and susceptibility testing of bacterial isolates. Other measures of clinical efficacy as detailed in the protocol will be assessed at baseline and at multiple time points during the study.

#### **3.4.2.1 Clinical Evaluation**

The following signs and symptoms of CABP will be assessed and evaluated:

- Pleuritic chest pain
- Frequency or severity of cough
- Dyspnea
- Sputum production (if present, change in character and quantity from baseline and purulence)

Symptom severity will be evaluated by the investigator on a 4-point scale (absent, mild, moderate, severe, see [Section 7.8](#) for definitions) with improvement defined as at least a 1-point improvement (decrease) from baseline to the assessment at 96 hours ( $\pm$  24 hours) after first dose of study drug (e.g., from severe to moderate, from moderate to mild, or from mild to absent). See [Appendix 7.8](#) for definitions of symptom intensity.

In addition, at EOT and TOC, the investigator will assess the subject's Clinical Outcome based on criteria in [Section 3.7.2.2](#). Subjects' outcomes will be assessed as Success, Failure, or Indeterminate/Missing. Subjects must receive at least 4 doses of study drug through study Day 3 before the investigator can consider the subject to be a clinical failure.

### **3.4.3 Study Assessments**

The following assessments will be performed to collect data needed for this research study. It is expected that the investigator and hospital staff will follow the usual standard of patient care and that local/regional laboratory results will be used to manage patient care.

#### **3.4.3.1 Chest Radiography**

A chest radiograph (chest x-ray; posteroanterior and lateral preferred; single view acceptable if conclusive) must be obtained prior to randomization with initial interpretation and included in the source documents. Computed tomography of the thorax may be used as an alternative, if available as per local standard of care. The presence of lobar, multilobar, or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia on a pulmonary imaging study is required for study entry. Chest radiography should be performed before

randomization and repeated at EOT or TOC only for lack of efficacy. Chest radiography obtained per local standard of care will not be repeated if obtained within 48 hours before the first dose of study drug. Findings will be recorded in the eCRF. Radiologic films must have a formal interpretation available in the source documents. Source, i.e., radiologist report and imaging, will be maintained by the site.

### 3.4.3.2 Microbiological Assessments

The following pathogens are examples of primary pathogens that will be used to determine the microbiological responses in the study: the typical bacterial pathogens include but may not be limited to *S. pneumoniae*, *H. influenzae*, *S. aureus*, *K. pneumoniae*, and *Moraxella catarrhalis*, and the atypical bacterial pathogens *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. The causative pathogen will be identified by isolation from a baseline culture specimen (either a respiratory specimen or blood), by urinary antigen, by serology, and/or by PCR.

Residual respiratory samples, nasopharyngeal swabs, and oropharyngeal swabs will be sent to specialty laboratories for possible culture, PCR, serotyping, and/or susceptibility testing (*S. pneumoniae*, *L. pneumophila*, *M. pneumoniae*). Respiratory and blood specimens will be sent to local/regional/specialty laboratories for culture, microorganism identification, and antibiotic sensitivity testing and will be processed according to standard recognized methods (Garcia 2010, Murray 2007). Sites will use local/regional culture results for patient management.

Two Gram stain slides of the sputum specimen will be prepared by the local/regional laboratories. One slide will be stained and read locally. Both slides, read and unread, will be sent to the central laboratory to confirm results. An additional Gram stain slide may be retained by the local microbiology laboratory, if required by local regulations. Culture will be performed at local or regional laboratories, as applicable. Rapid MRSA identification methods are acceptable to use if *S. aureus* is identified by the local/regional laboratory. Isolates that are not considered contaminants will be forwarded to the central microbiology laboratory for confirmation of identity and antimicrobial susceptibility testing and any further molecular or phenotypic characterization (e.g., PCR for Pantone-Valentine leukocidin and *mecA* genes, pulsed-field gel electrophoresis). Specific handling and shipping instructions that will maintain viability of all organisms will be provided in the laboratory manual. A duplicate sample of the isolate(s) (from all sources) submitted to the central microbiology laboratory will be maintained (in a frozen state) by the local laboratory or sent to the central laboratory until the conclusion of the study. Directions for collection, processing and handling of specimens are included in the laboratory manual.

Pathogens will be specifically identified to the genus and species levels. In vitro susceptibility of target pathogens to delafloxacin and moxifloxacin will be determined at the central laboratory according to Clinical Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines for broth and agar dilution and disk diffusion. Susceptibility to additional antibiotics will also be evaluated.

In all cases, the investigator should make decisions about subject withdrawal or continuation based on his or her best clinical judgment, and not based solely upon culture/susceptibility results.

#### **3.4.3.2.1 Respiratory Culture**

The collection of an adequate sputum sample for Gram stain, culture, and susceptibility testing, as applicable, will be attempted in all subjects at baseline. Other sources of respiratory specimens such as those obtained from bronchoalveolar lavage (BAL), protected specimen brush (PSB), transtracheal aspirate, and pleural fluid, if available, are acceptable to submit for culture. All respiratory specimens will be sent to the local/regional laboratory for gram stain, culture and susceptibility testing, as applicable.

All sputum and transtracheal aspirate samples will be evaluated to determine quality. A Gram stain will be performed immediately after the sample is delivered to the microbiology laboratory. A microscopic examination of the slide will be performed. A “good” sputum sample is one with polymorphonuclear leukocytes but few (or no) squamous epithelial cells on Gram stain. All efforts will be made to obtain a sputum or transtracheal aspirate specimen that yields an acceptable Gram-stain, defined as < 10 squamous epithelial cells and/or > 25 polymorphonuclear cells per low-power field.

All respiratory specimens will be sent for culture and susceptibility testing. In addition, any residual respiratory sample will be frozen and sent to the central laboratory for culture, *L. pneumophila* identification, antibiotic susceptibility testing, and serotyping at a specialty microbiology laboratory. The respiratory culture, if positive, will be used to identify isolates for submission to the central microbiology laboratory and to freeze for back-up storage.

Collection of a repeat respiratory specimen for culture should be attempted at EOT only for lack of efficacy, prior to any rescue therapy, at TOC if possible, or if clinically indicated.

The method used to obtain the respiratory culture will be documented in the subject’s source record and in the eCRF. Specimens will be collected and shipped using acceptable materials, timelines and shipping conditions to ensure specimen integrity and viability. Instructions for the processing of respiratory samples for Gram stain and culture are provided in the laboratory manual.

### **3.4.3.2.2 Blood Culture**

Two sets (aerobic and anaerobic) of blood specimens for culture will be obtained at baseline from anatomically different locations. Additional blood samples will be collected for culture at subsequent visits only if a previous culture was positive, or if clinically indicated. If positive, blood cultures will be repeated until they are negative. Culture will be performed at a local or regional laboratory, as applicable. The blood culture, if positive, will be used to identify isolates for submission to the central microbiology laboratory and to freeze for back-up storage.

### **3.4.3.2.3 Urine Antigen Testing**

Urine samples will be obtained for *L. pneumophila* and *S. pneumoniae* urine antigen testing at baseline and forwarded to the central laboratory.

### **3.4.3.2.4 Nasopharyngeal and Oropharyngeal Testing**

A nasopharyngeal swab will be obtained at baseline and forwarded to the central laboratory for *S. pneumoniae* PCR analysis and/or *S. pneumoniae* culture, serotyping and antibiotic susceptibility testing at a specialty microbiology laboratory. Two oropharyngeal swabs will be obtained at baseline and forwarded to the central laboratory for *M. pneumoniae* culture and/or PCR analysis, antibiotic susceptibility testing at a specialty microbiology laboratory.

### **3.4.3.2.5 Serology**

Serum serology samples will be tested for identification of atypical pathogens *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* at baseline, TOC, and FU.

### **3.4.3.3 Demographic Data/Medical History**

Demographic data and a complete medical, pulmonary, and surgical history including past and current alcohol use/abuse and smoking history will be collected at Screening. The medical history should include clinically significant medical, pulmonary or surgical history ongoing at baseline or with onset in the previous 2 years, as well as hospitalizations of more than 2 days within the last 90 days. Data related to the current infection under study should be recorded not in the medical history but on the CABP signs and symptoms form of the eCRF.

### **3.4.3.4 Prior Medications**

All medications taken once or more in the 14 days before Screening, including nonprescription medications and dietary supplements, will be recorded. Prior antibacterial treatments up to 30 days before the first dose of study drug will also be collected. Medications started after the first study dose (i.e., concomitant medications) will be collected as described in [Sections 3.4.3.11](#) and [3.4.3.12](#).



### 3.4.3.5 Clinical Laboratory Tests

Clinical laboratory testing will be performed according to the Schedule of Events ([Appendix 7.1](#)). Local results of pregnancy test, serum chemistry and coagulation profile, hematology, and urinalysis tests obtained within 24 hours before enrollment may be used for screening purposes and to verify entry criteria. However, blood and urine samples will be collected at Screening and on Day 1 prior to the first dose of study drug and will be sent to the central laboratory to serve as baseline values. Directions for collection, processing, and handling of specimens are included in the laboratory manual.

Tests to be performed are as follows:

**Serum Chemistry:** A serum chemistry panel will be taken to include sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, creatine phosphokinase, albumin, glucose, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, uric acid, and total bilirubin. Creatinine clearance (CrCl) will be calculated with every chemistry panel. Serum chemistry samples will be analyzed by a central laboratory.

**Other Chemistry:** Procalcitonin will be analyzed by a central laboratory.

**Hepatitis Serology:** Hepatitis B virus surface antigen and hepatitis C virus antibody will be tested at Screening and will not be exclusionary. If Hepatitis B or C is discovered based on this testing, this should be recorded as Medical History and not an adverse event. Hepatitis serology will be analyzed by a central laboratory.

**Hematology:** A hematology panel will be taken to include complete blood count with hematocrit, hemoglobin, platelet count, red blood cell count (RBC), RBC morphology and mean corpuscular volume, and white blood cell count with differential. Prothrombin time and international normalized ratio will also be measured at Screening. Hematology samples will be analyzed by a central laboratory.

**Urinalysis:** A urine panel will be taken at screening to include pH, specific gravity, leukocytes, nitrite, leukocyte esterase, protein, urobilinogen, bilirubin, blood, glucose, and a microscopic examination. The urine samples will be analyzed by a central laboratory.

**Pregnancy Test:** A urine or serum pregnancy test will be performed in women of childbearing potential. Pregnancy testing will be performed by a local laboratory.

### 3.4.3.6 Pharmacokinetic Blood Sample Collections

Serial blood samples for PK analysis will be obtained at select investigative sites on Day 3 ( $\pm 1$  day) of treatment within the 30 minutes before study drug administration and at 1.5 and

3 hours after the start of the infusion. All time points will have a  $\pm$  10-minute window. Subjects should have received a minimum of 3 consecutive doses of study drug prior to the start of PK blood collection. Subjects do not need to be fasted before dosing or during PK sample collections. Samples will be processed according to the laboratory manual and sent to the central laboratory for analysis.

All plasma samples will be assayed using a validated liquid chromatography coupled with tandem mass spectrometry assay for delafloxacin.

#### **3.4.3.7 Vital Sign Measurements**

Vital signs including body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure, and pulse oximetry will be obtained according to the Schedule of Events ([Appendix 7.1](#)). Arterial blood gases can be obtained at Screening if clinically warranted. Daily supplemental oxygen will be recorded. Blood pressure and pulse rate will be measured after subjects have been in a sitting position for at least 5 minutes. Respirations will be counted and documented in breaths per minute. Body temperature can be measured via different methods including oral, rectal, tympanic, and axillary. Vital signs should be measured at a consistent time each day while on IV therapy. Subjects who require pressor support should have regular blood pressure monitoring as per local standard of care.

#### **3.4.3.8 Physical Examination**

A complete physical examination, including height and weight, will be performed at Screening.

Targeted physical examinations will be performed during the study to assess changes from baseline parameters, AEs, and other relevant safety information.

#### **3.4.3.9 Electrocardiogram**

A 12-lead ECG will be performed at Screening, and if clinically indicated by the investigator after Screening. A single ECG will be recorded after the subject has been in a supine position and at rest for at least 3 minutes. The ECG tracings should be collected and retained with the source documents for study monitoring. The investigator or designee will be responsible for reviewing the 12-lead ECG to assess whether the results are within the reference limits and to determine the clinical significance of the results. These assessments will be recorded in the eCRF.

### **3.4.3.10 Health-Related Quality-of-Life Assessment**

#### **SF-12v2<sup>®</sup> Health Survey**

The SF-12v2<sup>®</sup> Health Survey (acute) is a multipurpose short form survey with 12 questions. This validated tool includes questions which were combined, scored, and weighted to create 2 scales that provide glimpses into mental and physical functioning and overall health-related quality of life. The “Acute” requires the patient’s recall of the patient’s status in the week prior to questioning. The SF-12v2<sup>®</sup> is a generic measure and does not target a specific age or disease group.

The SF-12v2<sup>®</sup> measures 8 attributes of functional health status: physical functioning, role limitations resulting from physical health problems, bodily pain, general health, vitality (energy and fatigue), social functioning, role limitations resulting from emotional problems, and mental health (psychological distress and psychological well-being). In addition, the SF-12v2<sup>®</sup> assesses overall physical and mental function using summary scales, Physical Component Summary Score (PCS-12), and Mental Component Summary Score (MCS-12), which are scored through comparison with population norms estimated from responses to the 1990 National Survey of Functional Health Status. This survey will be completed at baseline, EOT, TOC, and FU based on availability of the validated survey in local language.

Changes, i.e., worsening, will not be documented as AEs unless reported during the non-directed questioning for AEs (see [Section 3.4.4.2](#)). The SF-12v2<sup>®</sup> Health Survey is provided in [Appendix 7.6](#).

#### **Quality-of-Life Questions**

Quality-of-life questions will be asked/administered to determine the effect of the subject’s CABP under study on his/her usual daily activities of doing their job and earning income. The questions require the subject to recall their status in the 24 hours prior to questioning. Changes, i.e., worsening will not be documented as AEs unless reported during the non-directed questioning for AEs (see [Section 3.4.4.2](#)). The QoL assessment questions are provided in [Appendix 7.7](#).

### **3.4.3.11 Concomitant Medications**

All concomitant medications will be recorded in the source and eCRF from the time the subject signs informed consent through the EOT. Nonprescription medications, medications given as part of any surgical procedure, and dietary supplements will be included. Concomitant medications that are allowed or prohibited during the study are described in [Sections 3.6.7](#) and [3.6.8](#).

If an allergic reaction occurs, the investigator should discontinue treatment (if ongoing) and follow the usual standard of care. The reaction will be recorded as an AE, and all medications given will be recorded as concomitant medications.

#### **3.4.3.12 Post-Treatment Medications**

All medications, including nonprescription medications and dietary supplements, taken once or more from the EOT Visit through the FU Visit will be recorded in the subject source. The post-treatment medications recorded in the eCRF will be limited. Enter any antibiotics taken after EOT in the eCRF for all subjects. All other medications will only be entered in the eCRF through the TOC Visit, and only medications associated with an SAE from the TOC Visit through the FU Visit will be recorded in the eCRF. For subjects not required to have or missing the TOC Visit, post-treatment medications other than antibiotics will only be recorded in the eCRF if associated with an SAE through the Follow-up Visit.

#### **3.4.4 Safety Assessments**

Safety will be assessed by monitoring of AEs (including serious AEs [SAEs]), vital sign measurements and body temperature, clinical laboratory tests (including pregnancy testing), physical examination findings, electrocardiograms (ECGs) if clinically warranted, and concomitant medications.

##### **3.4.4.1 Adverse Event Definitions**

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

A pretreatment event is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of double-blind study medication; it does not necessarily have to have a causal relationship with study participation.

An AE is defined as any untoward medical occurrence associated with the use of a drug in a subject enrolled into this study regardless of its causal relationship to study treatment. Subjects or, where allowed by local regulations, their legally authorized representatives will be instructed to contact the principal investigator or subinvestigator at any time after signing the informed consent if any symptoms develop.

A treatment-emergent adverse event (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

A treatment-related AE is defined as any event with suspected causality to study drug.

An SAE is defined as any event that:

- Results in death,
- Is immediately life threatening,
- Requires in-subject hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, or
- Is a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in in-subject hospitalization, or the development of drug dependency or drug abuse.
- Pretreatment events that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner.

#### **3.4.4.2 Eliciting and Documenting Adverse Events**

All AEs that occur from the time the subject or authorized representative signs the ICF through the FU Visit must be reported in detail in the subject source and followed to satisfactory resolution or until the principal investigator or subinvestigator deems the event to be chronic or the subject to be stable. The description of the AE will include the onset date, duration, date of resolution, severity (refer to [Section 3.4.4.4](#)), seriousness, etiology, and the likelihood of relationship of the AE to study treatment.

Collection of pretreatment events will commence from the time the subject signs the informed consent to participate in the study and continues until the subject is first administered double-blind study medication. For subjects who discontinue study participation prior to double-blind study medication administration, pretreatment events are collected until the subject discontinues. Collection of TEAEs will commence from the time that the subject is first administered double-blind study drug through the FU Visit.

Assessment of relationship to study drug will only be captured after the subject is first administered study drug.

At every study visit, subjects will be asked a non-directed question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications). Patient-reported outcome instruments such as SF-12v2<sup>®</sup> Health Survey and QoL questions will not be used directly as a source of potential AE information.

In addition to subject observations, AEs will be documented from any data collected in the eCRF or other source documents (e.g., laboratory values, physical examination findings, ECG changes) that are relevant to subject safety. An allergic reaction to study drug must be reported as an AE.

#### **3.4.4.3 Reporting Adverse Events**

All AEs reported or observed during the study will be recorded in the AE eCRF from the time that the subject is first administered double-blind study drug through the EOT or TOC Visit, whichever is later. All SAEs will be recorded in the eCRF from the time the subject or authorized representative signs the ICF through the FU Visit.

Information to be collected includes drug treatment, dosage, type of event, time of onset, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities will be used to code all AEs.

#### **Preexisting conditions:**

Preexisting conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should not be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., “worsening of [condition]”).

#### **Insufficient clinical response (lack of efficacy):**

Insufficient clinical response, efficacy, or pharmacological action should NOT be recorded as an AE. The principal investigator must make the distinction between exacerbation of preexisting illness and lack of therapeutic efficacy. Progression of the current CABP due to lack of efficacy of the study drug will be recorded on the Clinical Response eCRF.

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy or further diagnosis beyond repeat testing for confirmation alone.

#### **3.4.4.4 Assessment of Severity**

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild: These events require minimal or no treatment and do not interfere with the subject's daily activities.

Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

#### **3.4.4.5 Assessment of Causality**

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the study drug, but could also have been produced by other factors.

**Probable:** This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely.

**Definite:** This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

#### **3.4.4.6 Reporting Serious Adverse Events**

Any AE considered serious by the principal investigator or subinvestigator or which meets the above seriousness criteria which occurs after the signing of the informed consent through the FU Visit (as described in [Section 3.4.4.1](#)) must be reported to the Medical Monitor or designee immediately or within 24 hours from the time study-site personnel first learn about the event. A copy of the initial SAE report must be submitted to the CRO Pharmacovigilance Department within 24 hours. The SAE report should provide as much of the required information as is available at the time. The following minimum information is required for reporting an SAE: subject identification, reporting source, causality, and an event outcome. Supplemental information may be transmitted using a follow-up report and should not delay the initial report. The study sponsor or its designee may contact the investigational site to solicit additional information or to follow up on the event. All sites will be supplied with SAE Reporting Instructions as part of the Onsite Study File; all necessary contact information including SAE reporting lines/faxes for communication of safety data will be provided in the Onsite Study File Contact Sheet.

Withdrawal from the study and all therapeutic measures will be performed at the discretion of the principal investigator or subinvestigator.

The sponsor or designee will be responsible for reporting all applicable SAEs to regulatory authorities, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. The sponsor or designee will prepare an expedited report for all SAEs that are unexpected and potentially related to the study medication, and copies will be distributed according to all applicable laws and regulations in countries with active investigators. The investigational site will also forward a copy of all expedited reports to their IRB or IEC, as applicable. Copies of SAE



correspondence with all principal investigator or subinvestigators, governing authorities, IECs, and the sponsor must be submitted to CRO for filing.

#### **3.4.4.7 Follow-up of Subjects Reporting Serious Adverse Events**

A subject experiencing 1 or more SAEs will receive treatment and follow-up evaluations by the principal investigator or subinvestigator or will be referred to another appropriate physician for treatment and follow-up. All SAEs will be followed until satisfactory resolution or until the principal investigator or subinvestigator deems the event to be chronic or the subject to be stable. The timelines and procedure for follow-up reports are the same as those for the initial report.

#### **3.4.4.8 Safety Monitoring Committee**

The sponsor may utilize an independent safety monitoring committee during the study. In that event, the membership, activities, and responsibilities of the safety monitoring committee will be described in detail in a separate charter document established for this study.

#### **3.4.4.9 Pregnancy**

Women with known or suspected pregnancy are excluded from the study. In the event a subject becomes pregnant during treatment, the subject will be requested to discontinue study drug immediately and will complete EOT Visit procedures as specified in [Section 3.3.2](#). The investigator must inform the subject of her right to receive treatment information. If pregnancy is discovered after administration of study drug, the investigator must report information using the Pregnancy Report Form to the Pharmacovigilance Department staff.

All subject pregnancies will be followed up to final outcome, using the pregnancy follow-up form. The outcome, including any premature termination, must be reported to the CRO. The pregnancy is not considered an AE; however, pregnancy complications, including miscarriage or spontaneous abortion, are considered AEs. Any untoward outcome for the mother or infant is considered an SAE.

#### **3.4.4.10 Criteria for Stopping Study**

The study may be terminated by the sponsor if new data becomes available which raises concern about the safety of the study drug, so that continuation might cause unacceptable risks to participants.

In addition, the Sponsor reserves the right to discontinue the study prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Investigator must promptly contact all subjects, assure appropriate therapy and follow-up for the subjects and provide written notification to the IRB/IEC.

### **3.5 Overdose Management**

Single oral doses of delafloxacin as high as 1600 mg and multiple doses of 1200 mg have been administered to subjects in Phase 1 trials. Single IV doses as high as 1200 mg have been administered to subjects in Phase 1 trials. In study RX-3341-302, 3 patients received 600 mg IV BID for up to 13 days due to pharmacy error ([Rib-X 2015](#)). There were no drug-related AEs reported. The most common AEs associated with the high doses of delafloxacin were gastrointestinal effects (diarrhea, abdominal pain/discomfort, nausea, vomiting) and headache. General supportive care is suggested for intentional or unintentional overdosage of delafloxacin.

Refer to the moxifloxacin and or linezolid Summary of Product Characteristics (SmPC) or prescribing information for treatment for intentional or unintentional overdose.

### **3.6 Study Treatments**

#### **3.6.1 Method of Assigning Subjects to Treatment Groups**

Each subject will be randomly assigned in a 1:1 ratio to the delafloxacin or moxifloxacin treatment group.

The investigator or designee will enter the enrollment information in the IXRS. The unblinded pharmacist or unblinded designee will obtain the treatment assignment from the IXRS as described in the IXRS manual. A statistician who is not otherwise involved in the conduct of the study will create the randomization code. Randomization will be stratified by PORT Risk Class, medical history of COPD/asthma, and by prior single-dose/regimen antibiotic use.

Subjects in PORT Risk Class II will be limited to no more than 25% of total randomized subjects, and prior single-dose/regimen antibiotic use limited to no more than 25% of total randomized subjects.

#### **3.6.2 Treatments Administered**

An unblinded pharmacist or an unblinded designee will prepare the study drug infusions.

- Delafloxacin 300 mg will be administered as a 1-hour IV infusion every 12 hours ( $\pm$  2 hours) for a minimum of 6 doses with an option to switch to delafloxacin 450 mg tablet administered orally every 12 hours ( $\pm$  2 hours) for the remaining doses.

- Moxifloxacin 400 mg will be administered as a 1-hour IV infusion every 24 hours ( $\pm$  2 hours) for a minimum of 3 active doses with an option to switch to moxifloxacin 400 mg (over-encapsulated tablet) administered orally every 24 hours ( $\pm$  2 hours) for the remaining doses.
- At local investigator discretion, subjects in the moxifloxacin arm with confirmed MRSA, in place of remaining moxifloxacin doses, can receive linezolid 600 mg administered as a 1-hour IV infusion every 12 hours ( $\pm$  2 hours) for the remaining doses.

Refer to [Section 3.6.4.3](#) for blinding information. Refer to the pharmacy manual for further details regarding dose preparation and administration.

### **3.6.3 Description of Investigational Product**

#### **Delafloxacin**

Delafloxacin for Injection, 300 mg/vial, is a light-yellow to tan-colored lyophilized powder provided in a 20 mL clear borosilicate glass vial. Each vial contains the following ingredients: 432.9 mg delafloxacin meglumine equivalent of 300 mg free acid, 58.56 mg meglumine, 2400 mg sulfobutyl ether sodium beta-cyclodextrin (Captisol<sup>®</sup>), and 2.6 mg ethylene-diamine-tetra-acetate disodium (as EDTA, amount as acid).

After reconstitution in the vial, the drug concentration is 25 mg/mL in an aqueous solution of 12.4 mL (0.4 mL as overage).

Oral delafloxacin is a capsule-shaped tablet in beige color with tan spots (delafloxacin particles) and with RX3341 debossed on one side. Each tablet contains the following ingredients: 649.35 mg delafloxacin meglumine equivalent of 450-mg free acid; cellulose; povidone; crospovidone; sodium bicarbonate; sodium phosphate; citric acid; and magnesium stearate. For more information on the description of delafloxacin, refer to the Investigator's Brochure ([Melinta 2016](#)).

#### **Moxifloxacin Hydrochloride**

Moxifloxacin hydrochloride is a synthetic broad spectrum fluoroquinolone antibacterial agent for IV and oral use. Moxifloxacin injection for IV use and moxifloxacin as film-coated tablets containing moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin) are planned to be used. For the description of the product, refer to its SmPC or prescribing information.

#### **Linezolid**

Linezolid is an oxazolidinone-class antibacterial. Linezolid injection for IV use is planned to be used. For the description of the product, refer to its SmPC or prescribing information.

