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PROTOCOL NUMBER ML-3341-306

NCT02679573

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

STATISTICAL ANALYSIS PLAN

Version 2

Date: October 2, 2018

Document History	
Version No.	**Summary of Changes**
1	Original Version
2	Amendment 1 • The baseline definition of Procalcitonin is updated to consider Day 1 assessment within 24 hours of first dose. • The baseline definition of serology testing is updated to consider any 4-fold increase between two subsequent visits. • For Haemophilus influenzae and Haemophilus parainfluenzae, minimum inhibitory concentration (MIC) interpretations for moxifloxacin, levofloxacin, and azithromycin (CLSI test methodology) derivation rule is added • Susceptibility Test Interpretive Criteria for Delafloxacin is added • Study drug exposure and compliance is revised based on the analyses needs. • Microbiological Response is updated to consider patient who received non-study antibiotic prior to TOC microbiological sample collection - response will be derived based on the clinical response at TOC if negative culture result is confounded by receipt of non-study antibiotic. • Fluoroquinolone non-susceptible definition is updated to include non-susceptible MIC interpretations. • Macrolide non-susceptible definition is updated to include non-susceptible MIC interpretations. • Clarification is added to PK analyses indicating only the planned timepoint will be used for the concentration summary.

Signature Page

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1 ABBREVIATIONS

Abbreviation or term	Explanation
ABG	Arterial Blood Gas
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BAL	Bronchoalveolar Lavage
BID	Every 12 Hours
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CABP	Community-acquired Bacterial Pneumonia
CE	Clinically Evaluable
CEECR	Clinically Evaluable at 96 Hours (± 24 hours) for Early Clinical Response
CEEOT	Clinically Evaluable at EOT for Clinical Outcome
CETOC	Clinically Evaluable at TOC for Clinical Outcome
CFU	Colony-forming Unit
CI	Confidence Interval
CLSI	Clinical Laboratory Standards Institute
COPD	Chronic Obstructive Pulmonary Disease
CrCL	Creatinine Clearance
CS	Clinical Significant
CT	Computed Tomography
CURB- 65	Scoring system based on confusion, urea, respiratory rate, blood pressure and age 65 or older
CV	Coefficient of Variation
D5W	Dextrose 5% in water
DBP	Diastolic Blood Pressure
ECG	12-lead Electrocardiogram
ECR	Early Clinical Response
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End of Treatment
EUCAST	European Committee on Antimicrobial Susceptibility Testing
ESBL	Extended-spectrum Beta-lactamases
ETA	Endotracheal Aspirate
FDA	U.S. Food and Drug Administration

Abbreviation or term	Explanation
FU	Follow-up
HLT	[MedDRA] High Level Term
ICH	the International Conference on Harmonization
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
IXRS	Interactive Voice and Web Response System
LLN	Lower Limit of Normal
LOE	Lack of Efficacy
lpf	low-power field
LS	Least Square
MCS	Mental Health Component Score
MDR	Multiple Drug Resistance
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MITT	Microbiological ITT
MMRM	Mixed Effect Model Repeated Measure
ModCE	Modified Clinically Evaluable
ModCEECR	Modified Clinically Evaluable at 96 Hours (± 24 hours) for Early Clinical Response
ModCEEOT	Modified Clinically Evaluable at EOT for Clinical Outcome
ModCETOC	Modified Clinically Evaluable at TOC for Clinical Outcome
ModITT	Modified ITT
ModME	Modified Microbiological Evaluable
ModMITT	Modified Microbiological ITT
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSP	Macrolide-resistant *Streptococcus pneumoniae*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NCS	Not Clinical Significant
NEC	Not Elsewhere Classified
NI	Noninferiority
NP	Nasopharyngeal
OMB	Office of Management and Budget
OP	Oropharyngeal
PCR	Polymerase Chain Reaction
PCS	Physical Health Component Score
PE	Physical Examination
PISP	Penicillin-Intermediate *Streptococcus pneumoniae*