### **3.6.4 Management of Clinical Supplies**

#### **3.6.4.1 Study Drug Packaging and Storage**

Delafloxacin for Injection (300 mg/vial) will be provided in a 20-mL clear borosilicate glass vial. The contents of the vial will be reconstituted and diluted before administration according to the pharmacy manual. Delafloxacin (450 mg) tablets will be supplied in blister packaging.

Do not store delafloxacin in conditions over 30°C. In the US, storage conditions will be specified as Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Moxifloxacin (400 mg) for IV use is intended to be provided in glass bottles or infusion bags as local availability allows. Moxifloxacin (400 mg) over-encapsulated tablets are intended to be supplied in daily dose bottles.

Moxifloxacin should be stored as per its SmPC or prescribing information.

Linezolid (600 mg) for IV use is intended to be provided as a ready-to-use sterile isotonic solution for IV infusion.

Linezolid should be stored as per its SmPC or prescribing information.

Vials, bottles, and blister packs of study drug will be provided to the study sites. Vials, bags, and bottles for IV use may be bulk or kitted as availability allows.

Additional study drug will be supplied as needed based on information provided via the IXRS.

Detailed information on study drug packaging, preparation, storage, and handling may be found in the pharmacy manual.

#### **3.6.4.2 Test Article Accountability**

The pharmacy and/or clinic will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used for each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable local regulations.

All study drug must be kept in a secure location with access restricted to only necessary study site personnel and hospital pharmacist.

### 3.6.4.3 Blinding

The majority of the involved parties in this study (subjects, investigators, laboratories, CRO, and sponsor personnel) will be blinded to the identity of study drug and randomization assignments until the study is formally unblinded. Unblinding will occur after all subjects have completed the study and after resolution of all data queries. Each site will document a blinding plan prior to study start.

The pharmacist will not be blinded, and will cover the IV infusion bag and tubing so that the identification of the study drug solution will not be seen by the blinded study staff or study subjects. Certain clinical research staff will not be blinded in order to monitor the pharmacy, administer study drug (if applicable), and monitor study administration records and will not reveal a subject's treatment assignment to study staff. The statistician who creates the randomization code will not be involved otherwise in the conduct of the study.

- All IV blinded dosing will be maintained with a 12-hour schedule.
- IV bags will be blinded. The IV infusion bag and tubing will be masked so that the delafloxacin, moxifloxacin, linezolid, and placebo solutions will be indistinguishable. Infusion lines from the study drug bag to the subject must be flushed after each administration to ensure the subject receives a complete dose.
- Subjects in the moxifloxacin treatment arm will receive once-daily active IV therapy alternating doses of IV moxifloxacin and IV placebo BID.
- Subjects in the delafloxacin arm, when on oral therapy, will receive oral placebo moxifloxacin QD or IV placebo linezolid BID to maintain blinding.
- Subjects in the moxifloxacin/linezolid arm, when on oral therapy or when meeting criteria for oral therapy, will receive placebo delafloxacin oral formulation (tablets identical in appearance to the delafloxacin tablets) to maintain blinding.

Treatment regimens are summarized in [Table 3-1](#).

**Table 3-1 Treatment Regimens**

|                              | <b>Regimens Given</b>   | <b>Subjects Randomized to Delafloxacin</b>   | <b>Subjects Randomized to Moxifloxacin</b>   |
|------------------------------|---|--|--|
| <b>WHILE ON IV THERAPY</b>   | <b>IV regimen given with blinding covers</b>  | IV active delafloxacin twice daily   | IV active moxifloxacin once daily, alternative with IV placebo to maintain blind for BID dosing                                    |
|                              | <b>If linezolid is prescribed during IV dosing period</b>   | Continue IV active delafloxacin twice daily  | Discontinue IV moxifloxacin/placebo and begin IV active linezolid twice daily  |
| <b>WHILE ON ORAL THERAPY</b> | <b>Delafloxacin</b>   | Oral active delafloxacin twice daily<br>AND  | Oral placebo delafloxacin twice daily<br>AND   |
|                              | <b>Moxifloxacin</b>   | Oral placebo moxifloxacin once daily   | Oral active moxifloxacin once daily  |
|                              | <b>If linezolid is prescribed for MRSA in moxifloxacin subjects a partial switch back to IV applies</b> | Oral placebo moxifloxacin will be discontinued (oral delafloxacin continues) and subjects randomized to delafloxacin will receive IV placebo linezolid twice daily | Oral active moxifloxacin will be discontinued and subjects randomized to moxifloxacin will receive IV active linezolid twice daily |

**3.6.5 Breaking the Blind**

A double-blind design is used to maintain blinding for all personnel involved with the evaluation of subject efficacy and safety during the study. The blind should only be broken in an emergency when it is essential for the Investigator to know which treatment an individual subject has received in order to provide appropriate care. In an emergency situation, the Investigator will be able to obtain the unblinded treatment assignment through the password-protected IXRS or the unblinded pharmacist. Instructions for obtaining the unblinded

treatment assignment will be provided to the site. The Investigator should discuss the subject with the Medical Monitor in an emergency situation if possible. If it was not possible to discuss the situation with the Medical Monitor prior to breaking the blind, this communication must occur as soon as possible after the blind was broken. In all cases where the blind is broken through the IXRS, a notification from the IXRS will be sent to the Medical Monitor. The date, time, and reason the blind is broken must be recorded in the subject source documents and recorded on the eCRF.

Every attempt will be made to maintain the blind throughout the study.

### **3.6.6 Treatment Compliance**

Compliance will be evaluated through review of study drug dispensing and administration records. For outpatient dosing, subjects will be required to bring study drug containers (used and unused) to each site visit, and a pill count will be conducted to assess compliance. All subjects will be instructed about the dosing requirements during the study. Noncompliance will be documented and the subject reinstructed as appropriate. The authorized study personnel conducting the education/reeducation must document the process in the subject source record.

### **3.6.7 Allowed Concomitant Treatment**

All concomitant medications will be recorded in the eCRF.

As with other quinolones, concurrent administration of oral delafloxacin and moxifloxacin with magnesium, aluminum, or calcium antacids as well as metal cations such as iron, and multivitamins preparations with zinc or didanosine chewable/buffered tablets should be avoided. The study drug may be taken 4 hours before or 8 hours after taking these food supplements or medicinal products.

Systemic steroid use during the treatment period is allowed for a short duration (e.g., steroid burst). Inhaled steroids are allowed without any restriction.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the principal investigator to ensure that details regarding the medication are recorded in full in the source and on the eCRF.

### **3.6.8 Prohibited Medications and Restrictions**

Concurrent systemic antimicrobial treatments are prohibited. Any subject who requires additional (i.e., nonstudy) antibiotics for any of the following reasons will be considered a treatment failure: lack of efficacy after at least 4 doses of study drug by the end of Day 3,

antibiotic therapy required for more than 20 delafloxacin/delafloxacin placebo doses. Study drug should be stopped for all treatment failures, and the subject should complete end of treatment procedures.

Subjects may not take other investigational products during the study.

Refer to the moxifloxacin and or linezolid SmPC or prescribing information for additional prohibited medications and restrictions, including, but not limited to contraindications for the concomitant use of monoamine oxidases (MAO) A or B inhibitor agents and adrenergic and serotonergic agents with linezolid.

### **3.7 Statistical Analysis Plans**

Continuous characteristics including baseline values will be summarized by treatment group using means, standard deviations, minimum, maximum, and median values. Categorical variables will be summarized by treatment group using frequency distributions. For the baseline characteristics, data will be presented overall as well. The differences in proportions for the responders from the 2 treatment groups will be tested for noninferiority using CIs generated by the Miettinen-Nurminen method, without stratification. Continuous secondary efficacy measures will be analyzed using an analysis of covariance (ANCOVA) model with treatment as the main effect and adjusted for PORT Class, medical history of COPD/asthma and prior antimicrobial therapy, and the baseline measure as the covariate. All statistical analyses, unless otherwise specified, will be based on 2-sided 95% CIs around the difference in treatment outcomes.

#### **3.7.1 Endpoints**

For FDA, in order to control Type 1 error rate of 5%, a gate-keeping statistical method of a fixed sequence procedure will be used to test for the secondary efficacy endpoints once the primary efficacy endpoint is claimed to be successful. If the noninferiority of delafloxacin is declared in the primary analysis, in order to control type 1 error, the secondary endpoints will be tested for superiority in a sequential (hierarchical) fashion using a fixed sequential procedure.

For EMA, all the primary and secondary endpoints will be analyzed for noninferiority with the possibility to switch to superiority.

The difference (delafloxacin – moxifloxacin) and CIs for all secondary endpoints will be reported. The primary and secondary efficacy endpoints are presented in the following text.



**3.7.1.1 Primary Efficacy Endpoint**

The primary efficacy endpoint is:

| <b>FDA</b>  | <b>EMA</b>   |
|---|--|
| The ECR defined as improvement at 96 hours ( $\pm$ 24 hours) after first dose of study drug in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum, and difficulty breathing, and no worsening in the other symptoms in the ITT population. | The Clinical Outcome responder rate at 5 to 10 days after the last dose of study drug (TOC) defined as resolution or near resolution of the symptoms of CABP present at study entry, and no use of additional antimicrobial therapy for the current infection, and no new symptoms associated with the current CABP infection (success) in the ModITT and ModCE populations. |

**3.7.1.2 Secondary Efficacy Endpoints**

The secondary efficacy endpoints are:

| <b>FDA</b>  | <b>EMA</b>  |
|---|---|
| ECR with the addition of improvement in vital signs and no worsening of the 4 symptoms required as Response in the ITT population | ECR defined as improvement at 96 hours ( $\pm$ 24 hours) after first dose of study drug in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum and difficulty breathing and no worsening of any of the other symptoms in the ModITT and ModCE populations |
| Clinical Outcome at TOC (CE and ITT populations)  | ECR with the addition of improvement in vital signs and no worsening of the 4 symptoms required as Response in the ModITT and ModCE populations   |
| Clinical Outcome at EOT   | Clinical Outcome at EOT (ModITT and ModCE)  |
| ECR in the MITT population  | Clinical Outcome at TOC in the ModMITT and ModME populations  |
| Microbiologic Response (ME and MITT)  | Microbiologic response (ModMITT and ModME)  |
| All-cause mortality (ITT)   | All-cause mortality (ModITT)  |

### 3.7.1.3 Exploratory Endpoints

Exploratory endpoints include:

- Shift of outcomes from the ECR to the Clinical Outcome at EOT
- Shift of outcomes from the ECR to the Clinical Outcome at TOC
- Shift of outcomes from the Clinical Outcome at EOT to the Clinical Outcome at TOC
- Change in individual signs and symptoms

### 3.7.1.4 Health-Related Quality-of-Life Endpoints

Health-related QoL (HRQoL) and Health Economic Outcomes Research (HEOR) endpoints include:

- Compare SF-12v2<sup>®</sup> from baseline to EOT to TOC
- Compare subject's ability to work and earn income from baseline to EOT and TOC
- Compare time to oral switch
- Compare time to hospital discharge

### 3.7.1.5 Pharmacokinetic Endpoints

The time course of delafloxacin plasma concentrations will be assessed.

## 3.7.2 Endpoint Definitions

### 3.7.2.1 Early Clinical Response

Symptoms for the Early Clinical Response will be evaluated by the investigator on a four-point scale (absent, mild, moderate, severe, see [Section 7.8](#) for definitions) with improvement defined as at least a 1-point improvement (decrease) from baseline to the assessment at 96 hours ( $\pm$  24 hours) after first dose of study drug (e.g., from severe to moderate, from moderate to mild, or from mild to absent).

**Responders:** Improvement at 96 hours ( $\pm$  24 hours) after first dose of study drug in at least 2 of the following symptoms: pleuritic chest pain, frequency or severity of cough, amount and quality of productive sputum, and dyspnea (difficulty breathing), and no worsening of the other symptoms.

**Non-responders:** Improvement is not achieved at 96 hours ( $\pm$  24 hours) after first dose of study drug in at least 2 of the following symptoms: pleuritic chest pain, frequency or severity of cough, amount and quality of productive sputum, and dyspnea (difficulty breathing); or

there is use of additional non-study antimicrobial therapy for treatment of the current CABP infection due to lack of efficacy; or the subject died from the current CABP infection. Indeterminate/missing assessments will be mapped to Non-responders in the statistical analysis of the ITT Population.

### 3.7.2.2 Clinical Outcome at EOT and TOC

The principal investigator will define the Clinical Outcome based on the assessment of the subject's signs and symptoms of infection at the EOT and TOC. The investigator's assessment of clinical response will be categorized as Success, Failure, or Indeterminate/missing.

**Success:** Resolution or near resolution of the symptoms of CABP present at study entry, and no use of additional antimicrobial therapy for the current infection, and no new symptoms associated with the current CABP infection.

**Failure:** Symptoms of CABP present at study entry have not resolved, or new symptoms of CABP have developed, or the subject died from pneumonia, or use of additional non-study antimicrobial therapy for treatment of the current CABP infection due to lack of efficacy. Failure outcome due to Lack of Efficacy (LOE) will be carried forward to later time points if the subject discontinues the trial for LOE. Subjects must receive at least 4 doses of study drug by the end of Day 3 to be called a Failure.

**Indeterminate/Missing:** A response cannot be determined because an efficacy assessment was not completed at the visit, or subject did not complete the planned course of study therapy for reasons other than lack of efficacy. Indeterminate/missing responses will be considered failures for purposes of the primary ITT/ModITT analyses and will be excluded from the CE and ME analysis populations.

### 3.7.2.3 Microbiologic Response

Microbiological response for subjects in the MITT and ME set will be based on results of the baseline and follow-up cultures and susceptibility testing or serology. When follow-up culture results are missing, the clinical response assigned by the investigator will be considered. Microbiological response will be generated at the TOC assessment at both the subject and the pathogen levels. The following microbiological responses will be considered:

**Eradication:** The respiratory and/or blood specimen at the TOC Visit shows all causative pathogen(s) present at enrollment eradicated and no use of additional antimicrobial therapy for the current infection.

**Presumed Eradication:** No respiratory and/or blood specimen was available at TOC with a clinical assessment of Success.

**Persistence:** The respiratory and/or blood specimen at the TOC Visit shows appearance of causative pathogen(s) present at enrollment.

**Presumed Persistence:** No respiratory and/or blood specimen was available for a case classified as clinical failure.

**Superinfection:** A culture taken during treatment shows appearance of a new pathogen causing respiratory infection associated with clinical failure.

Colonization/Contamination: A culture taken post-baseline through the TOC visit shows appearance of a new pathogen(s), with a clinical assessment of Success and no use of additional antimicrobial therapy for the current infection.

### 3.7.3 Safety Endpoints

Safety endpoints are as follows:

- AEs, including SAEs
- Vital sign measurements and body temperature
- Clinical laboratory test results
- Physical examination findings
- Concomitant medications
- ECGs (obtained after baseline only if clinically indicated)

### 3.7.4 Sample Size Calculations

| FDA  | EMA   |
|--|---|
| <p>At least 860 adult male and female subjects (430 subjects per treatment group) will be randomized. Used on a normal approximation approach (Miettinen and Nurminen's Likelihood Score Test), 860 subjects in the ITT population will provide a 90% power to assess noninferiority of delafloxacin vs. moxifloxacin based on the following assumptions: (1) a rate of Early Clinical Response for moxifloxacin therapy and delafloxacin of 77% and 74%, respectively; (2) 1-sided type I error (<math>\alpha</math>) of 0.025; (3) a noninferiority margin of 12.5%.</p> | <p>At least 860 adult male and female subjects (430 subjects per treatment group) will be randomized. Used on a normal approximation approach (Miettinen and Nurminen's Likelihood Score Test), and assuming approximately 12% of patients will be in PORT Class II, and 80% of patients will be clinically evaluable, 755 subjects in the ModITT population and 604 subjects in the ModCE population will provide, respectively, a power of 91% and 83% to assess noninferiority of delafloxacin vs. moxifloxacin based on the following assumptions: (1) a rate of Clinical Outcome at the TOC visit for moxifloxacin and delafloxacin of 88% and 86%, respectively; (2) 1-sided type I error (<math>\alpha</math>) of 0.025; (3) a noninferiority margin of 10%.</p> |

As Early Clinical Response is a new endpoint, as new information arises (without unblinding the study) that informs sample size, this information may be used to reassess sample size. If ever utilized, any potential sample size recalculation would be based on pooled information across the 2 treatment arms.

### 3.7.5 Analysis Populations

Data analysis will be based on different analysis populations according to the purpose of the analysis (e.g., safety or efficacy). Within the efficacy analysis, different combinations of analysis sets will be used for the clinical response and the microbiologic response. The analysis for clinical response will be generally presented using the ITT, MITT, CE, and ME populations for FDA and the ModITT, ModMITT, ModCE and ModME populations for EMA. The analysis for microbiologic response will be presented using the MITT and ME populations for FDA and the ModMITT and the ModME populations for EMA.

The number of subjects in each analysis population and the reasons for exclusion from a given analysis population will be summarized by treatment group. The following analysis populations will be considered in this study:

**Safety Population**

The Safety Population will include all randomized subjects who receive at least 1 dose of study drug, analyzed according to the treatment they received.

**Intent-to-Treat (ITT) Population**

All randomized subjects analyzed according to the treatment arm to which they were randomized.

**Modified ITT (ModITT) Population**

All randomized subjects who received at least one dose of study medication, classified as PORT Class III-V, analyzed according to the treatment arm to which they were randomized.

**Microbiological ITT (MITT) Population**

All subjects in the ITT population who had a baseline bacterial pathogen identified on culture of a respiratory or blood specimen, or a nonculture method of detection of bacterial pathogens (i.e., urinary antigen test, PCR and serologic testing) that is known to cause CABP against which the study drug has antibacterial activity.

**Modified MITT (ModMITT) Population**

All subjects in the MITT population classified as PORT Class III-V.

**Clinically Evaluable (CE) Population**

All subjects in the ITT population who met the following criteria:

- Evidence of acute onset of community-acquired bacterial pneumonia (CABP).
- Received the correct study drug based on the randomization assignment.
- Received 80% of the expected doses of study drug in the treatment period (e.g., at least 11 doses of delafloxacin for a 7-day treatment period).
- Did not receive any concomitant, systemic antibacterial therapy except for LOE.
- Had no protocol deviations that would affect assessment of efficacy.

A CE analysis population will be identified for the Early Clinical Response time point as well as the EOT and TOC time points.

**Modified CE (ModCE) Population**

All subjects in the CE population classified as PORT Class III-V.

**Microbiologically Evaluable (ME) Population**

All subjects in the MITT population who also met the criteria for the CE population. A ME analysis population will be identified for the Early Clinical Response time point as well as the EOT and TOC time points.

**Modified ME (ModME) Population**

All subjects in the ME population classified as PORT Class III-V.

**Pharmacokinetic (PK) Population**

All subjects who receive at least 3 consecutive IV doses of study drug prior to the start of the blood sample collections on Day 3 ( $\pm$  1 Day) and have at least one delafloxacin plasma concentration data available. The PK population will be used for PK analyses.

**3.8 Statistical Analysis****3.8.1 Demographics and Other Baseline Characteristics**

Demographics and other baseline characteristics including gender, age, race, ethnicity, height, weight, BMI and the data for PORT Class and CURB-65 score will be summarized for the ITT, Safety, ModITT, MITT, ModMITT, CE, ModCE, ME and ModME populations to assess the comparability of the treatment groups.

Medical history data including pulmonary and hospitalization history will be summarized for the ITT and ModITT populations using the number of observations and percentage of subjects reporting each category. Baseline radiograph findings and signs and symptoms required for study entry will be summarized for the ITT and ModITT populations using the number of observations and percentage of subjects reporting each category.

**3.8.2 Subject Disposition**

The numbers of subjects who are randomized and complete the study will be tabulated. Subjects who fail to complete the study will be tabulated and categorized by reason for termination (lost to follow-up, AE, etc). In addition, the following will be tabulated by treatment group, as applicable: the number of subjects dosed with study drug, the number of subjects randomly assigned to each treatment, and the numbers of subjects in each analysis population.

### 3.8.3 Primary Efficacy Analysis

The primary efficacy endpoint is:

| FDA  | EMA  |
|--|--|
| <p>The ECR defined as improvement at 96 hours (<math>\pm</math> 24 hours) in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum, and difficulty breathing, and no worsening of the other symptoms in the ITT population.</p> <p>Each treatment group's response rate will be defined as: (# Responders) / (# Responders + Non-responders).</p> <p>The treatment difference (delafloxacin – moxifloxacin) in the rates of this endpoint will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% confidence interval (CI) on the difference in response rate. This analysis will be performed using the ITT population.</p> <p>The lower bound of this CI will demonstrate the maximum extent to which the response rate for moxifloxacin may exceed that for delafloxacin. If the lower bound is greater than -12.5%, it will be concluded that delafloxacin is noninferior to moxifloxacin for treating patients with CABP. In addition, superiority will be claimed if the lower bound of the 95% CI exceeds 0.</p> <p>An indeterminate/missing response will be classified as Non-responders for purposes of the primary analysis.</p> | <p>The Clinical Outcome at TOC.</p> <p>For the assessment of Clinical Outcome at TOC, each treatment group's Clinical Outcome rate will be defined as: (# Success) / (# Success + Failure).</p> <p>The treatment difference (delafloxacin – moxifloxacin) in the rates of this endpoint will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% CI on the difference in response rate. This analysis will be performed using the ModCE and ModITT analysis populations, and the result at TOC will be tested for noninferiority with the possibility to switch to superiority.</p> <p>The lower bound of this CI for delafloxacin – moxifloxacin will demonstrate the maximum extent to which the response rate for moxifloxacin may exceed that for delafloxacin. If the lower bound is greater than 10%, it will be concluded that delafloxacin is noninferior to moxifloxacin for treating patients with CABP. In addition, superiority will be claimed if the lower bound of the 95% CI exceeds 0.</p> <p>A missing response will be classified as failure for purposes of the primary ModITT analysis.</p> |



### **3.8.4 Sensitivity Analysis of the Primary Endpoint for each Region (FDA and EMA)**

The following sensitivity analyses for the primary endpoint will be performed:

- The primary analysis stratified by baseline PORT classification, medical history of COPD and asthma, and prior systemic antimicrobial use using the same Miettinen-Nurminen test.
- The primary analysis performed on the MITT/ModMITT, CE and ME/ModME analysis populations as per the corresponding region.
- For EMA region, in order to control the possible age influence on the clinical evaluation, the primary endpoint will be tested including the age class, defined as Age < 65 and Age ≥ 65, as an additional factor in the model.
- The primary analysis performed for additional analysis populations to be specified in the SAP.

### **3.8.5 Subgroup Analyses of the Primary Endpoint for each Region (FDA and EMA)**

An exploration of homogeneity of efficacy across subgroups will be undertaken by constructing a 2-sided 95% CI similar to the primary efficacy analysis using nonstratified Miettinen-Nurminen methodology, within the subgroups identified below. In the event that there are large imbalances between treatment groups between these subgroups, further exploration will be undertaken as an adjusted analysis of the primary outcome.

- Demographic subgroups: age categories (age < 65, ≥ 65, ≥ 75), gender, BMI categories (BMI < 30 and ≥ 30), baseline PORT Risk Class, baseline CURB-65 Score, ethnicity, region, and race categories.
- Prior antibiotics for subjects classified as a Failure at study entry and single dose prior antibiotic (Yes/No).
- Presence or absence of: baseline bacteremia, multilobar pneumonia, diabetes, history of COPD/asthma, history of hepatitis, renal impairment/disease, baseline *S. pneumoniae* infection, baseline Gram stain adequacy.

These subgroup analyses will be performed using the ITT/ModITT population for the primary efficacy endpoint.

### **3.8.6 Secondary Efficacy Analyses**

For each of the FDA submissions, in order to control Type 1 error rate of 5%, a gate-keeping statistical method of a fixed-sequence procedure will be used to test for the secondary efficacy endpoints once the primary efficacy endpoint is claimed to be successful. If the noninferiority of delafloxacin is declared in the primary analysis, the secondary endpoints will be tested for superiority in a sequential (hierarchical) fashion using a fixed sequential procedure, in the order given in [Section 3.7.1.2](#). Unless specified otherwise in the endpoint definition, the testing will be performed in the ITT analysis population.

For EMA, all the primary and secondary endpoints will be tested for noninferiority with the possibility to switch to superiority.

Each test, both for FDA and EMA, will be performed using the type 1 error rate of 0.05.

The secondary endpoints with proportion will be tested, both for FDA and EMA, using Miettinen-Nurminen test for delafloxacin – moxifloxacin, without stratification. Superiority for the corresponding study endpoint will be claimed using a 5% significance level.

#### **3.8.6.1 Early Clinical Response with the Addition of Improvement in Vital Signs and No Worsening of the 4 Symptoms Required as Response**

The treatment difference (delafloxacin – moxifloxacin) of ECR with the addition of improvement in vital signs and no worsening of the 4 symptoms required as response will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% CI on the difference in ECR with the addition of improvement in vital signs and no worsening of the 4 symptoms required as response rate. This analysis will be performed using the ITT and ModITT/ModCE population, respectively for FDA and EMA.

#### **3.8.6.2 Clinical Outcome at EOT and TOC**

The treatment difference (delafloxacin – moxifloxacin) in the rates of this endpoint will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% CI on the difference in response rate. This analysis of clinical outcome at EOT and TOC will be performed using the CE and ITT analysis populations for FDA. The ModCE and ModITT analysis populations will be used to perform the analysis of clinical outcome at EOT for EMA. The ModMITT and ModME analysis populations will be used to perform the analysis of the EMA secondary endpoint of clinical outcome at TOC.

A missing response will be classified as failure for purposes of the primary ITT analysis. For the assessment of Clinical Outcome at EOT and TOC, each treatment group's Clinical Outcome rate will be defined as:  $(\# \text{ Success}) / (\# \text{ Success} + \text{ Failure})$ .

### **3.8.6.3 Early Clinical Response for Subjects in the MITT, ModITT and ModCE Populations**

The treatment difference (delafloxacin – moxifloxacin) of ECR for patients in the MITT and ModITT/ModCE populations respectively for FDA and EMA will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% CI on the difference in ECR rate.

### **3.8.6.4 Microbiologic Response**

The treatment difference (delafloxacin – moxifloxacin) of microbiologic response rate will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% CI on the difference in microbiologic response rate. This analysis will be performed using the ME and the MITT populations for FDA, and the ModME and ModMITT populations for EMA.

### **3.8.6.5 All-Cause Mortality**

All-cause mortality in adult subjects with CABP on Day 28 will be assessed and compared between the two treatment groups. Kaplan-Meier estimates will be used to summarize the time to all-cause mortality on Day 28. Patients who have not died by Day 28 will be censored at Day 28. The probabilities of all-cause mortality at each day with associated standard error and 95% CIs will be presented. The log-rank test will be used to compare the time to all-cause mortality between the 2 treatment groups. In addition, the hazard ratio for treatment and its 95% CI will be calculated from a Cox proportional hazards model.

The Cox proportional hazards regression model will be used to evaluate the difference between the 2 treatment groups adjusting for the baseline covariates including baseline PORT classification, history of COPD/asthma, and prior systemic antimicrobial use. Interactions between treatment and each covariate will be evaluated at the 0.10 significance level; if not significant, they will be removed from the final model. These analyses will be performed for ITT and ModITT populations respectively for FDA and EMA.

### **3.8.7 Exploratory Analyses**

The SAP will describe analyses on additional endpoints not specified as primary or secondary endpoints or linked to study objectives.

Exploratory efficacy analyses will include summaries for the primary and secondary endpoints measured at additional study time points and for different analysis population. As other exploratory analyses, secondary analyses of secondary endpoints that used nonstratified Miettinen-Nurminen CIs will be repeated using the same method but stratified by PORT Class/PSI score, medical history of COPD/asthma, and prior systemic antimicrobial use.

In addition, the following shift analyses will be performed:

- Shift of outcomes from the Early Clinical Response to the Clinical Outcome at EOT
- Shift of outcomes from the Early Clinical Response to the Clinical Outcome at TOC
- Shift of outcomes from the Clinical Outcome at EOT to the Clinical Outcome at TOC
- Change in individual signs and symptoms

### **3.8.8 Health-Related Quality-of-Life Analyses**

Within each treatment group, the following health-related quality-of-life scores will be compared between baseline score to EOT and baseline score to TOC score using a paired t-test. In addition, the change from baseline scores will be compared between the 2 treatment groups using an ANCOVA model adjusted by baseline characteristics.

- SF-12v2<sup>®</sup> domain scores and the total scores
- Subject's ability to work and earn income

In addition, the following 2 health economic related measurements will be compared using a Kaplan-Meier analysis method:

- Time to oral switch
- Time to hospital discharge

### **3.8.9 Interim Analysis**

No interim analysis will be performed for this study.

### **3.8.10 Safety Analyses**

All safety endpoints will be summarized for all subjects in the Safety set.

### **3.8.11 Adverse Events**

Adverse events will be summarized by treatment group and overall. Events that occur after a subject provides informed consent but before the time of the first dose of study drug will be considered "pretreatment AEs." Treatment-emergent AEs are defined as events that are newly occurring or worsening from the time of the first dose of study drug through the FU Visit.

The total number of subjects experiencing any event will be summarized by body system and preferred term. At each level of summarization, a subject will be counted once if the subject reports 1 or more events at that level. Separate summaries will be presented for all AEs, treatment-related AEs, SAEs, and TEAEs. In the case of duplicate preferred terms for a

subject, the most severe case will be reported in the severity table and related will be reported if any of the duplicate preferred terms for a subject are assessed as related.

In the event that only a partial end date (month/year) is available, and the month/year occurs before Day 1 of the study, the AE will not be considered treatment-emergent. However, if the onset date is a partial date (month/year) and the month/year occurs on or after Day 1 of the study, the following cases will be considered:

- If the month/year of the onset date is later than the month/year of Day 1 of the study, the AE will be considered treatment-emergent.
- If the month/year of the onset date is equal to the month/year of Day 1 of the study, and the end date is present, the end date will be used to determine when the AE resolved. If the end date is on or after Day 1 of the study, the AE will be considered treatment-emergent; otherwise, if the AE stopped before Day 1 of the study, then it will not be considered treatment-emergent.
- If the month/year of the onset date is equal to the month/year of Day 1 of the study, and the end date is a partial date, the AE will be considered treatment-emergent.

### **3.8.12 Vital Sign Measurements and Body Temperature**

Vital sign measurements (systolic and diastolic blood pressure [mmHg], heart rate [beats/minute], respiration rate [breaths/minute], and body temperature [°C]) will be summarized and tabulated. The number of subjects with the reported value, mean, median, standard deviation, minimum value, maximum value, and inner quartile percentiles will be reported. Change from baseline by visit will also be reported using the number of subjects with the reported value, mean, median, standard deviation, minimum value, maximum value, and inner quartile percentiles. Subjects with missing data for a given visit will not contribute to the tabulations for that visit.

### **3.8.13 Clinical Laboratory Test Results**

Laboratory test results will be summarized by treatment group and visit for absolute value and changes from baseline. Tables showing shift from baseline will also be presented.

### **3.8.14 Physical Examination Findings**

Changes from Screening in physical examination results will be listed by subject for all subjects in the Safety set. Height and weight will be summarized by reporting the number of subjects evaluated, mean, median, standard deviation, minimum value, maximum value, and inner quartile percentiles. The number of baseline findings and the percentage of subjects with findings will be reported.

### **3.8.15 Concomitant Medications**

Concomitant medications will be categorized and presented using the World Health Organization Anatomical Therapeutic Chemical drug classification system. The number and percentage of subjects using concomitant medications will be summarized by treatment group.

### **3.8.16 Pharmacokinetic Analyses**

Summary statistics will be calculated for the plasma concentration-time data including N, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, maximum, and geometric mean.

Plasma concentration data will be subjected to a separate population PK analysis.

### **3.8.17 Missing Data**

The following rules will be used for handling missing data:

1. Missing data for ECR will be considered Non-responders.
2. Missing data for Clinical Response based on the investigator assessment of signs and symptoms of pneumonia will be considered a Failure in the ITT/ModITT analysis.
3. For each secondary and exploratory efficacy endpoint, missing data will be imputed as the worst possible response. For instance, subjects missing assessment data at either the Early Clinical Response time point or the TOC will be considered as Failures or Non-responders in the ITT/ModITT analysis.
4. Missing values for safety data (except for dates) will not be imputed. Missing or partial dates will be imputed as described in the statistical analysis plan.
5. Failure outcome due to LOE will be carried forward to later time points (i.e., TOC) if the subject discontinues the trial for LOE. These subjects will be considered evaluable if other factors of evaluability are met.

## **4. Investigator's Obligations**

The following administrative items are meant to guide the principal investigator or subinvestigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

### **4.1 Confidentiality**

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject legal representative), except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, the EMA, other applicable regulatory authorities, or the IRB/IEC.

The principal investigator or subinvestigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

### **4.2 Ethics Committee/Institutional Review**

Federal or local regulations and the International Conference on Harmonisation (ICH) guidelines require that approval be obtained from relevant Regulatory bodies and an IRB/IEC before participation of human subjects in research studies. The Ethics Committee, including IRBs and IECs, must be constituted according to the applicable state and federal/local requirements of each participating region. Before the study onset, the protocol, informed consent, and advertisements to be used for subject recruitment and any other written information regarding this study to be provided to the subject or the subject's legal representative must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH E6(R2) will be maintained by the study site and will be available for review by the sponsor or its designee.

All IRB/IEC opinion letters should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title and/or protocol number, and the date approval and/or favorable opinion was granted.

Sites must adhere to all requirements stipulated by their respective IRB/IEC. This may include notification to the IRB/IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting

requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB/IEC, and submission of the investigator's final status report to the IRB/IEC. All IRB/IEC opinion letters and relevant documentation for these items must be provided to the sponsor or its designee.

### **4.3 Subject Consent**

A written informed consent in compliance with US Title 21 of the Code of Federal Regulations (CFR) Part 50, ICH E6(R2), and other applicable regulatory requirements shall be obtained from each subject or where allowed by local regulations, legally authorized representative before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to study sites. If any institution-specific modifications to study-related procedures are proposed or made by the study site, the consent should be reviewed by the sponsor and/or its designee, if appropriate, before IRB/IEC submission. Once reviewed, the consent will be submitted to the applicable IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects or their legally authorized representatives must sign the revised form.

Before recruitment and enrollment, each prospective subject or his/her legally authorized representative will be given a full explanation of the study and allowed to read the approved ICF. Once the principal investigator or subinvestigator is assured that the subject/legal representative understands the implications of participating in the study, the subject/legal representative will be asked to give consent to participate in the study by signing the ICF.

The principal investigator or subinvestigator shall sign the informed consent and provide a copy of the signed informed consent to the subject and/or legal representative. The original form shall be maintained in the subject medical records at the study site.

### **4.4 Study Reporting Requirements**

By participating in this study, the principal investigator or subinvestigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the principal investigator or subinvestigator agrees to submit periodic reports to his/her IRB/IEC in accordance with IRB/IEC requirements. The principal investigator or subinvestigator also agrees to provide the sponsor with an adequate report shortly after completion of the principal investigator's or subinvestigator's participation in the study.

### **4.5 Financial Disclosure and Obligations**

The principal investigators or subinvestigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or



disclosure statements required under US 21 CFR 54. In addition, the principal investigator or subinvestigators must provide to the sponsor a commitment to update promptly this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the sponsor nor CRO is financially responsible for further testing/treatment of any medical condition, which may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor CRO is financially responsible for further treatment of the subject disease.

#### **4.6 Investigator Documentation**

Before beginning the study, the principal investigator will be asked to comply with ICH E6(R2) 8.2, US. 21 CFR 54, European Commission Directive 2001/20/EC and other applicable regulations by providing the following essential documents, including but not limited to:

- An original investigator-signed Investigator Agreement page of the protocol.
- An IRB/IEC-approved informed consent, samples of study site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal representative.
- IRB/IEC approval.
- Form FDA 1572 or equivalent, fully executed, and all updates on a new fully executed Form FDA 1572 (or equivalent).
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. They will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under US. 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- Laboratory certifications and reference ranges for any local laboratories used by the study site, in accordance with US 42 CFR 493 or other applicable requirements.

## **4.7 Study Conduct**

The principal investigator agrees that the study will be conducted according to the principles of ICH E6(R2) and the principles of the World Medical Association Declaration of Helsinki. The principal investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

## **4.8 Data Collection**

### **4.8.1 Case Report Forms and Source Documents**

As part of the responsibilities assumed by participating in the study, the principal investigator or subinvestigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The principal investigator or subinvestigator agrees to maintain complete and accurate eCRFs and source documentation as part of the case histories. These source documents include laboratory reports and original ECGs, and electronic capture will be used to record the study data. The sponsor's representative will supply the eCRF. Refer to the eCRF Completion Guidelines for further details regarding requisite study data.

## **4.9 Adherence to Protocol**

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

## **4.10 Reporting Adverse Events**

By participating in this study the principal investigator or subinvestigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the principal investigator or subinvestigator agrees to submit annual reports to his/her IRB/IEC as appropriate. The principal investigator or subinvestigator also agrees to provide the sponsor with an adequate report shortly after completion of the principal investigator's or subinvestigator's participation in the study.

## **4.11 Investigator's Final Report**

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome, and the sponsor and regulatory authority(ies) with any reports required.

## **4.12 Records Retention**

Essential documents should be retained until at least 2 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 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the principal investigator or subinvestigator/institution as to when these documents no longer need to be retained.

## **4.13 Publications**

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

## **5. Study Management**

### **5.1 External Data Monitoring Groups**

An external data monitoring group (data safety monitoring board) may be employed in this study. In that event, the membership, activities, and responsibilities of the safety monitoring committee will be described in detail in a separate charter document established for this study.

### **5.2 Monitoring**

#### **5.2.1 Monitoring of the Study**

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. The monitor will visit the principal investigator or subinvestigator, other study staff, and the study facility at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the principal investigator or subinvestigator and staff. The monitor will assure that the hospital or clinic facility pharmacy staff maintains appropriate study drug accountability and dose-preparation records. The monitor will confirm the study drugs are stored under appropriate conditions.

All aspects of the study will be carefully monitored by the sponsor or its designee, for compliance with applicable government regulation with respect to ICH E6(R2) and current standard operating procedures.

#### **5.2.2 Inspection of Records**

The principal investigators or subinvestigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to all study records. In the event of an audit, the principal investigator or subinvestigator agrees to allow the sponsor, representatives of the sponsor, the FDA, or other regulatory agency access to all study records.

The principal investigator or subinvestigator should promptly notify the sponsor and CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

### **5.3 Management of Protocol Amendments and Deviations**

#### **5.3.1 Modification of the Protocol**

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its

designee. Amendments to the protocol must be submitted in writing to the principal investigator's or subinvestigator's IRB/IEC and, if applicable, to the appropriate regulatory authorities for approval before subjects can be enrolled into an amended protocol.

### **5.3.2 Protocol Deviations**

The principal investigator, subinvestigator, or designee must document and explain in the subject source documentation any deviation from the approved protocol. The principal investigator or subinvestigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the principal investigator or subinvestigator. A significant deviation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the subject when the subject, principal investigator, or subinvestigator has failed to adhere to significant protocol requirements. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the subject without sponsor approval, or when there is nonadherence to FDA or other applicable regulations and/or ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The monitor will notify the principal investigators or subinvestigators in writing of all deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

## **5.4 Study Termination**

Although the sponsor has every intention of completing the study, it reserves the right to discontinue the study at any time for clinical or administrative reasons or if required by the FDA or other review bodies. Both the sponsor and CRO medical monitors will review the safety of delafloxacin throughout the study. The study may be halted at any time for safety concerns.

## **5.5 Final Report**

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study

reports in marketing applications meet the standards of the ICH Harmonised Tripartite Guideline E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

## 6. References

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## **7. Appendices**

- 7.1 Appendix: Schedule of Events
- 7.2 Appendix: PSI/PORT Score: Pneumonia Severity Index for CAP
- 7.3 Appendix: CURB-65
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## 7.1 Appendix: Schedule of Events

| Assessment or Procedure  | Screening <sup>a</sup> | Treatment Period <sup>b</sup> |         |                |                   |                                 |             | End of Treatment (EOT)/ Early Term <sup>c</sup> | Reminder Contact <sup>d</sup> | Test of Cure (TOC) <sup>e</sup> | Follow-Up (FU) <sup>f</sup> |
|--|------------------------|-------------------------------|---------|----------------|-------------------|---------------------------------|-------------|---|-------------------------------|---------------------------------|-----------------------------|
|  |                        | Study Day(s)                  | -1 to 1 | 1 <sup>a</sup> | Daily while on IV | ECR 96 hrs ± 24 hr <sup>g</sup> | 5 (+ 1 day) |   |                               |                                 |                             |
| Informed consent   | X                      |                               |         |                |                   |                                 |             |   |                               |                                 |                             |
| Demographics, medical, pulmonary, surgical, alcohol and smoking history                                      | X                      |                               |         |                |                   |                                 |             |   |                               |                                 |                             |
| Prior/concomitant medications  | X                      | X                             | X       | X              | X                 | X                               |             | X   |                               |                                 |                             |
| Clinical signs/symptoms CABP <sup>i</sup>  | X                      | X                             | X       | X              | X                 | X                               |             | X   |                               | X                               |                             |
| Investigator assessment of clinical response   |                        |                               |         |                |                   |                                 |             | X   |                               | X                               |                             |
| Assess subject status for switch to oral   |                        |                               |         |                |                   |                                 | X           |   |                               |                                 |                             |
| Vital signs, body temperature, pulse oximetry <sup>j</sup>   | X                      | X                             | X       | X              | X                 | X                               |             | X   |                               | X                               |                             |
| 12-lead electrocardiogram <sup>k</sup>   | X                      |                               |         |                |                   |                                 |             |   |                               |                                 |                             |
| Complete physical examination with height and weight   | X                      |                               |         |                |                   |                                 |             |   |                               |                                 |                             |
| Targeted physical examination <sup>l</sup>   |                        |                               |         | X              |                   |                                 |             | X   |                               | X                               |                             |
| Chest radiograph or CT scan  | X                      |                               |         |                |                   |                                 |             | X <sup>m</sup>                                  |                               | X <sup>m</sup>                  |                             |
| Local laboratory tests for eligibility <sup>n</sup>  | X                      |                               |         |                |                   |                                 |             |   |                               |                                 |                             |
| Pregnancy test <sup>o</sup>  | X                      |                               |         |                |                   |                                 |             | X   |                               | X                               | X                           |
| Clinical laboratory tests (serum chemistry, coagulation <sup>p</sup> , hematology, urinalysis <sup>p</sup> ) | X                      |                               |         | X              |                   |                                 |             | X   |                               | X                               |                             |
| Hepatitis serology   | X                      |                               |         |                |                   |                                 |             |   |                               |                                 |                             |
| Blood culture <sup>q</sup>   | X                      |                               |         |                |                   |                                 |             |   |                               |                                 |                             |
| Respiratory specimen for Gram stain and culture <sup>r</sup>   | X                      | X                             |         |                |                   |                                 |             | X <sup>m</sup>                                  |                               | X                               |                             |
| Determine PORT Risk Class and CURB-65 Score  | X                      |                               |         |                |                   |                                 |             |   |                               |                                 |                             |
| SF-12v2 <sup>®</sup> Health Survey and QoL Questions   |                        | X                             |         |                |                   |                                 |             | X   |                               | X                               | X                           |
| Verify entry criteria  | X                      |                               |         |                |                   |                                 |             |   |                               |                                 |                             |
| <i>Chlamydia/Legionella/Mycoplasma</i> serology  |                        | X <sup>s</sup>                |         |                |                   |                                 |             |   |                               | X                               | X                           |
| Urine antigen testing for <i>L. pneumophila/S. pneumoniae</i>  |                        | X <sup>s</sup>                |         |                |                   |                                 |             |   |                               |                                 |                             |

| Assessment or Procedure                                   | Screening <sup>a</sup> | Treatment Period <sup>b</sup> |                                |                |                   |                                 |             | End of Treatment (EOT)/ Early Term <sup>c</sup> | Reminder Contact <sup>d</sup> | Test of Cure (TOC) <sup>e</sup> | Follow-Up (FU) <sup>f</sup> |
|---|------------------------|-------------------------------|--------------------------------|----------------|-------------------|---------------------------------|-------------|---|-------------------------------|---------------------------------|-----------------------------|
|   |                        | Study Day(s)                  | -1 to 1                        | 1 <sup>a</sup> | Daily while on IV | ECR 96 hrs ± 24 hr <sup>g</sup> | 5 (+ 1 day) |   |                               |                                 |                             |
| Nasopharyngeal and oropharyngeal swabs                    |                        | X <sup>s</sup>                |                                |                |                   |                                 |             |   |                               |                                 |                             |
| Blood sample for procalcitonin                            |                        | X                             |                                |                |                   |                                 |             |   |                               | X                               |                             |
| Study drug administration every 12 ± 2 hours              |                        | X <sup>t</sup>                | X                              | X              | X                 | X                               |             |   |                               |                                 |                             |
| Dispense oral study drug <sup>u</sup>                     |                        |                               |                                |                |                   |                                 | X           |   |                               |                                 |                             |
| Perform drug accountability on returned drug <sup>u</sup> |                        |                               |                                |                |                   |                                 |             | X   |                               |                                 |                             |
| Determine adequate treatment duration                     |                        |                               |                                |                | X <sup>v</sup>    | X <sup>v</sup>                  |             |   |                               |                                 |                             |
| PK blood sample collection                                |                        |                               | X (Day 3 ± 1 day) <sup>w</sup> |                |                   |                                 |             |   |                               |                                 |                             |
| Reminder Contact  |                        |                               |                                |                |                   |                                 |             | X   |                               |                                 |                             |
| Access IXRS to Register Screening                         | X                      |                               |                                |                |                   |                                 |             |   |                               |                                 |                             |
| Randomization by IXRS                                     | X                      |                               |                                |                |                   |                                 |             |   |                               |                                 |                             |
| Register oral switch status in IXRS                       |                        |                               |                                |                |                   |                                 | X           |   |                               |                                 |                             |
| Register completion status in IXRS                        |                        |                               |                                |                |                   |                                 |             | X   |                               |                                 |                             |
| Post treatment medications                                |                        |                               |                                |                |                   |                                 |             |   |                               | X                               | X <sup>x</sup>              |
| Adverse event evaluation <sup>y</sup>                     | X                      | X                             | X                              | X              | X                 | X                               |             | X   |                               | X                               | X                           |

**Abbreviations:** ECR = Early Clinical Response; EOT = End of Treatment; TOC = Test of Cure; FU = Follow-Up; CABP = community-acquired bacterial pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*; CT = Computed tomography, PORT = Patient Outcomes Research Team; CURB-65 = scoring system based on confusion, urea, respiratory rate, blood pressure and age 65 or older; PK = pharmacokinetics; IXRS = interactive voice and web response system.

<sup>a</sup> Screening procedures will occur within the 24 hours prior to the first dose. The first dose may be administered on the same day as Screening. If the first dose is administered the same day as screening, then the assessments listed for Day 1, but which were already completed for Screening will not be repeated.

<sup>b</sup> The total duration of treatment (IV and oral) is 5 days up to 10 days if clinically indicated (minimum 10 doses and up to 20 delafloxacin/delafloxacin placebo doses).

<sup>c</sup> Subjects who prematurely discontinue study drug or are completing treatment on day of visit can have EOT procedures performed that same day or up to 24 hours (+ 4 hours) after the last dose of study drug. Assessments already completed on the same day as the last dose of study drug can serve as EOT procedures and do not need to be repeated. Laboratory tests completed for a routine visit will not be repeated at EOT, if collected within 24 hours of the EOT visit.

<sup>d</sup> A reminder contact will be done 3-9 days after the last dose of study drug. Subjects will receive a telephone call or contact via other interactive method, e.g., text or email, to remind the subject about the upcoming Test-of-Cure Visit.

<sup>e</sup> TOC assessments will be performed 5 to 10 days after the last dose of study drug (see Section 3.3.2 for exception).

<sup>f</sup> All efforts will be made to have subjects return to the clinic for a Follow-up Visit. Telephone contact is permissible for subjects unable, unwilling or not required (see Section 3.3.2) to return to the clinic.

- <sup>g</sup> ECR Visit will occur 96 hours ( $\pm$  24 hours) after the first dose of study drug. Procedures already completed as specified in Sections 3.4.1.3 or 3.4.1.5 do not need to be repeated unless outside the ECR 96-hour ( $\pm$  24 hours) window.
- <sup>h</sup> Last day of IV therapy prior to oral switch. A minimum of 6 delafloxacin/delafloxacin placebo doses of IV study drug must be administered prior to oral switch. Refer to Schedule of Events for that day for assessments/procedures to be completed.
- <sup>i</sup> Clinical signs and symptoms of CABP will be assessed by the investigator using a 4-point severity scale (see Section 3.4.2.1).
- <sup>j</sup> Arterial blood gases can be obtained at Screening if clinically warranted. Body temperature can be measured via different routes and may include oral, rectal, tympanic and axillary. Pulse oximetry will be recorded for all subjects daily while on IV therapy and at ECR, and only if clinically indicated and/or for subjects on supplemental oxygen at Day 5, Day 7, EOT, and TOC. Vital signs should be measured at a consistent time each day while on IV therapy.
- <sup>k</sup> Electrocardiograms will be performed at screening and if clinically indicated as determined by the investigator after screening.
- <sup>l</sup> Targeted physical examinations will be performed during the study to assess changes from baseline parameters, adverse events, and other relevant safety information.
- <sup>m</sup> Will be performed only if lack of efficacy.
- <sup>n</sup> Local laboratory test results of pregnancy, hematology, serum chemistry, coagulation profile and urinalysis obtained within 24 hours before enrollment may be used for screening purposes and to verify entry criteria. Laboratory tests with exclusionary results judged by the investigator as not compatible with the subject's clinical status may be repeated for eligibility purposes once.
- <sup>o</sup> Pregnancy tests to be performed for women of childbearing potential only.
- <sup>p</sup> Urinalysis and coagulation at screening only.
- <sup>q</sup> Two sets of blood cultures will be collected from all subjects at screening. Additional blood cultures will be collected if a previous culture was positive or if clinically indicated after Screening. Rapid test for MRSA identification methods are acceptable to use if *S. Aureus* is identified by the local/regional laboratory.
- <sup>r</sup> All reasonable efforts will be made to obtain a sputum specimen for Gram stain and culture. Other sources of respiratory specimens such as those obtained from bronchoalveolar lavage, protected specimen brush, transtracheal aspirate, and pleural fluid, if available, are acceptable to submit for culture. A Gram stain will be performed on all sputum and transtracheal aspirate samples. Rapid MRSA identification methods are acceptable to use if *S. aureus* is identified by the local/regional laboratory.
- <sup>s</sup> Results are not required prior to dosing. Refer to the laboratory manual for detailed instructions on collection, processing and shipment.
- <sup>t</sup> If the first dose is started late in the day because of screening and eligibility verifications, a 1-time adjustment is allowed for a more customary dosing schedule that is within  $\pm$  4 hours of the normally scheduled second dose. The every-12-hours ( $\pm$  2 hours) dosing schedule is set after the first dose (or dose adjustment).
- <sup>u</sup> Oral study drug treatment can be completed in the hospital or clinic. For subjects discharged to home, dispense study drug. Instruct subjects to bring study drug container(s) (empty and/or full) to the clinic at their next scheduled visit.
- <sup>v</sup> Study drug may be stopped at the discretion of the investigator after completing a minimum of 10 delafloxacin/delafloxacin placebo doses. Criteria for determination of appropriate treatment duration are described in Section 3.4.1.8.1.
- <sup>w</sup> Blood samples for PK analysis will be obtained from subjects at select sites on Day 3 ( $\pm$  1 day) of treatment within the 30 minutes before study drug administration, and at 1.5 and 3 hours after the start of the infusion. Subjects should have received a minimum of 3 consecutive doses of study drug prior to the start of PK sample collection. All time points will have a  $\pm$  10-minute window. Subjects do not need to be fasted before dosing or during PK sample collections.
- <sup>x</sup> See Section 3.4.3.12 for collection of concomitant medications at FU.
- <sup>y</sup> Serious adverse events will be reported per protocol and recorded in the eCRF from the time subject provides informed consent through the FU visit.