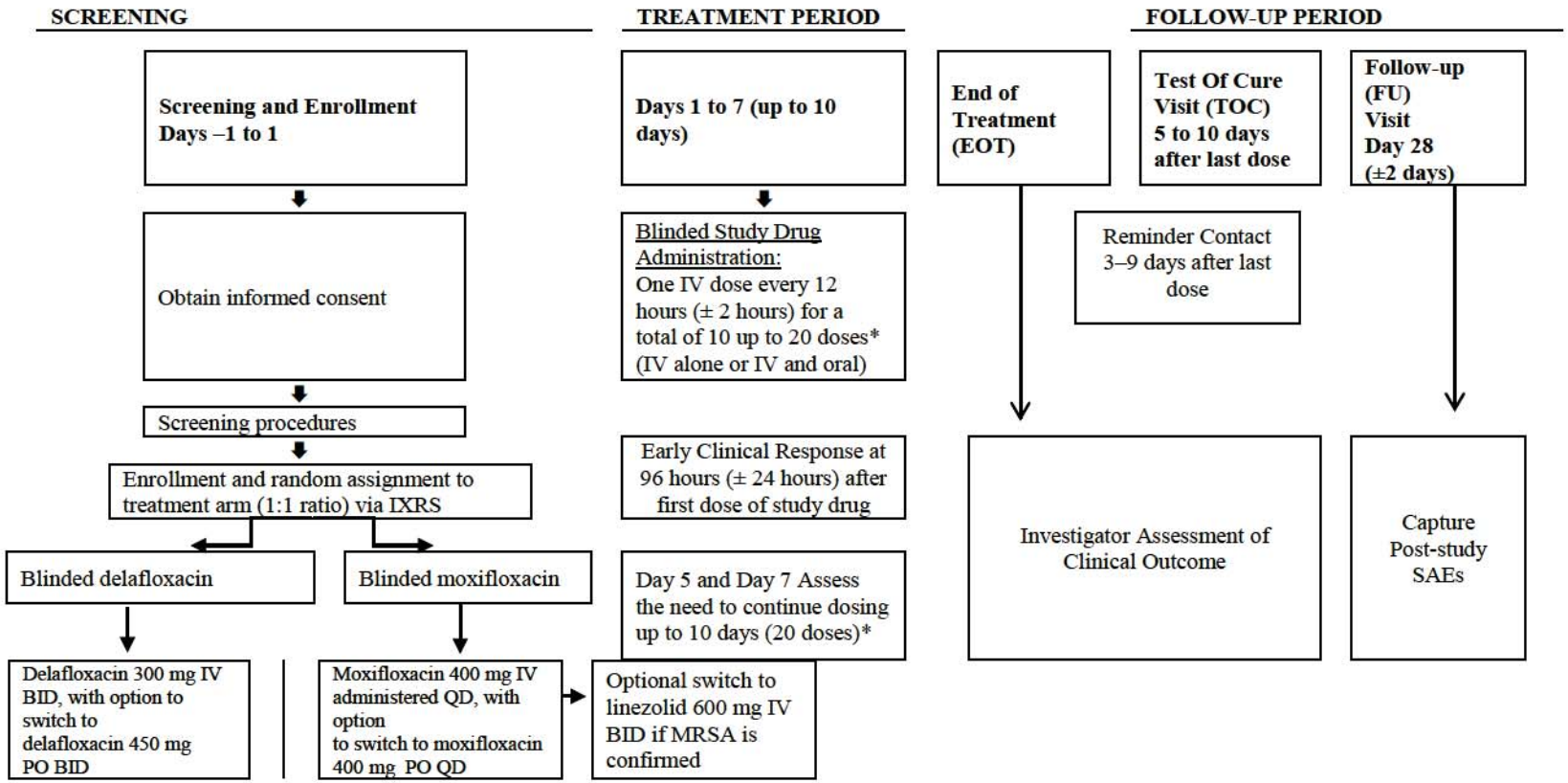
Abbreviation or term	Explanation
PK	Pharmacokinetics
PMN	Polymorphonuclear Neutrophil
PO	Oral administration
PORT	Patient Outcomes Research Team
PRSP	Penicillin-Resistant *Streptococcus pneumoniae*
PSB	Protected Specimen Brush
PSSP	Penicillin-Susceptible *Streptococcus pneumoniae*
PT	Preferred Terms
PVL	Panton-Valentine Leucocidin
QD	Every 24 hours
QoL	Quality of life
QRDR	Quinolone Resistance-Determining Region
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation
SEC	Squamous Epithelial Cells
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SP	*Streptococcus pneumoniae*
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
TOC	Test of Cure
UAT	Urine Antigen Test
ULN	Upper Limit of Normal
WHO Drug	World Health Organization Drug Dictionary