## 7.2 Appendix: PSI/PORT Score: Pneumonia Severity Index for CAP

### PSI/PORT Score: Pneumonia Severity Index for CAP

|   | <b>Assigned Points</b> |
|---|------------------------|
| Age (Years)                                     |                        |
| Men   | Age (Years)            |
| Women   | Age (Years) –10        |
| Nursing home resident                           | +10                    |
| Neoplastic disease                              | +30                    |
| Liver disease history                           | +20                    |
| Congestive heart failure history                | +10                    |
| Cerebrovascular disease history                 | +10                    |
| Renal disease history                           | +10                    |
| Altered mental status                           | +20                    |
| Respiratory rate > 29                           | +20                    |
| Systolic blood pressure < 90 mmHg               | +20                    |
| Temperature < 35°C (95°F) or > 39.9°C (103.8°F) | +15                    |
| Pulse > 124                                     | +10                    |
| Arterial pH < 7.35                              | +30                    |
| BUN > 29 mg/dL or urea > 10.9 mmol/L            | +20                    |
| Sodium < 130                                    | +20                    |
| Glucose > 249 (US) or > 13.8 (SI)               | +10                    |
| Hematocrit < 30%                                | +10                    |
| Partial pressure of Oxygen < 60 mmHg*           | +10                    |
| Pleural effusion on x-ray                       | +10                    |

\* An oxygen saturation of less than 90% on pulse oximetry or intubation before admission is also considered abnormal ([Fine 1997](#)).

**Step 1:**

- If the patient is > 50 years of age, assign to risk class II - V and proceed to step 2.
- If the patient is < 50 years of age, but has a history of neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease or liver disease, assign to risk class II - V and proceed to step 2.
- If the patient has an altered mental status, pulse  $\geq$  125/minute, respiratory rate  $\geq$  30/minute, systolic blood pressure  $\leq$  90 mm Hg, or temperature < 35°C or  $\geq$  40°C, assign to risk class II - V and proceed to step 2.
- If none of the above apply, assign to risk class I = low risk.

**Step 2:**

- Assign points based on age, gender, nursing home residence, co-morbid illness, physical examination findings, and laboratory and radiographic findings as listed above.
- Point distribution, score interpretation and suggested disposition based on local standard of care:

| <b>Score</b> | <b>Risk Class</b> | <b>Risk</b> | <b>Disposition</b>                   |
|--------------|-------------------|-------------|--------------------------------------|
| $\leq$ 70    | II                | Low         | Outpatient care                      |
| 71-90        | III               | Low         | Outpatient vs. Observation admission |
| 91-130       | IV                | Moderate    | Inpatient admission                  |
| >130         | V                 | High        | Inpatient admission                  |

Retrieved from <http://www.mdcalc.com/psi-port-score-pneumonia-severity-index-adult-cap/>

### 7.3 Appendix: CURB-65

Each risk factor scores 1 point, for a maximum score of 5:

| <b>CURB-65</b>                                     |               |
|--|---------------|
| <b>Symptom</b>                                     | <b>Points</b> |
| Confusion*   | 1             |
| Urea > 7 mmol/L or BUN > 19 mg/dL                  | 1             |
| Respiratory Rate $\geq$ 30 breaths/min             | 1             |
| Blood Pressure (SBP < 90 mmHG, DBP $\leq$ 60 mmHg) | 1             |
| Age $\geq$ 65 years                                | 1             |

Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure

\*defined as a Mental Test Score of 8 or less, or new disorientation in person, place, or time

Lim W, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377-382.

doi:10.1136/thorax.58.5.377.

## 7.4 Appendix: Child-Pugh Classification of Severity of Liver Disease

### Child-Pugh Classification of Severity of Liver Disease

| Clinical and Biochemical Measurements for<br>Child-Pugh Classification of Severity of Liver<br>Disease <sup>a,b,c</sup> | Points Scored for Increasing<br>Abnormality |         |                       |
|---|---|---------|-----------------------|
|   | 1   | 2       | 3                     |
| Hepatic encephalopathy (grade <sup>d</sup> )  | None  | 1 and 2 | 3 and 4               |
| Ascites   | Absent                                      | Slight  | Moderate <sup>e</sup> |
| Total bilirubin (mg/dL)   | < 2.0                                       | 2.0-3.0 | > 3.0                 |
| Serum albumin (g/dL)  | > 3.5                                       | 2.8-3.5 | < 2.8                 |
| Prothrombin time <sup>f</sup>   |   |         |                       |
| Seconds prolonged over the ULN  | < 4   | 4-6     | > 6                   |
| International normalized ratio  | < 1.7                                       | 1.7-2.3 | > 2.3                 |

Abbreviations: ULN, upper limit of normal.

<sup>a</sup> Pugh RN, Murray-Lyon IM, Dawson JL, et al. *Brit J Surg.* 1973;60(8):646-9.

<sup>b</sup> Lucey MR, Brown KA, Everson GT, et al. *Liver Transpl Surg.* 1997;3(6)628-37.

<sup>c</sup> Classification is based on total points assigned for the degree of encephalopathy, the degree of ascites, the plasma concentrations of bilirubin and albumin, and prothrombin time: Grade A = 5-6 points; Grade B = 7-9 points; Grade C = 10-15 points.

<sup>d</sup> Grading from Trey C, Burns DG, Saunders SJ. *N Engl J Med.* 1966;274(9):473-81.

<sup>e</sup> Moderate or controlled by diuretics.

<sup>f</sup> If there is a discrepancy for the points scored for the seconds prolonged over the ULN and the international normalized ratio, the points scored for the international normalized ratio should be used.



## 7.5 Appendix: Cockcroft-Gault Formula

The Cockcroft-Gault formula for estimating CrCl:

- When serum creatinine (SCr) is measured in mg/dL:

$$\text{CrCl (mL/min)} = \{(140 - \text{age}) \times \text{weight (kg)}\} / 72 \times \text{SCr in mg/dL} (\times 0.85 \text{ if subject is female})$$

- When SCr is measured in  $\mu\text{mol/L}$ :

$$\text{CrCl (mL/min)} = \{(140 - \text{age}) \times \text{weight (kg)} \times [1 - (0.15 \times \text{sex})]\} / (0.814 \times \text{SCr}),$$

where, sex = 0 if male; sex = 1 if female

## 7.6 Appendix: SF-12v2<sup>®</sup> Health Survey

# Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an  in the one box that best describes your answer.

**1. In general, would you say your health is:**

|                            |                            |                            |                            |                            |
|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| Excellent                  | Very good                  | Good                       | Fair                       | Poor                       |
| ▼                          | ▼                          | ▼                          | ▼                          | ▼                          |
| <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |

**2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?**

|  |                    |                       |                        |
|--|--------------------|-----------------------|------------------------|
|  | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|  | ▼                  | ▼                     | ▼                      |

a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....  1.....  2.....  3

b. Climbing several flights of stairs .....  1.....  2.....  3

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**3. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

|  | All of the time            | Most of the time           | Some of the time           | A little of the time       | None of the time           |
|--|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
|  | ▼                          | ▼                          | ▼                          | ▼                          | ▼                          |
| a. <u>Accomplished less</u> than you would like .....                | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| b. Were limited in the <u>kind</u> of work or other activities ..... | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |

**4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

|  | All of the time            | Most of the time           | Some of the time           | A little of the time       | None of the time           |
|--|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
|  | ▼                          | ▼                          | ▼                          | ▼                          | ▼                          |
| a. <u>Accomplished less</u> than you would like .....                  | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |
| b. Did work or other activities <u>less carefully than usual</u> ..... | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |

**5. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?**

| Not at all                 | A little bit               | Moderately                 | Quite a bit                | Extremely                  |
|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| ▼                          | ▼                          | ▼                          | ▼                          | ▼                          |
| <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |

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6. **These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...**

|                 |                  |                  |                      |                  |
|-----------------|------------------|------------------|----------------------|------------------|
| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
| ▼               | ▼                | ▼                | ▼                    | ▼                |

- a. Have you felt calm and peaceful?.....  1.....  2.....  3.....  4.....  5
- b. Did you have a lot of energy? .....  1.....  2.....  3.....  4.....  5
- c. Have you felt downhearted and depressed?.....  1.....  2.....  3.....  4.....  5

7. **During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

|                            |                            |                            |                            |                            |
|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| All of the time            | Most of the time           | Some of the time           | A little of the time       | None of the time           |
| ▼                          | ▼                          | ▼                          | ▼                          | ▼                          |
| <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 | <input type="checkbox"/> 4 | <input type="checkbox"/> 5 |

*Thank you for completing these questions!*

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## 7.7 Appendix: Quality-of-Life Questions

As a result of your infection, in the last 24 hours, have you experienced any difficulties in doing your usual daily activities?

If you answer “yes” to any item, please use the scale provided to tell us how important it has been to you (1 = little difficulty to 5 = tremendous difficulty).

|   | Have you had difficulty doing the following activities?<br>(check one)  | To what extent have you had difficulty?<br>(1 = little difficulty to<br>5 = tremendous difficulty) |
|---|---|--|
| Doing your job<br>(work, childcare,<br>housework, etc.) | <input type="checkbox"/> yes <input type="checkbox"/> no  | 1    2    3    4    5  |
| Earning an<br>income                                    | <input type="checkbox"/> yes <input type="checkbox"/> no<br><br><input type="checkbox"/> not applicable (I do not work) | 1    2    3    4    5  |

## 7.8 Appendix: Definitions of Symptom Intensity

| <b>Symptom (Points)</b>                     | <b>Absent (0)</b>                                      | <b>Mild (1)</b>  | <b>Moderate (2)</b>                                   | <b>Severe (3)</b>   |
|---|--|--|---|---|
| <b>Cough</b>                                | Absence of cough (or to pre-CABP baseline)             | Transient, does not interfere with normal activity     | Frequent, interferes with normal activity or sleep    | Constant, interferes with most or all activities or sleep |
| <b>Dyspnea/<br/>Shortness of<br/>Breath</b> | Absence of dyspnea (or to pre-CABP baseline)           | Dyspnea on exertion (e.g. climbing stairs)             | Dyspnea with normal/routine activities (e.g. walking) | Dyspnea at rest or requiring oxygen therapy               |
| <b>Chest Pain due to<br/>Pneumonia</b>      | 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 activities or sleep |
| <b>Sputum<br/>Production</b>                | Absence of sputum production (or to pre-CABP baseline) | Sputum production rarely causes difficulty or distress | Sputum production often causes difficulty or distress | Constant difficulty with sputum production                |

## 7.9 Appendix: Protocol Amendment 1

The following sections detail the changes made to the original protocol dated 03 September 2015.

### 7.9.1 Overview of Changes

- To allow for the inclusion of PORT Risk Class V subjects in the study.
- Added exclusion criterion to specify restrictions associated with use of linezolid: known uncontrolled arterial hypertension, pheochromocytoma, carcinoid thyrotoxicosis and restrictions associated with use of moxifloxacin (regional labeling): lactose intolerance, lactase deficiency and glucose-galactose malabsorption.
- Revised to reflect that local laboratory results should be obtained within the 24 hours prior to first dose of study drug to verify entry criteria in order to more accurately assess the subject's clinical condition at time of enrollment.
- To clarify that oropharyngeal and nasopharyngeal specimens may include culture and/or PCR.
- Revised to reflect CRP samples will not be collected.
- Clarified that local/regional laboratory results will be used for patient care.
- It was clarified that systemic steroid use during the treatment period is allowed for a short duration (e.g., steroid burst). Inhaled steroids are allowed without any restriction.
- Treatment regimens clarified.
- Description of delafloxacin was updated to be consistent with the Investigator Brochure.
- The statistical analysis section was revised to reflect that a shift table will be not used to analyze change from baseline for physical exam findings. Worsening from baseline will be captured as adverse events.

### 7.9.2 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the protocol text are shown in **bold** and deletions are shown in ~~strikethrough~~ text. Minor editorial and grammatical corrections are not specified. Any notes for the section are included in brackets.

#### *Title Page – Sponsor Contact*

~~Assistant~~ Director of Clinical Operations

***Title Page – Version of Protocol***15 December ~~September~~ 2015***Title Page – Previous Date and Version – [text added]***

03 September 2015, Original

***Protocol Synopsis – Study Population***

Adult male and female subjects 18 years of age or older with clinical and radiographic evidence of CABP and a Pneumonia Patient Outcomes Research Team (PORT) risk class of II, III, ~~or~~ IV, **or V** (Pneumonia Severity Index [PSI] score > 50 ~~and~~  $\leq 130$ ).

***Protocol Synopsis – Inclusion criterion 4 and Section 3.2.1 Inclusion Criteria***

PORT risk class of II, III, ~~or~~ IV, **or V** PSI score (~~51 to 130, inclusive~~ **greater than 50**). Subjects may be initially screened based on meeting CURB-65 score of 2 to 4. PORT risk class II will be limited to 25% of randomized subjects.

***Protocol Synopsis – Exclusion criterion 11 and Section 3.2.2 Exclusion Criterion 11 corrected***

11. Severe renal disease or creatinine clearance (CrCl)  $\leq 29$  mL/min using Cockcroft-Gault formula or need for hemodialysis or peritoneal dialysis.

***Protocol Synopsis – Exclusion criterion 22 and Section 3.2.2 Exclusion Criterion – added***

**Patients with known uncontrolled hypertension, pheochromocytoma, carcinoid thyrotoxicosis; and rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.**

***Subsequent exclusion criteria renumbered.***

***Protocol Synopsis – Study Design and Section 3.1 Study Design***

Subjects may be initially screened based on meeting CURB-65 score of 2 to 4, but will be eligible for enrollment only if classified as PORT Risk Class II, III, ~~or~~ IV, **or V**. A pretreatment sputum specimen will be collected for Gram stain and culture and susceptibility testing, if positive. Blood samples for procalcitonin ~~C-reactive protein~~, and serology will be obtained at Day 1 as well as nasopharyngeal and oropharyngeal swabs for **culture and/or** polymerase chain reaction (PCR) testing and urine samples for antigen testing.



***Protocol Synopsis – Criteria for Evaluation: Definitions***

**Presumed Eradication:** No sputum sample was available at TOC with a clinical assessment of Success.

**Persistence:** The sputum and/or blood culture collected at the EOT-TOC visit shows appearance of all causative pathogen(s) at enrollment.

***Protocol Synopsis – Microbiologic Measures***

The causative pathogen will be identified by isolation from a baseline specimen (either a sputum specimen or blood), by urinary antigen (*S. pneumoniae* and *L. pneumophila*), and/or serology and/or PCR (*L. pneumophila* and *M. pneumoniae*).

***Protocol Synopsis – Date of Final Protocol***

~~03 September~~ 15 December 2015

***List of Abbreviations***

|                        |  |
|------------------------|--|
| CRP                    | C-reactive protein [ <del>deleted</del> ]  |
| IXVRS/ <del>IWRS</del> | Interactive voice response system and Interactive web response system<br>web response system |
| RBC                    | Red blood cell [ <del>added</del> ]  |

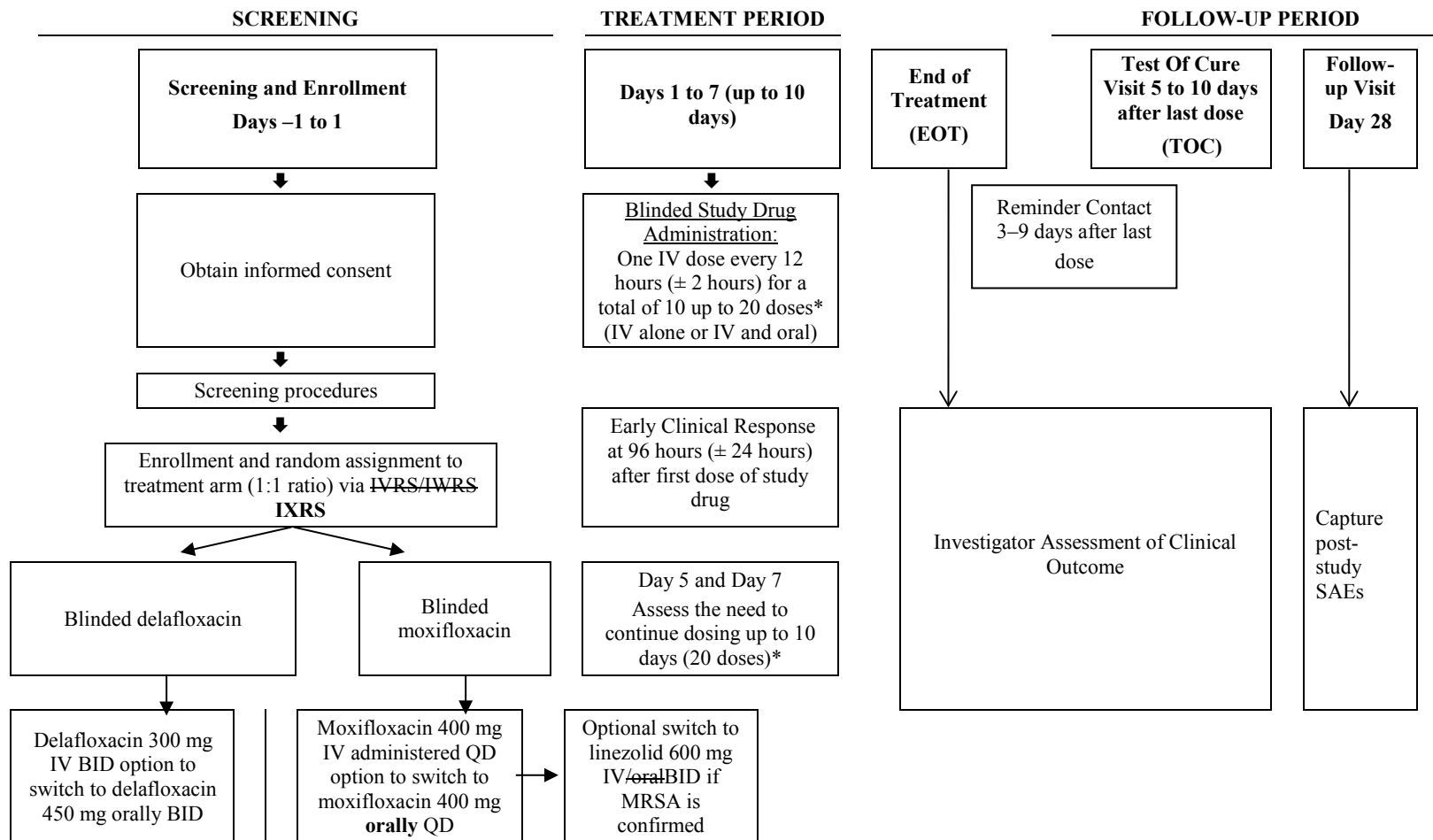
***Section 1.1.3 In Vivo Studies***

Against *S. pneumoniae* 5649, a multidrug-resistant strain, delafloxacin demonstrated a dose of ~~vaccine~~ required to protect 50% (PD<sub>50</sub>) of < 5.0 mg/kg/day, whereas levofloxacin and trovafloxacin resulted in PD<sub>50</sub>s of 12.9 and 10.2 mg/kg/day, respectively.

***Section 1.2.1 Pharmacokinetics, Safety, and Tolerability of IV and Oral Delafloxacin***

Single doses ranging from 50 ~~to~~ from 1200 mg were assessed for safety, tolerability, and pharmacokinetics (PK) in 5 Phase 1 studies with 4 different IV formulations. In the RX-3341-108 study (Rib-X Study RX-3341-108), a maximum tolerated dose (MTD) for single IV administration was 900 mg given over 1 hour.

**Figure 3-1 Schematic of Study Design**



\* delafloxacin/delafloxacin placebo doses Abbreviations: EOT = End of Treatment; TOC = Test of Cure; ~~IVRS/IWRS~~IXRS = interactive voice ~~and-response-system~~/interactive web response system; IV = intravenous; BID = every 12 hours; QD = every 24 hours; MRSA = methicillin-resistance *Staphylococcus aureus*

**Table 3-1 Treatment Regimens**

Changes to previously bolded text are italicized.

|                       | Regimens Given  | Subjects randomized to delafloxacin   | Subjects randomized to moxifloxacin  |
|-----------------------|---|---|--|
| WHILE ON IV THERAPY   | IV regimen given with blinding covers   | IV active delafloxacin twice daily  | IV active moxifloxacin once daily, alternative with IV placebo to maintain blind for BID dosing  |
|                       | If linezolid is prescribed during IV dosing period  | Continue IV active delafloxacin twice daily   | Discontinue IV moxifloxacin/ <b>placebo</b> and begin IV active linezolid twice daily  |
|                       |   |   |  |
| WHILE ON ORAL THERAPY | Delafloxacin  | Oral active delafloxacin twice daily and  | Oral placebo delafloxacin twice daily and  |
|                       | Moxifloxacin  | Oral placebo moxifloxacin once daily  | Oral active moxifloxacin once daily  |
|                       | If linezolid is prescribed for MRSA in moxifloxacin subjects ( <i>a partial switch back to IV applies</i> ) | Oral placebo moxifloxacin will be discontinued ( <b>oral delafloxacin continues</b> ) and subjects randomized to delafloxacin will receive IV placebo linezolid twice daily | Oral active moxifloxacin will be discontinued and subjects randomized to moxifloxacin will receive IV active linezolid twice daily <b>and continue oral placebo delafloxacin twice daily</b> |

**Section 3.2 Selection of Study Sample**

At least 860 male and female subjects, 18 years of age or older, with clinical and radiographic evidence of CABP and a pneumonia Patient Outcomes Research Team (PORT)

risk class of II, III, ~~or~~ IV, **or V** (pneumonia severity index score [PSI] **greater than 50–130 inclusive**) will be enrolled in the study.

### ***Section 3.2.2 Exclusion Criterion 9***

Severely compromised immune ~~symptoms~~ system, e.g.: .....

### ***Section 3.4.1 Study Visits***

..... Subjects may be treated as hospitalized inpatients or outpatients in accordance with local treatment guidelines for moderate to severe CABP, provided that all study-drug infusions are administered by study-site personnel or hospital staff **who that** have been trained on protocol specifics and the Sponsor-approved study drug-blinding plan.

#### ***Section 3.4.1 Screening – bullet one***

- Access interactive voice ~~response system/interactive~~ **and** web response system (~~IVRS/IWRS IXRS~~) to register screening.

#### ***Section 3.4.1 Screening – bullet 10***

- Obtain blood samples for hematology, serum chemistry, and coagulation profile and urine sample for urinalysis (the results of any of these tests obtained within ~~48~~ **24** hours of enrollment, may be used for screening purposes and to verify entry criteria by the local laboratory; however, blood and urine samples must be obtained at Screening (prior to the first dose) and sent to the central laboratory for analysis to serve as baseline values.

#### ***Section 3.4.1.2 Day 1 – bullet 7***

- Obtain blood samples for ~~C-reactive protein (CRP)~~, procalcitonin, and *Mycoplasma pneumoniae* and *L. pneumophila* serology.

#### ***Section 3.4.1.5 Day 5 – bullet 10***

- Subjects who continue **oral** treatment **as an outpatient** will be dispensed/administered study drug and instructed to return to the clinic on Day 7 with their study drug container(s).

#### ***3.4.1.8.1 Criteria for Determining Treatment Duration***

After completing 5 days of treatment (minimum of 10 doses of delafloxacin/delafloxacin placebo), the investigator will assess the subject for clinical response to treatment to determine adequate treatment duration. The following suggested criteria can be used to assess clinical response; however, the duration of therapy should be individualized based upon the

subject's clinical response to treatment and comorbidities up to a maximum treatment of 10 days (**20 delafloxacin/delafloxacin placebo doses**).

**Section 3.4.1.10 TOC Visit (5–10 Days after Last Dose of Study Drug) – bullet 9**

- Obtain blood samples for *M. pneumoniae* and *L. pneumophila* serology, ~~CRP~~, and procalcitonin.

**Section 3.4.1.11 Follow-up Visit (Day 28 ± 2 Days)**

All efforts will be made to have subjects return to the clinic for a Follow-up visit. Telephone contact is permissible for subjects unable, ~~or~~ unwilling **or not required (see Section 3.3.2)** to return to the clinic. The following procedures will be performed at the Follow-up Visit on Day 28 (± 2 days).

**Section 3.4.3 Study Assessments**

The following assessments will be performed to collect data needed for this research study. It is expected that the investigator and hospital staff will follow the usual standard of patient care **and that local/regional laboratory results will be used to manage patient care.**

**Section 3.4.3.2 Microbiological Assessments**

The following pathogens are examples of primary pathogens that will be used to determine the microbiological responses in the study: the typical bacterial pathogens include *S. pneumoniae*, *H. influenzae*, *S. aureus*, *Klebsiella pneumoniae*, and *Moraxella catarrhalis* and the atypical bacterial pathogens *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. The causative pathogen will be identified by isolation from a baseline specimen (either a sputum specimen or blood), by urinary antigen, **and/or** ~~*S. pneumoniae*, *L. pneumophila*~~ serology **and/or PCR. The residual sputum sample and/or nasopharyngeal swabs may be sent to specialty laboratories for culture and/or PCR (*S. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*).** Respiratory and blood specimens will be sent to local/regional/specialty laboratories for culture, microorganism identification, and antibiotic sensitivity testing and will be processed according to standard recognized methods (Garcia 2010, Murray 2007). **Sites will use local/regional culture results for patient management. The Two Gram stain slides of the sputum specimen will be prepared by performed at the local/regional laboratories. One slide will be stained and read locally. Both slides, read and unread, will be sent to the central laboratory to confirm results. An additional Gram stain slide may will be retained by the local microbiology laboratory, if required by local regulations.** Culture will be performed at local or regional laboratories, as applicable. Rapid MRSA identification methods are acceptable to use if *S. aureus* is identified by the

local/regional laboratory. Isolates **that are** not considered contaminants will be forwarded to the central microbiology laboratory for confirmation of identity and antimicrobial susceptibility testing and any further molecular or phenotypic characterization (e.g., PCR for Panton-Valentine leukocidin and *mecA* genes, pulsed-field gel electrophoresis). Specific handling and shipping instructions that will maintain viability of all organisms will be provided in the laboratory manual. A duplicate sample of the isolate(s) (from all sources) submitted to the central microbiology laboratory will be maintained (in frozen state) by the local laboratory **or sent to the central laboratory** until the conclusion of the study. Directions for collection, processing and handling of specimen are included in the laboratory manual.

#### ***Section 3.4.3.2.1 Respiratory Culture***

All respiratory specimens will be sent for culture and susceptibility testing. Other sources of respiratory specimens such as those obtained from bronchoalveolar lavage (BAL), protected specimen brush (PSB), transtracheal aspirate, and pleural fluid, if available, are acceptable to submit for culture. In addition, a residual respiratory sample will be frozen and **may be** sent to a specialty lab for culture, antibiotic sensitivity testing, and/or serotyping.

#### ***Section 3.4.3.2.3 Urine Antigen Testing***

Urine samples will be obtained for *L. pneumophila* and *S. pneumoniae* urine antigen testing at baseline. ~~The test kits will be provided by the sponsor and will be analyzed by the local/regional laboratory.~~

#### ***Section 3.4.3.2.4 Nasopharyngeal and Oropharyngeal Testing***

Nasopharyngeal swabs will be obtained at baseline for *S. pneumoniae* PCR analysis and/or *S. pneumoniae* culture and serotyping. Oropharyngeal swabs will be obtained at baseline for *Mycoplasma* culture and/or PCR antibiotic susceptibility testing at specialty microbiology laboratories.

#### ***Section 3.4.3.5 Clinical Laboratory Tests***

**Other Chemistry:** ~~CRP and~~ Procalcitonin.

**Hematology:** A hematology panel will be taken to include complete blood count with hematocrit, hemoglobin, platelet count, red blood cell count (**RBC**), **RBC morphology and** mean corpuscular volume, and white blood cell count with differential.

**Urinalysis:** A urine panel will be taken at screening to include pH, specific gravity, leukocytes, nitrite, **leukocyte esterase**, protein, urobilinogen, bilirubin, blood, glucose, and a microscopic examination. The urine samples will be analyzed by a central laboratory.

### ***Section 3.4.3.7 Vital Sign Measurements***

Subjects who require pressor support should have regular blood pressure monitoring as per local standard of care.

### ***Section 3.4.3.10 Health-Related Quality-of-Life Assessment***

This survey will be completed at baseline, EOT, TOC, and FU based on availability of the validated survey in local language.

### ***Section 3.6.1 Method of Assigning Subjects to Treatment Groups***

Each subject will be randomly assigned in a 1:1 ratio to delafloxacin or moxifloxacin treatment group.

The investigator or designee will enter the enrollment information in ~~IVRS/IWRS~~ **IXRS**. The unblinded pharmacist or unblinded designee will obtain the treatment assignment by the ~~IVRS/IWRS~~ **IXRS** as described in the ~~study operations~~ **IXRS** manual.

### ***Section 3.6.3 Description of Investigational Product***

Delafloxacin

Delafloxacin for Injection, 300 mg/vial, is a light-yellow to tan-colored lyophilized ~~cake~~ **powder provided in a 20 mL clear borosilicate glass vial**. Each vial contains **the following ingredients:** 433**2.9** mg delafloxacin meglumine equivalent of 300 mg free acid, 58.56 mg meglumine, 2400 mg sulfobutyl ether sodium beta cyclodextrin (Captisol®), and **2.6 mg** ethylene-diamine-tetra-acetate disodium (as ~~2.6~~ **EDTA, amount as acid**) ~~and water for injection~~. It may also contain hydrochloric acid and/or sodium hydroxide for pH adjustment. ~~When reconstituted with Sterile Water for Injection, USP, it forms a clear yellow to amber colored solution with a pH of 9.0, which will be further diluted into IV infusion bags.~~

After reconstitution in the vial, the drug concentration is 25 mg/mL in an aqueous solution of 12.4 mL (0.4 mL as overage).

The delafloxacin tablet formulation consists of delafloxacin as the free acid in a traditional wet granulation of drug substance with commonly used excipients and a blend of basic buffering agents. Each tablet contains the following ingredients: delafloxacin meglumine; povidone, as a binder; crospovidone as a disintegrant; microcrystalline cellulose as a filler; sodium bicarbonate; sodium phosphate monobasis; and citric acid for buffering effect; and

magnesium stearate as a lubricant. The modified capsule shaped, single-layer tablet is beige with tan spots, with “RX3341” embossed on 1 side.

Oral delafloxacin is a capsule-shaped tablet in beige color with tan spots (delafloxacin particles) and with RX3341 debossed on one side. Each tablet contains the following ingredients: 649.35 mg delafloxacin meglumine equivalent of 450-mg free acid; cellulose; povidone; crospovidone; sodium bicarbonate; sodium phosphate; citric acid; and magnesium stearate. For more information on the description of delafloxacin, refer to the Investigator’s Brochure (Melinta IB 2015).

#### ***Section 3.6.4.1 Study Drug Packaging and Storage***

Moxifloxacin (400 mg) for IV use is intended to be provided in glass bottles **or infusion bags as local availability allows**. Moxifloxacin (400 mg) over-encapsulated tablets are intended to be supplied in daily dose bottles.

.....

Additional study drug will be supplied as needed based on information provided via the IVRS/TWRS-IXRS.

#### ***Section 3.6.4.3 Blinding***

.....

Certain clinical research ~~associate~~ staff will not be blinded in order to monitor the pharmacy, administer study drug (if applicable), and monitor study administration records and will not reveal a subject’s treatment assignment to study staff. The statistician who creates the randomization code will not be involved otherwise in the conduct of the study.

#### ***..... Bullet 3***

- Subjects in the moxifloxacin treatment arm will receive once-daily active IV therapy alternating doses of IV moxifloxacin and IV placebo ~~every 12 hours (± 2 hours)~~ **BID**.

#### ***Section 3.6.7 Allowed Concomitant Treatment – [added text] Paragraph 2***

.....

**Systemic steroid use during the treatment period is allowed for a short duration (e.g., steroid burst). Inhaled steroids are allowed without any restriction.**

#### ***Section 3.7.2.2 Clinical Outcome at EOT and TOC***

**Indeterminate/Missing:** A response cannot be determined because an efficacy assessment was not completed at the visit. Indeterminate/missing responses will be considered failures



for purposes of the **primary** ITT analysis and will be excluded from the CE and ME analysis populations.

### ***Section 3.8.5 Subgroup Analyses of the Primary Endpoint – bullet one***

- Demographic subgroups: age categories (age  $\leq$  65,  $>$  65,  $>$  75), gender, BMI categories (BMI  $<$  30 and  $\geq$  30), baseline PORT score, ~~prior systemic antimicrobial use~~, baseline CURB-65 Score, ethnicity, and race categories.

### ***Section 3.8.14 Physical Examination Findings***

Changes from Screening in physical examination results will be listed by subject for all subjects in the Safety set. Height and weight will be summarized by reporting the number of subjects evaluated, mean, median, standard deviation, minimum value, maximum value, and inner quartile percentiles. The number of baseline findings and the percentage of subjects with findings will be reported. ~~A shift table will be provided for each of the body categories to report findings that represent changes from the baseline condition at each visit.~~

### ***Section 3.8.17 Missing Data – Number 5- [text added]***

5. Failure outcome due to LOE will be carried forward to later time points (i.e., TOC) if the subject discontinues the trial for LOE. These subjects will be considered evaluable **if other factors of evaluability are met.**

### ***IVRS/IWRS changed to IXRS in the following sections:***

Section 3.4.1.1 Screening – bullet 16

Section 3.4.1.5 Day 5 – bullet 9

Section 3.4.1.6 Day 7 – bullet 8

Section 3.4.1.7 End of IV treatment – bullet 4

Section 3.4.1.8.2 End of treatment or Early Termination Procedures – bullet 13

Section 3.6.5 Breaking the Blind – Paragraph one

Section 7.1 Appendix: Schedule of Events

### ***Section 7 Appendices***

7.1 Appendix: Schedule of Events

7.2 **Appendix: PSI/PORT Score: Pneumonia Severity Index for CAP [added]**

7.3 Appendix: CURB-65

- 7.4 Appendix: Child-Pugh Classification of Severity of Liver Disease
- 7.5 Appendix: Cockcroft Gault Formula
- 7.6 Appendix: SF-12v2® Health Survey
- 7.7 Appendix: Quality-of-Life Questions
- 7.7 **Appendix: Protocol Amendment 1 – [added]**

**Section 7.1 - Appendix: Schedule of Events [changed table cells are shaded gray]**

| Assessment or Procedure                | Screening <sup>a</sup> |                | Treatment Period <sup>b</sup> |                                |              |             |                        | End of Treatment (EOT)/ Early Term <sup>c</sup> | Reminder Contact <sup>d</sup> | Test of Cure (TOC) <sup>e</sup> | Follow-Up Visit <sup>f</sup> |
|--|------------------------|----------------|-------------------------------|--------------------------------|--------------|-------------|------------------------|---|-------------------------------|---------------------------------|------------------------------|
|  |                        |                | Daily while on IV             | 96 hr ± 24 hr <sup>g</sup> ECR | 5 (±± 1 day) | 7 (± 1 day) | End of IV <sup>h</sup> |   |                               |                                 |                              |
| Study Day(s)                           | -1 to 1                | 1 <sup>a</sup> |                               |                                |              |             |                        |   |                               | 5 to 10 days after last dose    | 28 (± 2 days)                |
| .....                                  |                        |                |                               |                                |              |             |                        |   |                               |                                 |                              |
| Blood sample for procalcitonin and CRP |                        | X              |                               |                                |              |             |                        |   |                               | X                               |                              |

**Schedule of Events – Abbreviations**

**Abbreviations:** ECR = Early Clinical Response; EOT = End of Treatment; TOC = Test of Cure; CABP = community-acquired bacterial pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*; CT = Computed tomography, PORT = Patient Outcomes Research Team; CURB-65 = scoring system based on confusion, urea, respiratory rate, blood pressure and age 65 or older; ~~CRP = C reactive protein~~; PK = pharmacokinetics; ~~IVRS/IXRS~~ **IXRS** = interactive web response system.

**Schedule of Events – footnote n**

<sup>n</sup> Local laboratory test results of pregnancy, hematology, serum chemistry, and coagulation profile and urinalysis obtained within 48 24 hours of enrollment may be used for screening purposes and to verify entry criteria by the local laboratory. Laboratory tests with exclusionary results judged by the investigator as not compatible with the subject’s clinical status may be repeated for eligibility purposes once.

**7.2 Appendix: PSI/PORT Score: Pneumonia Severity Index for CAP [added]**

**PSI/PORT Score: Pneumonia Severity Index for CAP**

|  | <b>Assigned Points</b> |
|--|------------------------|
| <b>Age (Years)</b>                                     |                        |
| <b>Men</b>   | <b>Age (Years)</b>     |
| <b>Women</b>   | <b>Age (Years) –10</b> |
| <b>Nursing home resident</b>                           | <b>+10</b>             |
| <b>Neoplastic disease</b>                              | <b>+30</b>             |
| <b>Liver disease history</b>                           | <b>+20</b>             |
| <b>Congestive heart failure history</b>                | <b>+10</b>             |
| <b>Cerebrovascular disease history</b>                 | <b>+10</b>             |
| <b>Renal disease history</b>                           | <b>+10</b>             |
| <b>Altered mental status</b>                           | <b>+20</b>             |
| <b>Respiratory rate &gt; 29</b>                        | <b>+20</b>             |
| <b>Systolic blood pressure &lt; 90 mmHg</b>            | <b>+20</b>             |
| <b>Temperature &lt; 35C (95F) or &gt; 39C (103.8F)</b> | <b>+15</b>             |
| <b>Pulse &gt; 124</b>                                  | <b>+10</b>             |
| <b>Arterial pH &lt; 7.35</b>                           | <b>+30</b>             |
| <b>BUN &gt; 29</b>                                     | <b>+20</b>             |
| <b>Sodium &lt; 130</b>                                 | <b>+20</b>             |
| <b>Glucose &gt; 249 (US) or 13.8 (SI)</b>              | <b>+10</b>             |
| <b>Hematocrit &lt; 30%</b>                             | <b>+10</b>             |
| <b>Partial pressure of Oxygen &lt; 60 mmHg</b>         | <b>+10</b>             |
| <b>Pleural effusion on x-ray</b>                       | <b>+10</b>             |

**Step 1:**

- **If the patient is >50 years of age, assign to risk class II - V and proceed to step 2.**
- **If the patient is <50 years of age, but has a history of neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease or liver disease, assign to risk class II - V and proceed to step 2.**
- **If the patient has an altered mental status, pulse  $\geq 125$ /minute, respiratory rate  $\geq 30$ /minute, systolic blood pressure  $\leq 90$  mm Hg, or temperature  $< 35^\circ$  C or  $\geq 40^\circ$  C, assign to risk class II - V and proceed to step 2**
- **If none of the above apply, assign to risk class I = low risk.**

**Step 2:**

- **Assign points based on age, gender, nursing home residence, co-morbid illness, physical examination findings, and laboratory and radiographic findings as listed above.**
- **Suggested disposition based on local standard of care:**

| Score     | Risk          | Disposition                          |
|-----------|---------------|--------------------------------------|
| $\leq 70$ | Low risk      | Outpatient care                      |
| 71-90     | Low risk      | Outpatient vs. Observation admission |
| 91-130    | Moderate risk | Inpatient admission                  |
| $>130$    | High risk     | Inpatient admission                  |

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**Downloaded 28/November 2015 <http://www.mdcalc.com/psi-port-score-pneumonia-severity-index-adult-cap/>**

## 7.10 Appendix: Protocol Amendment 2

The following sections detail the changes made to the Amendment 1 of the protocol dated 15 December 2015.

### 7.10.1 Overview of Changes

- Revised inclusion criterion 2 as follows, to be consistent with the draft guidance for industry “Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment”
  - removed “...or a change in the character of the sputum,” from, “Production of purulent sputum or a change in the character of the sputum consistent with a bacterial infection”
  - separated out the vital sign abnormalities from the other clinical signs and laboratory abnormalities
- Revised exclusion criterion 1 to include exclusion of medical history of significant hypersensitivity or allergic reaction to study drug excipients in the judgment of the investigator.
- Revised exclusion criterion 4 to include criteria for documenting treatment failure based on clinical evidence and not pulmonary imaging alone.
- Revised exclusion criterion 12 to include exclusion of known uncorrected hypomagnesemia at study entry.
- Revised the primary efficacy endpoint definition of improvement to include no worsening of any of the other CABP symptoms as described in the references provided in the draft guidance for industry document.
- Modified the suggested criteria for IV to oral switch to improved stability if vital sign indices, e.g. no worsening.
- Revised the Responders definition to include no worsening of other symptoms.
- The Nonresponders definition was revised to further clarify that additional antimicrobial treatment of the current CABP infection would only meet the Nonresponders definition if the reason for treatment was due to lack of efficacy.
- The Failure definition was revised to clarify that additional antimicrobial treatment of the current CABP infection would only meet the Failure definition if the reason for treatment was due to lack of efficacy.

- Indeterminate/Missing definition was revised to clarify that a response could not be determined if the subject did not complete the planned course of study therapy for reason other than lack of efficacy.
- Clarified that if ever utilized, any potential sample size recalculation would be based on pooled information across the 2 treatment arms.
- Added a table that includes the definitions of symptom intensity ranging from absent (0 points), to mild (1), moderate (2), and severe (3).

### 7.10.2 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the protocol text are shown in **bold** and deletions are shown in ~~strikethrough~~ text. Minor editorial and grammatical corrections are not specified. Any notes for the section are included in brackets.

#### *Title Page – Version of Protocol*

~~15 December 2015~~–29 March 2016

#### *Title Page – Previous Date and Version – [text added]*

15 December 2015, Amendment 1

#### *Protocol Approval Page – Protocol Date*

~~15 December 2015~~ 29 March 2016

#### *Protocol Synopsis – Inclusion criterion 2 and Section 3.2.1 Inclusion Criteria*

2. Evidence of acute onset of CABP.

Subjects must have at least ~~2~~ **3** of the following clinical signs and symptoms (new or worsening):

- Cough
- Production of purulent sputum ~~or a change in the character of the sputum~~ consistent with a bacterial infection
- Difficulty breathing (dyspnea)
- Chest pain due to pneumonia

**AND**

Subjects must also have at least 2 of the following findings:

- Fever (oral temperature  $> 38^{\circ}\text{C}$  or equivalent) within 24 hours prior to randomization
- Hypothermia (oral temperature  $< 35^{\circ}\text{C}$  or equivalent) within 24 hours prior to randomization
- Tachycardia ( $> 100$  beats per minute)
- Tachypnea (elevated respiratory rate  $> 18$  breaths per minute)

**AND**

Subjects must also have **at least 1 of the following findings:**

- Hypoxemia (oxygen saturation  $< 90\%$  or  $\text{PaO}_2 < 60$  mmHg on room air or with subject's baseline [pre-CABP under study] supplemental oxygen flow rate)
- Clinical evidence of pulmonary consolidation and/or presence of pulmonary rales
- An elevated white blood cell count (WBC)  $> 10,000/\text{mm}^3$  or 15% immature neutrophils (bands), regardless of total peripheral WBC count or leukopenia with  $\text{WBC} < 4500/\text{mm}^3$

***Protocol Synopsis – Exclusion criterion 1 and Section 3.2.2 Exclusion criterion 1***

Medical history of significant hypersensitivity or allergic reaction to antibiotics of the quinolone or oxazolidinone class **or study drug excipients** in the judgment of the investigator.

***Protocol Synopsis – Exclusion criterion 4 and Section 3.2.2 Exclusion Criterion 4:***

4. Receipt of systemic antibiotic therapy in the 7 days before enrollment unless one of the following is documented:
  - The subject received at least 48 hours of antibiotic therapy for CABP **and** the clinic notes ~~or pulmonary imaging~~ document treatment failure (i.e., not by patient history **or pulmonary imaging alone**) ~~and/or isolation of a resistant pathogen~~ **with new or worsening signs or symptoms have developed while on pre-study therapy or identification of a respiratory pathogen that is resistant to a pre-study antibiotic, which would be susceptible to study drug (delafloxacin or moxifloxacin) in subjects with new or worsening signs and symptoms of CABP.**



- The subject received 1 dose of a single, potentially effective, short-acting antimicrobial drug or a short-acting antimicrobial drug regimen for treatment of the CABP under study within 24 hours of enrollment. (Note: 1 dose of a regimen is defined as the standard therapy for CABP at the study site.) Subjects who received prior antimicrobial drug under this criterion will be limited to no more than 25% of total randomized subjects.

***Protocol Synopsis – Exclusion criterion 12 and Section 3.2.2 Exclusion criterion 12***

12. Uncorrected hypokalemia or **known uncorrected hypomagnesemia** at time of enrollment.

***Protocol Synopsis – Efficacy Endpoints and Section 3.7.1.1 Primary Efficacy Endpoint***

Primary Efficacy Endpoint: The primary efficacy endpoint is the ECR defined as improvement at 96 hours ( $\pm$  24 hours) after first dose of study drug in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum and difficulty breathing **and no worsening of any of the other symptoms** in the ITT population.

***Protocol Synopsis – Criteria for Evaluation: Definitions and 3.7.2 Endpoint Definitions***

For Early Clinical Response: [Section 3.7.2.1]

Responders: Improvement at 96 hours ( $\pm$  24 hours) after first dose of study drug in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum, and difficulty breathing **and no worsening in the other symptoms**.

Nonresponders: Improvement is not achieved at 96 hours ( $\pm$  24 hours) after the first dose of study drug in at least 2 of the following symptoms (chest pain, frequency or severity of cough, amount and quality of productive sputum, and difficulty breathing); or there is use of additional nonstudy antimicrobial therapy for **treatment of the current CABP infection due to lack of efficacy**; or the subject dies from the current CABP infection.

For Clinical Outcome at EOT and TOC: [Section 3.7.2.2]

Failure: Symptoms of CABP present at study entry have not resolved, or new symptoms have developed, or the subject dies from pneumonia, or use of additional nonstudy antimicrobial therapy **for treatment of the current CABP infection due to lack of efficacy**.

Subjects must receive at least 4 doses **of study drug** by the end of Day 3 to be called a Failure.

Indeterminate/Missing: A response cannot be determined because an efficacy assessment was not completed at the visit, ~~including~~ or subjects ~~who~~ **did not complete the planned course of study therapy for reasons other than lack of efficacy.**

***Protocol Synopsis – Date of Final Protocol***

~~15 December 2015~~ 29 March 2016

***3.4.1.7 End of IV Treatment***

After a minimum of 6 delafloxacin/delafloxacin placebo doses, subjects can switch to oral treatment if, in the past 24 hours, the subject meets the following suggested criteria for switch to oral treatment:

- Is able to ingest intact large tablets capsules,
- Has a normally functioning gastrointestinal tract, and
- Is clinically stable, ~~and~~ has improved stability of vital sign indices, such as, no worsening from entry vital signs.

~~Does not have more than 2 of the following findings:~~

- ~~○ Oral temperature higher than 37.5°C (or equivalent)~~
- ~~○ Respiratory rate greater than 24 breaths per minute~~
- ~~○ Systolic blood pressure 90 mmHg or lower~~
- ~~○ Oxygen saturation under 90% or PaO<sub>2</sub> < 60 mmHg on room air (or with subject's pre-CABP under study supplemental oxygen flow rate)~~
- ~~Abnormal mental status~~

***3.4.2.1 Clinical Evaluation***

The following signs and symptoms of CABP will be assessed and evaluated:

- Pleuritic chest pain
- Frequency or severity of cough
- Dyspnea
- Sputum production (if present, change in character and quantity from baseline and purulence)

Symptom severity will be evaluated by the investigator on a 4-point scale (absent, mild, moderate, severe) with improvement defined as at least a 1-point improvement from baseline to the assessment at 96 hours ( $\pm$  24 hours) after first dose of study drug (e.g., from severe to moderate, from moderate to mild, or from mild to absent). **See Appendix 7.8 for definitions of symptom intensity.**

#### ***Section 3.7.4 Sample Size Calculations***

At least 860 adult male and female subjects (430 subjects per treatment group) will be randomized. Use on a normal approximation approach (Miettinen and Nurminen's Likelihood Score Test), 860 subjects in the ITT population will provide a 90% power to assess noninferiority of delafloxacin vs. moxifloxacin based on the following assumptions: (1) a rate of Early Clinical Response for moxifloxacin therapy and delafloxacin of 77% and 74%, respectively; (2) 1-sided type I error ( $\alpha$ ) of 0.025; (3) a noninferiority margin of 12.5%. As Early Clinical Response is a new endpoint as new information arises (without unblinding the study) that informs sample size, this information may be used to reassess sample size. **If ever utilized, any potential sample size recalculation would be based on pooled information across the 2 treatment arms.**

#### ***Section 7 Appendices***

- 7.1 Appendix: Schedule of Events
- 7.2 Appendix: PSI/PORT Score: Pneumonia Severity Index for CAP [added]
- 7.3 Appendix: CURB-65
- 7.4 Appendix: Child-Pugh Classification of Severity of Liver Disease
- 7.5 Appendix: Cockcroft Gault Formula
- 7.6 Appendix: SF-12v2® Health Survey
- 7.7 Appendix: Quality-of-Life Questions
- 7.8 *Appendix: Symptom Severity Definitions – [added]***
- 7.9 Appendix: Protocol Amendment 1
- 7.9 *Appendix: Protocol Amendment 2 – [added]***

#### ***Section 7.1 Appendix: Schedule of Events***

Added footnote “y” to Screening Adverse Event Evaluation cell to clarify that serious adverse events will be reported per protocol and recorded in the eCRF.

***Section 7.1 Appendix: Schedule of Events – footnote ‘f’***

[Footnote ‘f’ was revised to include “not required” as a reason for telephone contact by follow-up.]

All efforts will be made to have subjects return to the clinic for a Follow-up Visit. Telephone contact is permissible for subjects unable, or unwilling **or not required** to return to the clinic.

***Section 7.8 Appendix Definitions of Symptom Intensity [added]***

| <b>Symptom</b>                     | <b>Absent (0)</b>   | <b>Mild (1)</b>   | <b>Moderate (2)</b>  | <b>Severe (3)</b>  |
|------------------------------------|---|---|--|--|
| <b>Cough</b>                       | <b>Absence of cough (or to pre-CABP baseline)</b>             | <b>Transient, does not interfere with normal activity</b>     | <b>Frequent, interferes with normal activity or sleep</b>    | <b>Constant, interferes with most or all activities or sleep</b> |
| <b>Dyspnea/Shortness of Breath</b> | <b>Absence of dyspnea (or to pre-CABP baseline)</b>           | <b>Dyspnea on exertion (e.g. climbing stairs)</b>             | <b>Dyspnea with normal/routine activities (e.g. walking)</b> | <b>Dyspnea at rest or requiring oxygen therapy</b>               |
| <b>Chest Pain due to Pneumonia</b> | <b>Absence of chest pain related to CABP</b>                  | <b>Transient, does not interfere with normal activity</b>     | <b>Frequent, interferes with normal activity or sleep</b>    | <b>Constant, interferes with most or all activities or sleep</b> |
| <b>Sputum Production</b>           | <b>Absence of sputum production (or to pre-CABP baseline)</b> | <b>Sputum production rarely causes difficulty or distress</b> | <b>Sputum production often causes difficulty or distress</b> | <b>Constant difficulty with sputum production</b>                |

## 7.11 Appendix: Protocol Amendment 3

Amendment 3 is a global amendment which applies to all study sites, and all changes made in global Amendments 1 and 2, and in Administrative Change Numbers 1, 2, and 3 are incorporated into this amendment. The following sections detail the changes made in Amendment 3 of the protocol, dated 04 December 2017.

### 7.11.1 Overview of Changes

- Administrative Change Number 1: to clarify that the procedures of chest radiography and clinical laboratory collection are to be performed prior to the first dose of study drug.
- Administrative Change Number 2: to clarify that all screening procedures are to be performed in the 24 hour period prior to the first dose of study drug (unless otherwise noted).
- Administrative Change Number 3:
  - To add serology testing for Chlamydia at Day 1, TOC, and Follow-up
  - In the PSI/PORT scoring appendix, to correct a minor discrepancy in Temperature, add a converted value from BUN to urea, and add the Risk Class to the scoring table.
  - To add a converted value from urea to BUN in the CURB-65 scoring appendix.
- Primary and secondary objectives and endpoints, sample size calculations, populations and analyses were clarified for EMA submissions.
- Clarifications were added to Inclusion 4 and Exclusions 4, 5, and 12.
- Timing of vital signs was updated at all visits after first dose to clarify that they may be performed at any time, but should be consistent each day.
- The window for the Day 7 (oral treatment) visit was updated from  $\pm 1$  day to + 1 Day so it would not coincide with the Day 5 (oral treatment) visit.
- Procedures at the EOT and TOC visits were updated to clarify that a CXR or CT scan is also required to be done only for lack of efficacy.
- General references to “sputum specimens” were changed to “respiratory specimens” throughout the protocol to clarify that other types of samples are accepted.
- PK sections were updated to specify endpoints and analyses to be performed.
- The Post-Treatment Medications section was updated to clarify which data should be recorded in the eCRF.

- The Adverse Events section was updated to clarify the required time period to record data in the CRF and to note that progression of disease under study is not recorded as an AE.
- All references to ICH guideline E6(R1): Good Clinical Practice were updated to (R2) to align with global regulatory requirements.
- Abbreviations were added or exchanged for text throughout the protocol as per the List of Abbreviations. These are not detailed in [Section 7.11.2](#).
- In-text citations and Section 6 References were updated to align with APA style. These are only detailed in [Section 7.11.2](#) if a new or revised reference was added.
- Minor grammatical and formatting changes were made throughout the text. These are only detailed in [Section 7.11.2](#) if they altered the content of the protocol.

### 7.11.2 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the protocol. Additions to the protocol text are shown in **bold** and deletions are shown in ~~strikethrough~~ text. Minor editorial and grammatical corrections are not specified. Any notes for the section are included in brackets [ ].

***Title Page – CONFIDENTIAL, Sections 4.2 - Ethics Committee/Institutional Review, 4.3 - Subject Consent, 4.6 - Investigator Documentation, 4.7 - Study Conduct, 4.9 - Adherence to Protocol, 5.2.1 - Monitoring of the Study, 5.3.2 - Protocol Deviations***

[All references to the International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1): Good Clinical Practice in the above listed sections were updated]

E6(R~~1~~2)

#### ***Title Page – Sponsor Contact***

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Director of Clinical Operations

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#### ***Title Page – Version of Protocol***

Amendment ~~2~~3

***Title Page – Date of Protocol***

~~29~~ ~~March~~ ~~December~~ ~~2016~~ **2017**

***Title Page – Previous Date and Version [text added]***

**29 March 2016, Amendment 2**

***Title Page – CONFIDENTIAL***

...

The study will be conducted according to the International Conference on Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice, FDA and EU clinical trial guidelines. **(Sites in regions which have not yet implemented the E6(R2) addendum are subjecting themselves to it voluntarily.)**

***Protocol Approval***

Protocol Date: ~~29~~ ~~March~~ ~~December~~ ~~2016~~ **2017**

Protocol accepted and approved by:

Sue Cammarata, MD

Chief Medical Officer

Melinta Therapeutics, Inc.

~~300 George Street~~ **TriState International**, Suite ~~301~~ **272**

~~New Haven, CT~~ **Lincolnshire, IL 60069**, USA

***Protocol Synopsis – Objectives*****FOR FDA****Primary Objective:**

- To assess the ~~noninferiority~~ clinical efficacy of intravenous (IV) to oral delafloxacin in adult subjects with community-acquired bacterial pneumonia (CABP) based on Early Clinical Response (ECR) defined as improvement at 96 hours ( $\pm$  24 hours) after the first dose of study drug compared to IV to oral moxifloxacin in the Intent-to-Treat (ITT) population.

...

**Secondary Objective(s):**

...

- To assess the ~~noninferiority~~ clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on ECR compared to IV to oral moxifloxacin in the microbiologic ITT (MITT) population.

...

**FOR EMA****Primary Objective:**

- **To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at 5 to 10 days after the last dose of study drug (TOC) compared to IV to oral comparator study drug arm in the Modified ITT (ModITT) and Modified CE (ModCE) populations.**

**Secondary Objective(s):**

- **To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on ECR defined as improvement at 96 hours ( $\pm$  24 hours) after the first dose of study drug compared to IV to oral moxifloxacin in the ModITT and ModCE populations.**
- **To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at the TOC visit compared to IV to oral moxifloxacin in the Modified MITT (ModMITT) and Modified ME (ModME) populations.**
- **To assess the microbiologic response to delafloxacin in respiratory pathogens in the ModMITT and ModME populations.**
- **To assess the safety and tolerability of IV to oral delafloxacin in adult subjects with CABP in safety population.**
- **To assess the all-cause mortality in adult subjects with CABP on Day 28 in ModITT.**
- **To assess delafloxacin PK in adult subjects with CABP in PK population.**



***Protocol Synopsis – Inclusion Criteria***

4. PORT Risk Class of II, III, IV, or V (PSI Score greater than 50) (Fine 1997) (Appendix 7.2). Subjects may be initially **pre**-screened based on meeting CURB-65 Score (Appendix 7.3) of 2 to 4. PORT Risk Class II will be limited to **no more than 25%** of randomized subjects.

***Protocol Synopsis - Exclusion Criteria***

4. Receipt of systemic antibiotic therapy in the 7 days before enrollment unless one **or more** of the following ~~is~~**are** documented:  
...
5. Respiratory infection confirmed or suspected to be secondary to hospital-acquired or ventilator-associated pneumonia or that requires treatment in an intensive care setting **(because they are hemodynamically unstable, and/or likely to need mechanical ventilation)** at the time of informed consent.
12. Uncorrected hypokalemia, or known uncorrected hypomagnesemia, at **the** time of enrollment. **If treatment normalizes the serum potassium or magnesium, confirmed by retest during the screening period, the patient may then be enrolled.**

***Protocol Synopsis - Study Design***

...

Subjects will be evaluated for baseline characteristics that include chest radiography within 48 hours ~~of~~**before** the first dose of study drug, and medical history, physical examination, ~~and~~ clinical laboratory evaluation, and blood cultures within 24 hours ~~of~~**before** the first dose of study drug. Subjects may be initially **pre**-screened based on meeting CURB-65 score of 2 to 4, but will be eligible for enrollment only if classified as PORT Risk Class II, III, IV, or V. A pretreatment **respiratory** specimen will be collected for Gram stain and culture and susceptibility testing, if positive.

...

Randomization will be stratified by PORT Class, medical history of chronic obstructive pulmonary disease (COPD)/asthma, and prior **single-dose/regimen** systemic antimicrobial use. Enrollment will be limited to no more than 25% PORT Class II and no more than 25% of subjects ~~with prior antibacterial use~~**who received 1 dose of a single, potentially effective, short-acting antimicrobial drug or drug regimen for treatment of the CABP under study within 24 hours of enrollment.**

...

The investigator may elect to switch subjects from moxifloxacin/moxifloxacin placebo to

linezolid (600 mg **IV** BID)/**linezolid placebo** if methicillin-resistant *Staphylococcus aureus* (MRSA) is confirmed (up to 10 days total moxifloxacin and linezolid duration of therapy).

...

Key visits will be **ECR** at (96 hours ( $\pm$  24 hours) after the **start of the** first dose of study drug, ~~at~~ End of Treatment (EOT), and ~~at~~ TOC, **5-10 days after last dose**. A Follow-up (FU) Visit **or phone contact** will **also** be conducted **at Day 28** ~~to collect patient reported outcomes, capture serious adverse events, obtain a blood sample for convalescent serology and urine or serum pregnancy testing, if applicable.~~

### ***Protocol Synopsis - Pharmacokinetic Assessments***

Serial blood samples for PK analysis will be obtained at select investigative sites on Day 3 ( $\pm$  1 day) of treatment within **the** 30 minutes before ~~the first~~ study drug administration ~~of the day~~ and at 1.5 and 3 hours after the start of the infusion. All time points will have a  $\pm$  10 minute window. Subjects should have received a minimum of 3 consecutive doses of study drug prior to the start of **PK** blood collection. Subjects do not need to be fasted before dosing or during PK sample collections.

### ***Protocol Synopsis - Sample Size***

**FOR FDA PRIMARY ENDPOINT:** At least 860 adult male and female subjects (430 subjects per treatment group) will be randomized.

...

**FOR EMA PRIMARY ENDPOINT:** At least 860 adult male and female subjects (430 subjects per treatment group) will be randomized. Used on a normal approximation approach (Miettinen and Nurminen's Likelihood Score Test), and assuming approximately 12% of patients will be in PORT Class II, and 80% of patients will be clinically evaluable, 755 subjects in the ModITT population and 604 subjects in the ModCE population will provide, respectively, a power of 91% and 83% to assess noninferiority of delafloxacin vs. moxifloxacin based on the following assumptions: (1) a rate of Clinical Outcome at the TOC visit for moxifloxacin and delafloxacin of 88% and 86%, respectively; (2) 1-sided type I error ( $\alpha$ ) of 0.025; (3) a noninferiority margin of 10%.

***Protocol Synopsis - Efficacy Endpoints*****FOR FDA**

...

Primary Efficacy Endpoint: ~~The primary efficacy endpoint is the~~ ECR defined as improvement at 96 hours ( $\pm$  24 hours) after first dose of study drug in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum, and difficulty breathing, and no worsening ~~of in any of the other~~ symptoms in the ITT population.

...

**FOR EMA**

All the primary and secondary endpoints will be analyzed for noninferiority with the possibility to switch to superiority.

**Primary Efficacy Endpoint: The Clinical Outcome responder rate at 5 to 10 days after the last dose of study drug (TOC) defined as resolution or near resolution of the symptoms of CABP present at study entry, and no use of additional antimicrobial therapy for the current infection, and no new symptoms associated with the current CABP infection (success) in the ModITT and ModCE populations.**

**Secondary Efficacy Endpoint(s):**

- **ECR defined as improvement at 96 hours ( $\pm$  24 hours) after first dose of study drug in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum and difficulty breathing and no worsening of any of the other symptoms in the ModITT and ModCE populations**
- **ECR with the addition of improvement in vital signs and no worsening of the 4 symptoms required as Response in the ModITT and ModCE populations**
- **Clinical Outcome at EOT (ModITT and ModCE)**
- **Clinical Outcome at TOC in the ModMITT and ModME populations**
- **Microbiologic response (ModMITT and ModME)**
- **All-cause mortality (ModITT)**

***Protocol Synopsis - Pharmacokinetic Endpoints***

~~Pharmacokinetic results will be reported in a separate PK report. The time course of~~ **delafloxacin plasma concentrations will be assessed.**

***Protocol Synopsis - Analysis Populations***

...

**Modified ITT (ModITT): All randomized subjects who received at least one dose of study medication, classified as PORT Class III-V, analyzed according to the treatment arm to which they were randomized.**

**Microbiological ITT (MITT): All subjects in the ITT population who had a baseline bacterial pathogen **identified** on culture of ~~sputum~~ **respiratory specimen** or blood **specimen**, or a nonculture method of detection of bacterial pathogens (i.e., urinary antigen test, PCR, and serologic testing) ~~identified~~ that is known to cause CABP against which the study drug has antibacterial activity.**

**Modified MITT (ModMITT): All subjects in the MITT population classified as PORT Class III-V.**

Clinically Evaluable (CE): All subjects in the ITT population who met the following criteria:

...

- Received 80% of the expected doses of study drug in the treatment period (e.g., ~~for subjects receiving delafloxacin,~~ at least 11 doses of delafloxacin for a 7-day treatment period).

...

**Modified CE (ModCE): All subjects in the CE population classified as PORT Class III-V.**

...

**Modified ME (ModME): All subjects in the ME population classified as PORT Class III-V.**

Pharmacokinetic (PK): All subjects who receive at least 3 consecutive IV doses of study drug prior to the start of the blood sample collections on Day 3 ( $\pm$  1 Day), and have ~~sufficient plasma concentration data to facilitate calculation of PK parameters~~ **at least one delafloxacin plasma concentration data available**. The PK population will be used for PK analyses.

***Protocol Synopsis - Criteria for Evaluation - Definitions***

For Early Clinical Response:

Responders: Improvement at 96 hours ( $\pm$  24 hours) after first dose of study drug in at least 2 of the following symptoms: **pleuritic** chest pain, frequency or severity of cough, amount and quality of productive sputum, and **dyspnea** (difficulty breathing), and no worsening ~~in~~ of the other symptoms.

Non-responders: Improvement is not achieved at 96 hours ( $\pm$  24 hours) after first dose of study drug in at least 2 of the following symptoms: ~~(pleuritic~~ chest pain, frequency or severity of cough, amount and quality of productive sputum, and **dyspnea** (difficulty breathing); or there is use of additional non-study antimicrobial therapy for treatment of the current CABP infection due to lack of efficacy; or the subject ~~dies~~d from the current CABP infection. Indeterminate/missing assessments will be mapped to Non-responders in the statistical analysis of the ITT population.

Symptoms for the Early Clinical Response will be evaluated on a 4-point scale (absent, mild, moderate, severe) with improvement defined as at least a 1-point improvement (**decrease**) from baseline to the assessment at 96 hours ( $\pm$ 24 hours) after the first dose of study drug (e.g., from severe to moderate, from moderate to ~~absent~~mild, or from mild to absent).

For Clinical Outcome at EOT and TOC:

Success: Resolution or near resolution of the symptoms of CABP present at study entry, and no use of additional antimicrobial therapy for the current infection, and no new symptoms **associated with the current CABP infection**.

Failure: Symptoms of CABP present at study entry have not resolved, or new symptoms **of CABP** have developed, or the subject ~~dies~~d from pneumonia, or use of additional non-study antimicrobial therapy for treatment of the current CABP infection due to lack of efficacy. Subjects must receive at least 4 doses of study drug by the end of Day 3 to be called a Failure.

Indeterminate/Missing: A response cannot be determined because an efficacy assessment was not completed at the visit, or subject did not complete the planned course of study therapy for reasons other than lack of efficacy. Indeterminate/missing responses will be considered failures for purposes of the primary ITT/**ModITT** analyses and will be excluded from the CE and ME populations.

For Microbiologic Response

Eradication: The ~~sputum~~**respiratory and/or blood specimen** at the TOC Visit shows all causative pathogen(s) at enrollment eradicated and no use of additional antimicrobial therapy for the current infection.

Presumed Eradication: No ~~sputum~~**respiratory and/or blood sample**specimen was available at TOC with a clinical assessment of Success.

Persistence: The ~~sputum~~**respiratory and/or blood culture-collected**specimen at the TOC visit shows appearance of ~~all~~causative pathogen(s) **present** at enrollment.

Presumed Persistence: No ~~sputum~~ **respiratory and/or blood sample specimen** was available for a case classified as clinical failure.

Superinfection: A culture taken during treatment shows appearance of a new pathogen causing respiratory infection associated with clinical failure.

**Colonization/Contamination: A culture taken post-baseline through the TOC visit shows appearance of a new pathogen(s), with a clinical assessment of Success and no use of additional antimicrobial therapy for the current infection.**

### *Protocol Synopsis - Microbiologic Measures*

The following pathogens are examples of primary pathogens that will be used to determine the microbiological responses in the study: the typical bacterial pathogens include **but may not be limited to** *Streptococcus pneumoniae*, *Haemophilus influenzae*, *S. aureus*, *Klebsiella pneumoniae*, and *Moraxella catarrhalis*, and the atypical bacterial pathogens *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*. The causative pathogen will be identified by isolation from a baseline **culture** specimen (either a ~~sputum~~ **respiratory** specimen or blood), by urinary antigen, ~~and/or~~ **by** serology, and/or by PCR.

### *List of Abbreviations*

|                |   |
|----------------|---|
| <b>CLSI</b>    | <b>Clinical Laboratory Standards Institute</b>                    |
| <b>CV</b>      | <b>Coefficient of variation</b>                                   |
| <b>EUCAST</b>  | <b>European Committee on Antimicrobial Susceptibility Testing</b> |
| <b>ModCE</b>   | <b>Modified clinically evaluable</b>                              |
| <b>ModITT</b>  | <b>Modified intent-to-treat</b>                                   |
| <b>ModME</b>   | <b>Modified microbiologically evaluable</b>                       |
| <b>ModMITT</b> | <b>Modified microbiological intent-to-treat</b>                   |
| <b>QSSP</b>    | <b>Quinolone-susceptible <i>S.treptococcus pneumoniae</i></b>     |
| <b>SD</b>      | <b>Standard deviation</b>   |

### *Section 1.1.2 - In Vitro Studies - Comparative Antibacterial Activity*

In a recent survey of 2014 US and European isolates, delafloxacin's MIC50 and MIC90 were 0.008 µg/mL and 0.015 µg/mL, respectively for *S.treptococcus pneumoniae*.

...

### ***Section 1.1.3 - In Vivo Studies***

...

Against *S. pneumoniae* 5649, a multidrug-resistant strain, delafloxacin demonstrated a dose required to protect 50% (PDED<sub>50</sub>) of < 5.0 mg/kg/day, whereas levofloxacin and trovafloxacin resulted in PDED<sub>50</sub>s of 12.9 and 10.2 mg/kg/day, respectively. Against *H. influenzae*, all compounds were highly efficacious in this rat lung-infection model, with delafloxacin, levofloxacin, and trovafloxacin demonstrating PDED<sub>50</sub>s of 2.1, 6.9, and 5.9 mg/kg/day, respectively.

### ***Section 1.2.2 - Phase 2 Study for Community-Acquired Pneumonia: Study M01-344***

...

The primary endpoint of this trial was the investigators' assessment of clinical response rate at the TOC time point in the **Clinically Evaluable (CE)** group.

...

**Table 1-1** Proportion of Patients Achieving Endpoints in (Study M01-344)

**Table 1-2** Target Pathogen Eradication Rates at the TOC Visit (Study M01-344)

### ***Section 1.2.3 - Treatment of Acute Bacterial Skin and Skin Structure Infections: Study RX-3341-302***

**Table 1-3** Proportion of Patients Achieving Endpoints in (Study RX-3341-302)

### ***Section 1.3 - Dose Selection of Delafloxacin for This Study***

- Delafloxacin has shown evidence of efficacy in a completed phase 2 community-acquired pneumonia (CAP) trial (M01-344 [Abbott 2003]). In addition, a phase 2 trial in acute bacterial exacerbation of chronic bronchitis (M01-298 [Abbott 2003]) and 2 phase 2 ABSSSI trials (studies RX-3341-201 [Rib-X 2009] and RX-3341-202 [Rib-X 2014]) provide evidence of efficacy of delafloxacin in these indications.
- Delafloxacin has shown evidence of efficacy in a completed Phase 3 ABSSSI trial (RX-3341-302 [Melinta 2015]) using the intended 300 mg IV BID dose.
- Delafloxacin has been well tolerated at the 300 mg IV BID dose used in 2 phase 2 ABSSSI trials (studies RX-3341-201 [Rib-X 2009] and RX-3341-202 [Rib-X 2014]) and 1 Phase 3 ABSSSI trial (study RX-3341-302).

***Section 2.1 - Primary Objective [table format added]***

The primary objective is:

| FDA   | EMA  |
|---|--|
| To assess the <del>noninferiority</del> of clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on Early Clinical Response (ECR) defined as improvement at 96 hours ( $\pm$ 24 hours) after the first dose of study drug compared to IV to oral moxifloxacin in the ITT population. | <b>To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at 5 to 10 days after the last dose of study drug (TOC) compared to IV to oral comparator study drug arm in the Modified ITT (ModITT) and Modified CE (ModCE) populations.</b> |

***Section 2.2 - Secondary Objective(s) [table format added]***

The secondary objectives are:

| FDA   | EMA   |
|---|---|
| To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on clinical outcome at the TOC visit, 5 to 10 days after the last dose of study drug compared to IV to oral comparator study drug arm in the CE and ITT populations. | <b>To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on ECR defined as improvement at 96 hours (<math>\pm</math> 24 hours) after the first dose of study drug compared to IV to oral moxifloxacin in the ModITT and ModCE populations.</b> |
| To assess the <del>noninferiority</del> of clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on ECR compared to IV to oral moxifloxacin in the <b>Microbiological ITT (MITT)</b> population  | <b>To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at the TOC visit compared to IV to oral moxifloxacin in the Modified MITT (ModMITT) and Modified ME (ModME) populations.</b>  |
| To assess the microbiologic response to delafloxacin in respiratory pathogens.  | <b>To assess the microbiologic response to delafloxacin in respiratory pathogens in the ModMITT and ModME populations.</b>  |



| <b>FDA</b>   | <b>EMA</b>  |
|--|---|
| To assess the safety and tolerability of IV to oral delafloxacin in adult subjects with CABP | <b>To assess the safety and tolerability of IV to oral delafloxacin in adult subjects with CABP in safety population.</b> |
| To assess the all-cause mortality in adult subjects with CABP on Day 28                      | <b>To assess the all-cause mortality in adult subjects with CABP on Day 28 in ModITT population.</b>                      |
| To assess delafloxacin PK in adult subjects with CABP  | <b>To assess delafloxacin PK in adult subjects with CABP in PK population.</b>  |

***Section 3.1 - Study Design***

This is a Phase 3, randomized, double-blind, comparator-controlled, multicenter, global study. Subjects who consent to the study will have screening procedures performed. Subjects will be evaluated for baseline characteristics that include chest radiography within 48 hours ~~of~~ **before** the first dose of study drug, and medical history, physical examination, clinical laboratory evaluation, and blood cultures within 24 hours ~~of~~ **before** the first dose of study drug. Subjects may be initially **pre**-screened based on meeting CURB-65 score of 2 to 4, but will be eligible for enrollment only if classified as Pneumonia Patient Outcomes Research Team (PORT) Risk Class II, III, IV or V. A pretreatment ~~sputum~~ **respiratory** specimen will be collected for Gram stain and culture, and susceptibility testing, if positive.

...

Subjects who meet the entry criteria will be randomly assigned in a 1:1 ratio to receive delafloxacin or moxifloxacin. Randomization will be stratified by PORT Class, medical history of COPD/asthma, and prior **single-dose/regimen** systemic antimicrobial use. Enrollment will be limited to no more than 25% PORT Class II and no more than 25% of subjects ~~with prior antibacterial use~~ **who received 1 dose of a single, potentially effective, short-acting antimicrobial drug or drug regimen for treatment of the CABP under study within 24 hours of enrollment.**

...

The investigator may elect to switch subjects from moxifloxacin/moxifloxacin placebo to linezolid (600 mg **IV** BID)/ **linezolid placebo** if MRSA is confirmed (up to 10 days total moxifloxacin and linezolid duration of therapy).

***Section 3.2.1 - Inclusion Criteria***

- Evidence of acute onset of CABP.

...

- Tachypnea (elevated respiratory rate > 18 **breaths** per minute)
4. PORT Risk Class of II, III, IV, or V (PSI Score greater than 50) (Fine 1997) (Appendix 7.2). Subjects may be initially **pre**-screened based on meeting CURB-65 Score (Appendix 7.3) of 2 to 4. PORT Risk Class II will be limited to **no more than** 25% of randomized subjects.

### ***Section 3.2.2 - Exclusion Criteria***

4. Receipt of systemic antibiotic therapy in the 7 days before enrollment unless one **or more** of the following ~~is~~**are** documented:
- ...
5. Respiratory infection confirmed or suspected to be secondary to hospital-acquired or ventilator-associated pneumonia or that requires treatment in an intensive care setting **(because they are hemodynamically unstable, and/or likely to need mechanical ventilation)** at the time of informed consent.
12. Uncorrected hypokalemia, or known uncorrected hypomagnesemia, at **the** time of enrollment. **If treatment normalizes the serum potassium or magnesium, confirmed by retest during the screening period, the patient may then be enrolled.**

### ***Section 3.3.2 - Handling of Withdrawals***

Subjects who discontinue study drug and receive a non-study antibiotic for CABP will have EOT visit procedures performed with clinical assessment, but will not return for further on-site visits. Additional specimens for microbiological cultures and ~~chest radiograph~~**CXR** should be collected before initiation of any rescue therapy and/or if the subject is a clinical failure, if possible. **These subjects should be contacted by phone for the FU visit.**

Subjects who discontinue study drug and do not receive additional non-study antibiotic for CABP will have EOT visit procedures performed and should return to the site for the TOC and FU visits. ~~Every attempt will be made to collect all cause mortality data on Day 28 for all subjects who receive at least 1 dose of study drug.~~ [sentence moved below]

Should a subject's study participation be discontinued after receiving study drug, efforts must be made to perform all required EOT procedures with corresponding data recorded in the electronic case report form (eCRF). **Subjects who prematurely discontinue study treatment should be encouraged to return to the study site for these safety evaluations.** ~~Subjects who withdraw consent will not be contacted after withdrawal.~~ [sentence moved below]

**Every attempt will be made to contact all subjects who received at least 1 dose of study drug to collect all-cause mortality data on Day 28 (FU visit). Subjects who withdraw consent will not be contacted after withdrawal.**

...

#### ***Section 3.4.1.1 - Screening***

Screening **procedures** will occur ~~within~~ **the 24 hours of prior to the first dose of study drug.**

...

- Obtain posteroanterior (PA) and lateral ~~chest radiograph (CXR)~~. A CT scan of the thorax is an acceptable alternative, if available **per local standard of care**. The CXR or CT scan obtained per local standard of care will not be repeated if obtained within 48 hours ~~of~~ **before the first dose of study drug.**

...

- Obtain blood samples for hematology, serum chemistry, and coagulation profile and urine sample for urinalysis. The results of any of these tests obtained within 24 hours ~~of~~ **before** enrollment may be used for screening purposes and to verify entry criteria by the local laboratory; however, blood and urine samples must be obtained at Screening (prior to the first dose **of study drug**) and sent to the central laboratory for analysis to serve as baseline values.

#### ***Section 3.4.1.2 - Day 1***

Treatment may begin immediately after enrolling the subject via **the IXRS**. Subjects must begin study drug within 24 hours **after the start** of Screening **procedures**. If the first dose is administered the same day as Screening, then assessments that are required on Day 1, but already completed for Screening, will not be repeated unless otherwise specified below (assessments should be recorded in the Screening eCRF and NOT duplicated in the Day 1 eCRF). If not already performed on that day **as part of the Screening visit**, the following procedures will be performed on Day 1 ~~prior to dosing~~:

...

- Record vital signs, body temperature, and pulse oximetry ~~at~~ **around the time of the first daily dose.**
- Collect deep cough sputum specimen for Gram stain and culture **prior to dosing** if not collected or determined to be not acceptable at Screening (if possible). **Additionally, other respiratory sources are acceptable if available (refer to Section 3.4.3.2.1).**

...

- Obtain blood samples for procalcitonin and *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *L. pneumophila* serology.
- Obtain nasopharyngeal and oropharyngeal swabs **prior to dosing**.
- ...
- Administer second dose of study drug after 12 hours ( $\pm 2$  hours). If the first dose is started late ~~on Day 1~~ **in the day** because of screening and eligibility verifications, a 1-time adjustment is allowed for a more customary dosing schedule that is within  $\pm 4$  hours of the normally scheduled second dose. The every-12-hour ( $\pm 2$  hours) dosing schedule is set after the first dose (or dose adjustment).

#### ***Section 3.4.1.3 - Daily While on IV Therapy***

The following procedures will be performed daily **only** while on IV therapy:

...

- Record vital signs, body temperature, and pulse oximetry at **a consistent time of first daily dose each day**.
- ...
- For sites participating in PK assessments, blood samples for PK analysis will be obtained on Day 3 ( $\pm 1$  day) of treatment within **the** 30 minutes before ~~the first~~ study drug administration, and at 1.5 and 3 hours after the start of the infusion. All time points have a  $\pm 10$ -minute window. Subjects should have received a minimum of 3 consecutive doses of study drug prior to the start of **PK** blood sample collections. Subjects do not need to be fasted before dosing or during PK sample collections. Refer to Section 3.4.3.6 Pharmacokinetic Blood Sample Collections for details.

#### ***Section 3.4.1.4 - Early Clinical Response at 96 Hours ( $\pm 24$ hours)***

- **Subjects who continue oral treatment as an outpatient will be dispensed/administered study drug and instructed to return to the clinic on Day 5 (if applicable) with their study drug container(s).** [bullet 9 added]

#### ***Section 3.4.1.5 - Day 5 (+ 1 Day)***

The assessments that are required on Day 5, but already completed as specified in Section 3.4.1.3 **or** 3.4.1.4 do not need to be repeated. ~~Assessment should be recorded in the Day 5 eCRF and NOT duplicated in the Daily IV eCRF.~~ If not already performed on that day, the following procedures will be performed:

...

- Administer study drug every 12 hours ( $\pm$  2 hours) ~~to total 10 delafloxacin/delafloxacin placebo doses.~~
- Perform study drug accountability on returned **oral** drug (outpatient subjects).
- ...

#### ***Section 3.4.1.6 - Day 7 (+ 1 Day)***

[Section heading updated to change the visit window from  $\pm$  1 Day to **+ 1 Day**.]

**The assessments that are required on Day 7 but already completed as specified in Section 3.4.1.3 do not need to be repeated. If not already performed on that day, the following procedures will be performed:**

- Perform study drug accountability on returned **oral** drug (outpatient subjects).
- ...
- Study drug may be stopped at the discretion of the investigator ~~on Day 7~~. **Subjects may be evaluated and study drug may be administered/dispensed as described above until the subject completes the investigator's planned course of therapy, up to a maximum 10 days of treatment (20 doses delafloxacin/delafloxacin placebo).** Criteria for determination of appropriate treatment duration ~~is~~ are described in Section 3.4.1.8.1. ~~EOT procedures are detailed in Section 3.4.1.8.2.~~
- ...
- Subjects who continue on treatment will be dispensed/administered sufficient quantity of study drug to complete treatment and will be instructed to return to the clinic (outpatient ~~patients~~ subjects) ~~on~~ for the ~~planned EOT day~~ visit (~~Day 8, 9, and/or 10~~) with their study drug container(s).
- ~~Subjects may be evaluated and study drug may be administered/dispensed as described above until the subject completes 10 days of treatment (20 doses delafloxacin/delafloxacin placebo).~~ [moved to bullet above]

#### ***Section 3.4.1.7 - End of IV Treatment***

...

Register **the** IV to oral switch in **the** IXRS. For subjects completing treatment as an outpatient, dispense **oral** study drug. **Outpatient** subjects will be instructed to return to the clinic on Day 5 (+ 1 day), **Day 7 (+ 1 day) as applicable, and at EOT** with their study drug container(s). Refer to Section 3.6.6.

***Section 3.4.1.8.2 - End of Treatment or Early Termination Procedures***

Subjects who prematurely discontinue study drug or are completing treatment will have EOT procedures performed that same day or up to 24 hours (+4 hours) after the last dose of study drug. Assessments already completed on the same day ~~as~~ the last dose of study drug is administered can serve as EOT procedures, **and do not need to be repeated.**

...

- ONLY FOR LACK OF EFFICACY, ~~obtain~~ ~~collect~~ ~~repeat~~ **deep cough** sputum specimen for Gram stain and culture, **if possible. Additionally, other respiratory sources are acceptable if available (refer to Section 3.4.3.2.1).**
- ONLY FOR LACK OF EFFICACY, ~~and~~ **obtain a repeat CXR.**

***Section 3.4.1.10 - Test of Cure (TOC Visit, 5–10 Days After Last Dose of Study Drug)***

...

- Collect **deep cough** sputum specimen for culture, if possible. **Additionally, other respiratory sources are acceptable if available (refer to Section 3.4.3.2.1).**
- ONLY FOR LACK OF EFFICACY, **obtain a repeat CXR.**

...

- Obtain blood samples for *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* serology and procalcitonin.

***Section 3.4.1.11 - Follow-up Visit (FU, Day 28 ± 2 Days)***

...

- Obtain blood sample for *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* serology (for subjects who return to the clinic).

...

- Record post-treatment medications in the subject's source, **particularly any antibiotics taken after EOT** (~~only post-treatment medications associated with and SAE will be collected in the eCRF~~).

***Section 3.4.2.1 - Clinical Evaluation***

...

Symptom severity will be evaluated by the investigator on a 4-point scale (absent, mild, moderate, severe, **see Section 7.8 for definitions**) with improvement defined as at least a 1-point improvement (**decrease**) from baseline to the assessment at 96 hours (± 24 hours)

after first dose of study drug (e.g., from severe to moderate, from moderate to mild, or from mild to absent). See Appendix 7.8 ~~below~~ for definitions of symptom intensity.

### ***Section 3.4.3.1 - Chest Radiography***

A chest radiograph (chest x-ray; posteroanterior and lateral preferred; single view acceptable if conclusive) must be obtained **prior to randomization** with initial interpretation and included in **the** source documents. Computed tomography of the thorax may be used as an alternative, if available as per local standard of care. The presence of lobar, multilobar, or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia on a pulmonary imaging study is required for study entry. Chest radiography should be performed before ~~the first dose of study drug~~ **randomization** and repeated at ~~the end of treatment~~ **EOT or TOC** only for lack of efficacy. Chest radiography obtained per local standard of care will not be repeated if obtained within 48 hours before the first dose of study drug. Findings will be recorded ~~ing~~ in the eCRF. Radiologic films must have a formal interpretation available in **the** source documents. Source, i.e., radiologist report and imaging, will be maintained by the site.

### ***3.4.3.2 - Microbiological Assessments***

The following pathogens are examples of primary pathogens that will be used to determine the microbiological responses in the study: the typical bacterial pathogens include **but may not be limited to** *S. pneumoniae*, *H. influenzae*, *S. aureus*, ~~*K. lebsiella pneumoniae*~~, and *Moraxella catarrhalis*, and the atypical bacterial pathogens *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. The causative pathogen will be identified by isolation from a baseline **culture** specimen (either a ~~sputum~~ **respiratory** specimen or blood), by urinary antigen, ~~and/or~~ **by** serology, and/or **by** PCR.

**Residual ~~sputum~~ respiratory samples, and/or nasopharyngeal swabs, and oropharyngeal swabs may will** be sent to specialty laboratories for **possible** culture, ~~and/or~~ **PCR, serotyping, and/or susceptibility testing** (*S. pneumoniae*, *L. pneumophila*, *M. pneumoniae*).

...

Pathogens will be specifically identified to the genus and species levels. In vitro susceptibility of target pathogens to delafloxacin and moxifloxacin will be determined at the central laboratory according to Clinical Laboratory Standards Institute (CLSI) and **European Committee on Antimicrobial Susceptibility Testing (EUCAST)** guidelines for broth and agar dilution and disk diffusion. Susceptibility to additional antibiotics ~~may will~~ also be evaluated.

***Section 3.4.3.2.1 - Respiratory Culture***

The collection of **an** adequate sputum samples for Gram stain, culture, and susceptibility testing, **as applicable**, will be attempted in all subjects at baseline ~~and~~. **Other sources of respiratory specimens such as those obtained from bronchoalveolar lavage (BAL), protected specimen brush (PSB), transtracheal aspirate, and pleural fluid, if available, are acceptable to submit for culture. All respiratory specimens will be sent to the local/regional laboratories for gram stain, culture and susceptibility testing, as applicable.**

All sputum **and transtracheal aspirate** samples will be evaluated to determine quality. A Gram stain will be performed immediately after the sample is delivered to **the** microbiology laboratory. A microscopic examination of the slide will be performed. A “good” sputum sample is one with polymorphonuclear leukocytes but few (or no) squamous epithelial cells on Gram stain. All efforts will be made to obtain **a sputum or transtracheal aspirate specimen that yields** an acceptable Gram-stain, defined as < 10 squamous epithelial cells and/or > 25 polymorphonuclear cells per low-power field.

All respiratory specimens will be sent for culture and susceptibility testing. ~~Other sources of respiratory specimens such as those obtained from bronchoalveolar lavage (BAL), protected specimen brush (PSB), transtracheal aspirate, and pleural fluid, if available, are acceptable to submit for culture.~~ [sentence moved up] In addition, **any** residual respiratory sample will be frozen and ~~may be sent to a specialty lab~~ **the central laboratory** for culture, **L. pneumophila identification**, antibiotic ~~sensitivity~~ **susceptibility** testing, and/or serotyping **at a specialty microbiology laboratory**. The respiratory culture, if positive, will be used to identify ~~and freeze-isolates for subcultures~~ **submission to the central microbiology laboratory and to freeze for back-up storage.**

Collection of a repeat respiratory specimen for culture should be attempted at EOT **only** for lack of efficacy, prior to any rescue therapy, ~~and~~ at TOC **if possible**, or if clinically indicated.

...

NOTE: ~~References to sputum culture in the protocol are intended apply to culture from respiratory specimens as well.~~

***Section 3.4.3.2.2 - Blood Culture***

Two sets (**aerobic and anaerobic**) of blood specimens for culture will be obtained at baseline **from anatomically different locations**. Additional blood samples will be collected for culture at subsequent visits only if a previous culture was positive, or if clinically indicated. If positive, blood cultures will be repeated ~~daily~~ until they are negative. ~~The 2 sets~~



~~of blood cultures should be obtained from anatomically different locations.~~ **Culture will be performed at a local or regional laboratory, as applicable. The blood culture, if positive, will be used to identify isolates for submission to the central microbiology laboratory and to freeze for back-up storage.**

#### ***Section 3.4.3.2.3 - Urine Antigen Testing***

Urine samples will be obtained for *L. pneumophila* and *S. pneumoniae* urine antigen testing at baseline **and forwarded to the central laboratory.**

#### ***Section 3.4.3.2.4 - Nasopharyngeal and Oropharyngeal Testing***

A nasopharyngeal swabs will be obtained at baseline **and forwarded to the central laboratory** for *S. pneumoniae* PCR analysis and/or *S. pneumoniae* culture, ~~and~~ serotyping **and antibiotic susceptibility testing at a specialty microbiology laboratory. Two** oropharyngeal swabs will be obtained at baseline **and forwarded to the central laboratory** for ~~*M.ycoplasma pneumoniae*~~ *M.ycoplasma pneumoniae* culture and/or PCR **analysis**, antibiotic susceptibility testing at a specialty microbiology laboratoriesy.

#### ***Section 3.4.3.2.5 - Serology***

Serum serology samples will be tested for identification of atypical pathogens *C. pneumoniae*, ~~*M.ycoplasma pneumoniae*~~ *M.ycoplasma pneumoniae* and ~~*L.egionella pneumophila*~~ *L.egionella pneumophila* at baseline, TOC, and FU.

#### ***Section 3.4.3.3 - Demographic Data/Medical History***

...

The medical history should include clinically significant medical, **pulmonary** or surgical history ongoing at baseline or with onset in the previous 2 years, as well as hospitalizations of more than 2 days within the last 90 days.

...

#### ***Section 3.4.3.5 - Clinical Laboratory Tests***

Clinical laboratory testing will be performed according to the Schedule of Events (Appendix 7.1). Local results of pregnancy test, serum chemistry and coagulation profile, hematology, and urinalysis tests obtained within 24 hours ~~of~~ **before** enrollment may be used for screening purposes and to verify entry criteria. However, blood **and urine** samples will be collected ~~either~~ at Screening ~~or~~ **and** on Day 1 prior to the first dose of study drug and will be sent to the central laboratory ~~and will~~ **to** serve as baseline values. Directions for collection,

processing, and handling of specimens are included in the laboratory manual.

...

Other Chemistry: Procalcitonin **will be analyzed by a central laboratory.**

#### ***Section 3.4.3.6 - Pharmacokinetic Blood Sample Collections***

Serial blood samples for PK analysis will be obtained at select investigative sites on Day 3 ( $\pm 1$  day) of treatment within **the** 30 minutes before ~~the first~~ study drug administration ~~of the day~~ and at 1.5 and 3 hours after the start of the infusion. All time points will have a  $\pm 10$  minute window. Subjects should have received a minimum of 3 consecutive doses of study drug prior to the start of **PK** blood collection. Subjects do not need to be fasted before dosing or during PK sample collections. Samples will be processed according to the laboratory manual and sent to the central laboratory for analysis.

**All plasma samples will be assayed using a validated liquid chromatography coupled with tandem mass spectrometry assay for delafloxacin.**

#### ***Section 3.4.3.7 - Vital Sign Measurements***

Vital signs including body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure, and pulse oximetry will be obtained **according to the Schedule of Events (Appendix 7.1)**. Arterial blood gases can be obtained at Screening if clinically warranted. ~~Any Daily~~ supplemental oxygen ~~at the time of pulse oximetry~~ will be recorded. Blood pressure and pulse rate will be measured after subjects have been in a sitting position for at least 5 minutes. Respirations will be counted and documented in breaths per minute. Body temperature can be measured via different ~~routes~~ **methods** and ~~may include~~ oral, rectal, tympanic, and axillary. Vital signs should be measured ~~around the~~ **at a consistent** time ~~of the first daily dose of study drug each day~~ while on IV therapy. Subjects who require pressor support should have regular blood pressure monitoring as per local standard of care.

#### ***Section 3.4.3.10 - Health-Related Quality-of-Life Assessment***

##### Quality-of-Life Questions

Quality-of-life questions will be asked/administered to determine the effect of the subject's CABP under study ~~and its effect~~ on his/her usual daily activities of doing their job and earning income. The questions require **the patient's subject to** recall ~~of the patient's~~ **their** status in the 24 hours prior to questioning.

...

### ***Section 3.4.3.11 - Concomitant Medications***

All concomitant medications will be recorded **in the source and eCRF** from the time the subject signs informed consent through the EOT.

...

### ***Section 3.4.3.12 - Post-Treatment Medications***

All medications, including nonprescription medications and dietary supplements, taken once or more from the ~~End of Treatment~~**EOT** Visit assessments through the ~~TOC Visit and only~~**TOC Visit** and ~~only~~**medications associated with an SAE from the TOC Visit through Follow-up** ~~FU~~**Visit** will be recorded in the subject source. **The post-treatment medications recorded in the eCRF will be limited. Enter any antibiotics taken after EOT in the eCRF for all subjects. All other medications will only be entered in the eCRF through the TOC Visit, will be recorded in the eCRF and only medications associated with an SAE from the TOC Visit through the Follow-up** ~~FU~~**Visit** will be recorded in the eCRF. **For subjects not required to have or missing the TOC Visit, post-treatment medications other than antibiotics will only be recorded in the eCRF if associated with an SAE through the Follow-up Visit.**

### ***Section 3.4.4.1 - Adverse Event Definitions***

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A ~~TE~~**treatment-related** AE is defined as any event with suspected causality to study drug.

...

### ***Section 3.4.4.2 - Eliciting and Documenting Adverse Events***

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In addition to subject observations, AEs will be documented from any data collected in the eCRF **or other source documents** (e.g., laboratory values, physical examination findings, ECG changes), ~~or other documents (e.g., subject diaries)~~ that are relevant to subject safety. An allergic reaction to study drug must be reported as an AE.

### ***Section 3.4.4.3 - Reporting Adverse Events***

All AEs reported or observed during the study will be recorded in the AE eCRF from the time that the subject is first administered double-blind study drug through the **EOT or TOC Visit, whichever is later**. ~~Only SAEs will be collected from the TOC Visit through the Follow-up Visit.~~ **All Serious adverse event** ~~AEs~~**AEs will be collected** ~~recorded in the eCRF~~**recorded in the eCRF** from the time the subject or authorized representative signs the ICF through the ~~Follow-up~~**Follow-up** ~~FU~~**Visit** Visit.

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Insufficient clinical response (lack of efficacy):

Insufficient clinical response, efficacy, or pharmacological action should NOT be recorded as an AE. The principal investigator must make the distinction between exacerbation of preexisting illness and lack of therapeutic efficacy. **Progression of the current CABP due to lack of efficacy of the study drug will be recorded on the Clinical Response eCRF.**

### ***Section 3.5 - Overdose Management***

Single oral doses of delafloxacin as high as 1600 mg and multiple doses of 1200 mg have been administered to subjects in Phase 1 trials. Single IV doses as high as 1200 mg have been administered to subjects in Phase 1 trials. In study RX-3341-302, 3 patients received 600 mg IV BID for up to 13 days due to pharmacy error (**Rib-X 2015**).

...

### ***Section 3.6.1 - Method of Assigning Subjects to Treatment Groups***

...

The investigator or designee will enter the enrollment information in the IXRS. The unblinded pharmacist or unblinded designee will obtain the treatment assignment ~~by~~ **from** the IXRS as described in the IXRS manual. A statistician who is not otherwise involved in the conduct of the study will create the randomization code. Randomization will be stratified by PORT Risk Class, medical history of COPD/asthma, and by prior **single-dose/regimen** antibiotic use.

Subjects in PORT Risk Class II will be limited to no more than 25% of total randomized subjects, and prior **single-dose/regimen** antibiotic use **limited** to no more than 25% of total randomized subjects.

### ***Section 3.6.7 - Allowed Concomitant Treatment***

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Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the principal investigator to ensure that details regarding the medication are recorded in full **in the source and** on the eCRF.

### ***Section 3.6.8 - Prohibited Medications and Restrictions***

Concurrent systemic antimicrobial treatments are prohibited. Any subject who requires additional (i.e., nonstudy) antibiotics for any of the following reasons will be considered a treatment failure: lack of efficacy after at least 4 doses of study drug **by the end of Day 3**, ~~treatment related AE requiring a nonstudy antibiotic~~, antibiotic therapy required for more

than 20 delafloxacin/delafloxacin placebo doses. Study drug should be stopped for all treatment failures, and the subject should complete end of treatment procedures.

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### ***Section 3.7.1 - Endpoints***

**For FDA**, in order to control Type 1 error rate of 5%, a gate-keeping statistical method of a fixed sequence procedure will be used to test for the secondary efficacy endpoints once the primary efficacy endpoint is claimed to be successful. If the noninferiority of delafloxacin is declared in the primary analysis, in order to control type 1 error, the secondary endpoints will be tested for superiority in a sequential (hierarchical) fashion using a fixed sequential procedure.

**For EMA, all the primary and secondary endpoints will be analyzed for noninferiority with the possibility to switch to superiority.**

The difference (delafloxacin – moxifloxacin) and CIs for all secondary endpoints will be reported. The primary and secondary efficacy endpoints are presented in the following text.

#### ***Section 3.7.1.1 - Primary Efficacy Endpoint [table format added]***

The primary efficacy endpoint is:

| <b>FDA</b>  | <b>EMA</b>  |
|---|---|
| The ECR defined as improvement at 96 hours ( $\pm$ 24 hours) after first dose of study drug in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum, and difficulty breathing, and no worsening in the other symptoms in the ITT population. | <b>The Clinical Outcome responder rate at 5 to 10 days after the last dose of study drug (TOC) defined as resolution or near resolution of the symptoms of CABP present at study entry, and no use of additional antimicrobial therapy for the current infection, and no new symptoms associated with the current CABP infection (success) in the ModITT and ModCE populations.</b> |

#### ***3.7.1.2 - Secondary Efficacy Endpoints [table format added]***

The secondary efficacy endpoints are:

| <b>FDA</b>  | <b>EMA</b>  |
|---|---|
| ECR with the addition of improvement in vital signs and | <b>ECR defined as improvement at 96 hours (<math>\pm</math> 24 hours) after first dose of study drug in at least 2 of the</b> |

| FDA   | EMA   |
|---|---|
| no worsening of the 4 symptoms required as Response in the ITT population | <b>following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum and difficulty breathing and no worsening of any of the other symptoms in the ModITT and ModCE populations</b> |
| Clinical Outcome at TOC (CE and ITT populations)                          | <b>ECR with the addition of improvement in vital signs and no worsening of the 4 symptoms required as Response in the ModITT and ModCE populations</b>  |
| Clinical Outcome at <del>the</del> EOT                                    | <b>Clinical outcome at EOT (ModITT and ModCE)</b>   |
| ECR in the MITT population  | <b>Clinical Outcome at TOC in the ModMITT and ModME populations</b>   |
| Microbiologic Response (ME and MITT)                                      | <b>Microbiologic response (ModMITT and ModME)</b>   |
| All-cause mortality (ITT)   | <b>All-cause mortality (ModITT)</b>   |

***Section 3.7.1.5 - Pharmacokinetic Endpoints***

~~Pharmacokinetic results will be reported in a separate PK report.~~ **The time course of delafloxacin plasma concentrations will be assessed.**

***Section 3.7.2.1 - Early Clinical Response***

Symptoms for the Early Clinical Response will be evaluated by the investigator on a four-point scale (absent, mild, moderate, severe, **see Section 7.8 for definitions**) with improvement defined as at least a 1-point improvement (**decrease**) from baseline to the assessment at 96 hours ( $\pm$  24 hours) after first dose of study drug (e.g., from severe to moderate, from moderate to ~~absent~~**mild**, or from mild to absent).

Responders: Improvement at 96 hours ( $\pm$  24 hours) after first dose of study drug in at least 2 of the following symptoms: **pleuritic** chest pain, frequency or severity of cough, amount and quality of productive sputum, and **dyspnea** (difficulty breathing), and no worsening of the other symptoms.

Non-responders: Improvement is not achieved at 96 hours ( $\pm$  24 hours) after first dose of study drug in at least 2 of the following symptoms: ~~(pleuritic~~ chest pain, frequency or severity of cough, amount and quality of productive sputum, and **dyspnea** (difficulty breathing); or there is use of additional non-study antimicrobial therapy for treatment of the

current CABP infection due to lack of efficacy; or the subject **diesd** from the current CABP infection. Indeterminate/missing assessments will be mapped to Non-responders in the statistical analysis of the ITT Population.

### ***Section 3.7.2.2 - Clinical Outcome at EOT and TOC***

...

Success: Resolution or near resolution of the symptoms of CABP present at study entry, ~~at~~ and no use of additional antimicrobial therapy for the current infection, and no new symptoms **associated with the current CABP infection**.

Failure: Symptoms of CABP present at study entry have not resolved, or new symptoms **of CABP** have developed, or the subject **diesd** from pneumonia, or use of additional non-study antimicrobial therapy for treatment of the current CABP infection due to lack of efficacy. Failure outcome due to Lack of Efficacy (LOE) will be carried forward to later time points if the subject discontinues the trial for LOE. Subjects must receive at least 4 doses of study drug by the end of Day 3 to be called a Failure.

Indeterminate/Missing: A response cannot be determined because an efficacy assessment was not completed at the visit, or subject did not complete the planned course of study therapy for reasons other than lack of efficacy. Indeterminate/missing responses will be considered failures for purposes of the primary ITT/**ModITT** analyses and will be excluded from the CE and ME analysis populations.

### ***Section 3.7.2.3 - Microbiologic Response***

Microbiological response for subjects in the MITT and ME set will be based on results of the baseline and follow up cultures and susceptibility testing or serology. When **follow-up** culture results are missing, the clinical response assigned by the investigator will be considered. Microbiological responses will be generated at the TOC assessments at both the subject and the pathogen levels. The following microbiological responses will be considered:

Eradication: The ~~sputum~~**respiratory and/or blood specimen** at the TOC Visit shows all causative pathogen(s) **present** at enrollment eradicated and no use of additional antimicrobial therapy for the current infection.

Presumed Eradication: No ~~sputum sample~~**respiratory and/or blood specimen** was available at TOC with a clinical assessment of Success.

Persistence: The ~~sputum~~**respiratory and/or blood culture collectedspecimen** at the TOC Visit shows appearance of ~~all~~causative pathogen(s) **present** at enrollment.

Presumed Persistence: No ~~sputum sample~~ **respiratory and/or blood specimen** was available for a case classified as clinical failure.

Superinfection: A culture taken during treatment shows appearance of a new pathogen causing respiratory infection associated with clinical failure.

**Colonization/Contamination: A culture taken post-baseline through the TOC visit shows appearance of a new pathogen(s), with a clinical assessment of Success and no use of additional antimicrobial therapy for the current infection.**

***Section 3.7.4 - Sample Size Calculations [table format added]***

| FDA  | EMA  |
|--|--|
| <p>At least 860 adult male and female subjects (430 subjects per treatment group) will be randomized. Used on a normal approximation approach (Miettinen and Nurminen’s Likelihood Score Test), 860 subjects in the ITT population will provide a 90% power to assess noninferiority of delafloxacin vs. moxifloxacin based on the following assumptions: (1) a rate of Early Clinical Response for moxifloxacin therapy and delafloxacin of 77% and 74%, respectively; (2) 1-sided type I error (<math>\alpha</math>) of 0.025; (3) a noninferiority margin of 12.5%.</p> | <p><b>At least 860 adult male and female subjects (430 subjects per treatment group) will be randomized. Used on a normal approximation approach (Miettinen and Nurminen’s Likelihood Score Test), and assuming approximately 12% of patients will be in PORT Class II, and 80% of patients will be clinically evaluable, 755 subjects in the ModITT population and 604 subjects in the ModCE population will provide, respectively, a power of 91% and 83% to assess noninferiority of delafloxacin vs. moxifloxacin based on the following assumptions: (1) a rate of Clinical Outcome at the TOC visit for moxifloxacin and delafloxacin of 88% and 86%, respectively; (2) 1-sided type I error (<math>\alpha</math>) of 0.025; (3) a noninferiority margin of 10%.</b></p> |

...

***Section 3.7.5 - Analysis Populations***

Data analysis will be based on different analysis populations according to the purpose of the analysis (e.g., safety or efficacy). Within the efficacy analysis, different combinations of analysis sets will be used for the clinical response and the microbiologic response. The analysis for clinical response will be **generally** presented using the ITT, MITT, CE, and ME populations **for FDA and the ModITT, ModMITT, ModCE and ModME populations for EMA**. The analysis for microbiologic response will be presented using the MITT and ME



populations for FDA and the ModMITT and the ModME populations for EMA.

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#### **Modified ITT (ModITT) Population**

**All randomized subjects who received at least one dose of study medication, classified as PORT Class III-V, analyzed according to the treatment arm to which they were randomized.**

#### **Microbiological ITT (MITT) Population**

All subjects in the ITT population who had a baseline bacterial pathogen **identified** on culture of ~~sputum specimen~~ **respiratory** or blood **specimen**, or a nonculture method of detection of bacterial pathogens (i.e., urinary antigen test, PCR and serologic testing) ~~identified~~ that is known to cause CABP against which the study drug has antibacterial activity.

#### **Modified MITT (ModMITT) Population**

**All subjects in the MITT population classified as PORT Class III-V.**

...

#### **Modified CE (ModCE) Population**

**All subjects in the CE population classified as PORT Class III-V.**

...

#### **Modified ME (ModME) Population**

**All subjects in the ME population classified as PORT Class III-V.**

#### **Pharmacokinetic (PK) Population**

All subjects who receive at least 3 consecutive IV doses of study drug prior to the start of the blood sample collections on Day 3 ( $\pm$  1 Day) and have ~~sufficient plasma concentration data to facilitate calculation of PK parameters~~ **at least one delafloxacin plasma concentration data available**. The PK population will be used for PK analyses.

#### ***Section 3.8.1 - Demographics and Other Baseline Characteristics***

Demographics and other baseline characteristics including gender, age, race, ethnicity, height, weight, **BMI** and the data for ~~baseline infection types at Screening~~ **PORT Class and CURB-65 score** will be summarized for the ITT, Safety, **ModITT**, **MITT**, **ModMITT**, **CE**, **ModCE**, **ME** and **ModME** populations to assess the comparability of the treatment groups.

Medical history data including pulmonary and hospitalization history will be summarized for the **ITT and ModITT** populations using the number of observations and percentage of

subjects reporting each category. Baseline radiograph findings and signs and symptoms required for study entry will be summarized for the ITT **and ModITT** populations using the number of observations and percentage of subjects reporting each category.

***Section 3.8.3 - Primary Efficacy Analysis [table format added]***

The primary efficacy endpoint is:

| FDA   | EMA  |
|---|--|
| <p>The <del>Early Clinical Response</del> <b>ECR</b> defined as improvement at <del>Day 4</del> <b>96 hours</b> (<b>± 24 hours</b>) in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum, and difficulty breathing, and no worsening of the other symptoms in the ITT population.</p> <p>Each treatment group's response rate will be defined as: (# Responders) / (# Responders + Non-responders).</p> <p>The treatment difference (delafloxacin – moxifloxacin) in the rates of this endpoint will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% confidence interval (CI) on the difference in response rate. This analysis will be performed using the ITT population.</p> <p>The lower bound of this CI will demonstrate the maximum extent to which the response rate for moxifloxacin may exceed that for delafloxacin. If the lower bound is greater than -12.5%, it will be concluded that delafloxacin is noninferior to moxifloxacin for treating patients with CABP. In addition, superiority will be claimed if the lower bound of the 95% CI exceeds 0.</p> <p>An indeterminate/missing response will be</p> | <p><b>The Clinical Outcome at TOC.</b></p> <p><b>For the assessment of Clinical Outcome at TOC, each treatment group's Clinical Outcome rate will be defined as: (# Success) / (# Success + Failure).</b></p> <p><b>The treatment difference (delafloxacin – moxifloxacin) in the rates of this endpoint will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% CI on the difference in response rate. This analysis will be performed using the ModCE and ModITT analysis populations, and the result at TOC will be tested for noninferiority with the possibility to switch to superiority.</b></p> <p><b>The lower bound of this CI for delafloxacin – moxifloxacin will demonstrate the maximum extent to which the response rate for moxifloxacin may exceed that for delafloxacin. If the lower bound is greater than 10%, it will be concluded that delafloxacin is noninferior to moxifloxacin for treating patients with CABP. In addition, superiority will be claimed if the lower bound of the 95% CI exceeds 0.</b></p> <p><b>A missing response will be classified as failure for purposes of the primary</b></p> |

| FDA  | EMA                     |
|--|-------------------------|
| classified as Non-responders for purposes of the primary analysis. | <b>ModITT analysis.</b> |

***Section 3.8.4 - Sensitivity Analysis of the Primary Endpoint for each Region (FDA and EMA)***

The following sensitivity analyses for the primary endpoint will be performed:

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- The primary analysis performed on the **MITT/ModMITT**, CE and ME/**ModME** analysis populations **as per the corresponding region**.
- **For EMA region, in order to control the possible age influence on the clinical evaluation, the primary endpoint will be tested including the age class, defined as Age < 65 and Age ≥ 65, as an additional factor in the model.**

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***Section 3.8.5 - Subgroup Analyses of the Primary Endpoint for each Region (FDA and EMA)***

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- Demographic subgroups: age categories (age < 65, ≥ 65, ≥ 75), gender, BMI categories (BMI < 30 and ≥ 30), baseline PORT score, ~~score~~ **Risk Class**, baseline CURB-65 Score, ethnicity, region, and race categories.

...

- Presence or absence of: baseline bacteremia, multilobar pneumonia, diabetes, **history of COPD/asthma, history of hepatitis, renal impairment/disease**, baseline MRSA **S. pneumoniae** infection, baseline ~~adequate~~ Gram stain **adequacy**.

These subgroup analyses will be performed using the ITT/**ModITT** population for the primary efficacy endpoint.

***Section 3.8.6 - Secondary Efficacy Analyses***

**For each of the FDA submissions**, in order to control Type 1 error rate of 5%, a gate-keeping statistical method of a fixed-sequence procedure will be used to test for the secondary efficacy endpoints once the primary efficacy endpoint is claimed to be successful. ~~For each of the FDA (and EMA) submissions,~~ **If the noninferiority of delafloxacin is declared in the primary analysis, the secondary endpoints will be tested for superiority in a**

sequential (hierarchical) fashion using a fixed sequential procedure, in the order given in Section 3.7.1.2. Unless specified otherwise in the endpoint definition, the testing will be performed in the ITT analysis population.

**For EMA, all the primary and secondary endpoints will be tested for noninferiority with the possibility to switch to superiority.**

Each test, **both for FDA and EMA**, will be performed using the type 1 error rate of 0.05.

The secondary endpoints with proportion will be tested, **both for FDA and EMA**, using Miettinen-Nurminen test for delafloxacin – moxifloxacin, without stratification. Superiority for the corresponding study endpoint will be claimed using a 5% significance level.

#### ***Section 3.8.6.1 - Early Clinical Response with the Addition of Improvement in Vital Signs and No Worsening of the 4 Symptoms Required as Response***

The treatment difference (delafloxacin – moxifloxacin) of ECR with the addition of improvement in vital signs and no worsening of the 4 symptoms required as response will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% CI on the difference in ECR with the addition of improvement in vital signs and no worsening of the 4 symptoms required as response rate. This analysis will be performed using the ITT **and ModITT/ModCE population, respectively for FDA and EMA.**

#### ***Section 3.8.6.2 - Clinical Outcome at EOT and TOC***

The treatment difference (delafloxacin – moxifloxacin) in the rates of this endpoint will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2 sided 95% CI on the difference in response rate. This analysis **of clinical outcome at EOT and TOC** will be performed using the CE and ITT analysis populations **for FDA. The ModCE and ModITT analysis populations will be used to perform the analysis of clinical outcome at EOT for EMA. The ModMITT and ModME analysis populations will be used to perform the analysis of the EMA secondary endpoint of clinical outcome;** ~~and the result at TOC will be tested for noninferiority for EMA use, which will be outlined in the statistical analysis plan (SAP).~~

~~The lower bound of this CI for delafloxacin – moxifloxacin will demonstrate the maximum extent to which the response rate for moxifloxacin may exceed that for delafloxacin. If the lower bound is greater than 12.5%, it will be concluded that delafloxacin is noninferior to moxifloxacin for treating patients with CABP.~~

A missing response will be classified as failure for purposes of the primary ITT analysis. For the assessment of Clinical Outcome at EOT and TOC, each treatment group's Clinical Outcome rate will be defined as:  $(\# \text{ Success}) / (\# \text{ Success} + \text{Failure})$ .

~~The assessment of Clinical Outcome at TOC will be performed stratified by baseline PORT classification, medical history of COPD/asthma and prior systemic antimicrobial use. In addition, this analysis will be performed on the MITT, CE, and ME analysis populations at TOC. In addition, subgroup analyses listed in Section 3.8.5 will also be performed for the assessment of Clinical Outcome at the TOC for EMA use.~~

### ***Section 3.8.6.3 - Early Clinical Response for Subjects in the MITT, ModITT and ModCE Populations***

The treatment difference (delafloxacin – moxifloxacin) of ECR for patients in the MITT **and ModITT/ModCE populations respectively for FDA and EMA** will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% CI on the difference in ECR rate. ~~This analysis will be performed using the ITT population for patients in the MITT population.~~

### ***Section 3.8.6.4 - Microbiologic Response***

The treatment difference (delafloxacin – moxifloxacin) of microbiologic response rate will be presented, and the Miettinen-Nurminen test, without stratification, will be used for the 2-sided 95% CI on the difference in microbiologic response rate. This analysis will be performed using the ME and the MITT populations **for FDA, and the ModME and ModMITT populations for EMA.**

### ***Section 3.8.6.5 - All-Cause Mortality***

All-cause mortality in adult subjects with CABP on Day 28 will be assessed and compared between the two treatment groups. Kaplan-Meier estimates will be used to summarize the time to all-cause mortality on Day 28. Patients who ~~do~~**have not died at** Day 28 will be censored at Day 28.

...

The Cox proportional hazards regression model will be used to evaluate the difference between the 2 treatment groups adjusting for the baseline covariates including baseline PORT classification, history of COPD/asthma, and prior systemic antimicrobial use. Interactions between treatment and each covariate will be evaluated at the 0.10 significance level; if not significant, they will be removed from the final model. These analyses will be performed for ITT **and ModITT populations respectively for FDA and EMA.**

### ***Section 3.8.7 - Exploratory Analyses***

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Exploratory efficacy analyses will include summaries for the primary and secondary endpoints measured at additional study time points and for different analysis population. As other exploratory analyses, secondary analyses of secondary endpoints that used nonstratified Miettinen-Nurminen CIs will be repeated using the same method but stratified by PORT **Class/PSI** score, medical history of COPD/asthma, and prior systemic antimicrobial use.

In addition, the following shift analyses will be performed ~~as exploratory analyses using a chi-squared test if appropriate:~~

...

### ***Section 3.8.16 - Pharmacokinetic Analyses***

~~Pharmacokinetic analyses will be detailed in the separate PK report.~~ **Summary statistics will be calculated for the plasma concentration-time data including N, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, maximum, and geometric mean.**

**Plasma concentration data will be subjected to a separate population PK analysis.**

### ***Section 3.8.17 - Missing Data***

...

2. Missing data for Clinical Response based on the investigator assessment of signs and symptoms of pneumonia will be considered a Failure in the ITT/**ModITT** analysis.
3. For each secondary and exploratory efficacy endpoint, missing data will be imputed as the worst possible response. For instance, subjects missing assessment data at either the Early Clinical Response time point or the TOC will be considered as Failures or Non responders in the ITT/**ModITT** analysis.

...

### ***Section 5.1 - External Data Monitoring Groups***

**An external data monitoring group (data safety monitoring board) may be employed in this study. In that event, the membership, activities, and responsibilities of the safety monitoring committee will be described in detail in a separate charter document established for this study.**

**Section 6. – References**

Abbott Laboratories (Abbott Park, IL). A phase 2b comparative study of the safety and efficacy of three oral doses of ~~RX-3341~~**ABT-492** for the treatment of subjects with community acquired pneumonia. **2003 Dec 15. Clinical Study Report R&D/03/393.** (Study Protocol M01-344).

**Abbott Laboratories (Abbott Park, IL). A phase 2a comparative study of the safety and efficacy of ABT-492 100 mg QD, 200 mg QD, 400 mg QD and levofloxacin 500 mg QD for the treatment of subjects with acute bacterial exacerbation of chronic bronchitis. 2003 Dec 16. Clinical Study Report R&D/03/392. Protocol M01-298.**

**Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (US). Draft guidance. Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment. January 2014. Available from: <https://www.fda.gov/downloads/drugs/guidances/ucm123686.pdf>.**

**European Medicines Agency (EMA). Committee for Human Medicinal Products (CHMP). Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. London, 24 October 2013.**

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Evaluation of delafloxacin in a murine respiratory tract infection model against *S. pneumoniae* D39. **2015 Apr 28. Melinta Report #EF-3341-006.**

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~~Melinta IB-2015~~. Melinta Therapeutics, Inc. (~~Melinta~~) (New Haven, CT).

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~~Rib-X Study RX-3341-108~~. Rib-X Pharmaceuticals, Inc. (~~Rib-X~~) (New Haven, CT). A Phase 1, single-dose, safety, tolerability, and pharmacokinetic study of IV and oral formulations, and a maximum tolerated dose study of delafloxacin in healthy subjects. **2011 Sep 21. Clinical Study Report. Protocol RX-3341-108.**

**Rib-X Pharmaceuticals, Inc. (New Haven, CT). A randomized, double-blind, multicenter study of the safety and efficacy of RX-3341 compared with tigecycline for the treatment of complicated skin and skin structure infections. 2009 Jul 21. Clinical Study Report. Protocol RX-3341-201.**

~~Rib-X Study RX-3341-202~~. Rib-X Pharmaceuticals, Inc. (~~Rib-X~~) (New Haven, CT). A phase 2 exploratory study of objective endpoints in subjects with acute bacterial skin and skin structure infections treated with delafloxacin, vancomycin, or linezolid. **2014 Aug 11. Clinical Study Report. Protocol RX-3341-202.**

### *Section 7. - Appendices*

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**7.11 Appendix: Protocol Amendment 3 [added]**



**Section 7.1 - Appendix: Schedule of Events**

[Only updated table rows are shown. Changed table cells are shaded gray.]

[In header, abbreviations updated, and Day 7 visit window changed from  $\pm 1$  day to + 1 day. Chest radiograph or CT scan added at TOC with footnote m. Footnote m added to Sputum for Gram stain and culture at EOT. *Chlamydia* added to serology. Footnote y added to Adverse event evaluation and removed from Screening and FU]

| Assessment or Procedure   | Screening <sup>a</sup> | Treatment Period <sup>b</sup> |                |                   |                                     |             |             | End of Treatment (EOT)/ Early Term <sup>c</sup> | Reminder Contact <sup>d</sup> | Test of Cure (TOC) <sup>e</sup> | Follow-Up (FU) <sup>f</sup> |
|---|------------------------|-------------------------------|----------------|-------------------|-------------------------------------|-------------|-------------|---|-------------------------------|---------------------------------|-----------------------------|
|   |                        | Study Day(s)                  | 1 <sup>a</sup> | Daily while on IV | ECR 96 hrs $\pm$ 24 hr <sup>g</sup> | 5 (+ 1 day) | 7 (+ 1 day) |   |                               |                                 |                             |
| Chest radiograph or CT scan   | X                      |                               |                |                   |                                     |             |             | X <sup>m</sup>                                  |                               | X <sup>m</sup>                  |                             |
| Sputum Respiratory specimen for Gram stain and culture <sup>f</sup> | X                      | X                             |                |                   |                                     |             |             | X <sup>m</sup>                                  |                               | X                               |                             |
| <i>Chlamydia</i> / <i>Legionella</i> / <i>Mycoplasma</i> serology   |                        | X <sup>s</sup>                |                |                   |                                     |             |             |   |                               | X                               | X                           |
| Adverse event evaluation <sup>y</sup>                               | X <sup>y</sup>         | X                             | X              | X                 | X                                   | X           |             | X   |                               | X                               | X <sup>y</sup>              |

**Abbreviations:** ECR = Early Clinical Response; EOT = End of Treatment; TOC = Test of Cure; **FU = Follow-Up**; CABP = community-acquired bacterial pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*; CT = Computed tomography, PORT = Patient Outcomes Research Team; CURB-65 = scoring system based on confusion, urea, respiratory rate, blood pressure and age 65 or older; PK = pharmacokinetics; IXRS = interactive voice and web response system.

<sup>a</sup> Screening **procedures** will occur within **the** 24 hours ~~of~~**prior to** the first dose. The first dose may be administered on the same day as Screening. If the first dose is administered the same day as screening, then the assessments listed for Day 1, but **which** were already completed for Screening will not be repeated.

<sup>b</sup> The total duration of treatment (IV and oral) is 5 days up to 10 days if clinically indicated (minimum 10 doses and up to 20 delafloxacin/delafloxacin placebo doses).

<sup>c</sup> Subjects who prematurely discontinue study drug or are completing treatment on day of visit can have EOT procedures performed that same day or up to 24 hours (+ 4 hours) after the last dose of study drug. Assessments already completed on the same day ~~as~~ the last dose of study drug ~~is administered~~ can serve as EOT procedures **and do not need to be repeated**. Laboratory tests completed for a routine visit will not be repeated at EOT, if collected within 24 hours of the EOT visit.

<sup>d</sup> A reminder contact will be done 3- 9 days after the last dose of study drug. Subjects will receive a telephone call or contact via other interactive method, e.g., text or email, to remind the subject about the upcoming Test-of-Cure Visit.

<sup>e</sup> TOC assessments will be performed 5 to 10 days after the last dose of study drug (see Section 3.3.2 for exception).

- <sup>f</sup> All efforts will be made to have subjects return to the clinic for a Follow-up Visit. Telephone contact is permissible for subjects unable, unwilling or not required (**see Section 3.3.2**) to return to the clinic.
- <sup>g</sup> ECR Visit will occur 96 hours ( $\pm$  24 hours) after the first dose of study drug. Procedures already completed as specified in Sections 3.4.1.3 or 3.4.1.5 do not need to be repeated unless outside the ECR 96-hour ( $\pm$  24 hours) window.
- <sup>h</sup> Last day of IV therapy prior to oral switch. A minimum of 6 delafloxacin/delafloxacin placebo doses of IV study drug must be administered prior to oral switch. Refer to Schedule of Events for that day for assessments/procedures to be completed.
- <sup>i</sup> Clinical signs and symptoms of CABP will be assessed by the investigator using a 4-point severity scale (see Section 3.4.2.1).
- <sup>j</sup> Arterial blood gases can be obtained at Screening if clinically warranted. Body temperature can be measured via different routes and may include oral, rectal, tympanic and axillary. Pulse oximetry will be recorded for all subjects daily while on IV therapy **and** at ECR, and ~~Day 5 and Day 7, EOT, and TOC~~ **only** if clinically indicated and/or for subjects on supplemental oxygen **at Day 5, Day 7, EOT, and TOC**. Vital signs should be measured ~~around the~~ **a consistent time of the first daily dose of study drug each day** while on IV therapy.
- <sup>k</sup> Electrocardiograms will be performed at screening and if clinically indicated as determined by the investigator after screening.
- <sup>l</sup> Targeted physical examinations will be performed during the study to assess changes from baseline parameters, adverse events, and other relevant safety information.
- <sup>m</sup> Will be performed only if lack of efficacy.
- <sup>n</sup> Local laboratory test results of pregnancy, hematology, serum chemistry, ~~and~~ coagulation profile and urinalysis obtained within 24 hours ~~of~~ **before** enrollment may be used for screening purposes and to verify entry criteria. Laboratory tests with exclusionary results judged by the investigator as not compatible with the subject's clinical status may be repeated for eligibility purposes once.
- <sup>o</sup> Pregnancy tests to be performed for women of childbearing potential only.
- <sup>p</sup> Urinalysis and coagulation at screening only.
- <sup>q</sup> Two sets of blood cultures will be collected from all subjects at screening. Additional blood cultures will be collected if a previous culture was positive or if clinically indicated after Screening. Rapid test for MRSA identification methods are acceptable to use if *S. Aureus* is identified by the local/regional laboratory.
- <sup>r</sup> All reasonable efforts will be made to obtain a sputum specimen for Gram stain and culture. Other sources of respiratory specimens such as those obtained from bronchoalveolar lavage, protected specimen brush, transtracheal aspirate, and pleural fluid, if available, are acceptable to submit for culture. **A Gram stain will be performed on all sputum and transtracheal aspirate samples.** Rapid ~~test for~~ MRSA identification methods are acceptable to use if *S. aureus* is identified by the local/regional laboratory.
- <sup>s</sup> Results are not required prior to dosing. Refer to the laboratory manual for detailed instructions on collection, processing and shipment.
- <sup>t</sup> If the first dose is started late ~~on Day 1 in the day~~ because of screening and eligibility verifications, a 1-time adjustment is allowed for a more customary dosing schedule that is within  $\pm$  4 hours of the normally scheduled second dose. The every-12-hours ( $\pm$  2 hours) dosing schedule is set after the first dose (or dose adjustment).
- <sup>u</sup> Oral study drug treatment can be completed in the hospital or clinic. For subjects discharged to home, dispense study drug. Instruct subjects to bring study drug container(s) (empty and/or full) to the clinic at their next scheduled visit.
- <sup>v</sup> Study drug may be stopped at the discretion of the investigator after completing a minimum of 10 delafloxacin/delafloxacin placebo doses. Criteria for determination of appropriate treatment duration ~~is~~ **are** described in Section 3.4.1.8.1.
- <sup>w</sup> Blood samples for PK analysis will be obtained from subjects at select sites on Day 3 ( $\pm$  1 day) of treatment within **the** 30 minutes before ~~the first~~ study drug administration, ~~of the day~~ and at 1.5 and 3 hours after the start of the infusion. Subjects should have received a minimum of 3 **consecutive** doses of study drug prior to the start of **PK** sample collection. All time points will have a  $\pm$  10-minute window. Subjects do not need to be fasted before dosing or during PK sample collections.
- <sup>x</sup> **See Section 3.4.3.12 for collection of concomitant medications at FU** ~~associated with serious adverse events will be entered in the eCRF.~~

<sup>y</sup> Serious adverse events will be reported per protocol and recorded in the eCRF from the time ~~of~~ **subject provides** informed consent through the FU visit.

**Section 7.2 - Appendix: PSI/PORT Score: Pneumonia Severity Index for CAP**

[Only updated table rows are shown. Changed table cells are shaded gray.]

|   | <b>Assigned Points</b> |
|---|------------------------|
| Temperature < 35°C (95°F) or > 39.9°C (103.8°F) | +15                    |
| BUN > 29 mg/dL or urea > 10.9 mmol/L            | +20                    |
| Glucose > 249 (US) or > 13.8 (SI)               | +10                    |
| Partial pressure of Oxygen < 60 mmHg*           | +10                    |

\* An oxygen saturation of less than 90% on pulse oximetry or intubation before admission is also considered abnormal (Fine 1997).

...

**Step 2:**

- Assign points based on age, gender, nursing home residence, co-morbid illness, physical examination findings, and laboratory and radiographic findings as listed above.
- **Point distribution, score interpretation and suggested disposition** based on local standard of care:

| Score  | Risk Class | Risk     | Disposition                          |
|--------|------------|----------|--------------------------------------|
| ≤70    | II         | Low      | Outpatient care                      |
| 71-90  | III        | Low      | Outpatient vs. Observation admission |
| 91-130 | IV         | Moderate | Inpatient admission                  |
| >130   | V          | High     | Inpatient admission                  |

[Risk Class was added to the table]

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**Section 7.3 - Appendix: CURB-65**

[Only updated table rows are shown. Changed table cells are shaded gray.]

| <b>CURB-65</b>                    |               |
|-----------------------------------|---------------|
| <b>Symptom</b>                    | <b>Points</b> |
| Urea > 7 mmol/L or BUN > 19 mg/dL | 1             |

**Section 7.6 - Appendix: SF-12v2® Health Survey**

[Sample questionnaire replaced with actual United States (English) version of questionnaire]

**Section 7.8 - Appendix: Definitions of Symptom Intensity**

[Only updated table rows are shown. Changed table cells are shaded gray.]

| <b>Symptom (Points)</b> | Absent (0) | Mild (1) | Moderate (2) | Severe (3) |
|-------------------------|------------|----------|--------------|------------|
|-------------------------|------------|----------|--------------|------------|