2 INTRODUCTION

This Statistical Analysis Plan (SAP) contains the detailed technical specifications for the data analysis described in the ML-3341-306 Protocol Amendment 3 (dated 04 December 2017) and includes detailed procedures for executing statistical analyses on the efficacy and safety data. The SAP will be finalized and signed prior to lock of the database.

This study will be submitted to two regulatory agencies, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). This SAP will be used for both submissions. Analyses that are specific for a regulatory agency are detailed within this SAP.

3 FLOW CHART AND VISIT SCHEDULE



* 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-resistant *Staphylococcus aureus*; SAE = Serious Adverse Event

Schedule of Events

Assessment or Procedure	Screening[a]	Treatment Period[b]						End of Treatment (EOT)/ Early Term[c]	Reminder Contact[d]	Test of Cure (TOC)[e]	Follow-Up Visit[f]
Study Day(s)	–1 to 1	1[a]	Daily while on IV	ECR (96 hr ± 24 hr[g])	5 (+ 1 day)	7 (+1 day)	End of IV[h]			5 to 10 days after last dose	28 (± 2 days)
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[i]	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[j]	X	X	X	X	X	X		X		X	
12-lead electrocardiogram[k]	X										
Complete physical examination with height and weight	X										
Targeted physical examination[l]				X				X		X	
Chest radiograph or CT scan	X							X[m]			
Local laboratory tests for eligibility[n]	X										
Pregnancy test[o]	X							X		X	X
Clinical laboratory tests (serum chemistry, coagulation[p], hematology, urinalysis[p])	X			X				X		X	
Hepatitis serology	X										
Blood culture[q]	X										
Respiratory specimen for Gram stain and culture[r]	X	X						X		X	
Determine PORT Risk Class and CURB- 65 Score	X										
SF-12v2® Health Survey and QoL Questions		X						X		X	X
Verify entry criteria	X										
Chlamydia /Legionella/Mycoplasma serology		X[s]								X	X
Urine antigen testing for *L. pneumophila/S. pneumoniae*		X[s]									
Nasopharyngeal and oropharyngeal swabs		X[s]									
Blood sample for procalcitonin		X								X	

Assessment or Procedure	Screening[a]	Treatment Period[b]						End of Treatment (EOT)/ Early Term[c]	Reminder Contact[d]	Test of Cure (TOC)[e]	Follow-Up Visit[f]
Study Day(s)	–1 to 1	1[a]	Daily while on IV	ECR (96 hr ± 24 hr[g])	5 (+ 1 day)	7 (+1 day)	End of IV[h]			5 to 10 days after last dose	28 (± 2 days)
Study drug administration every 12 ±2 hours		X[t]	X	X	X	X					
Dispense oral study drug[u]							X				
Perform drug accountability on returned drug[u]								X			
Determine adequate treatment duration					X[v]	X[v]					
PK blood sample collection			X (Day 3 ±1 day)[w]								
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[x]
Adverse event evaluation[y]	X[y]	X	X	X	X	X		X		X	X[y]

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.

[a] 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.

[b] 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).

[c] 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.

[d] 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.

[e] TOC assessments will be performed 5 to 10 days after the last dose of study drug (see protocol Section 3.3.2 for exception).

[f] 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 protocol Section 3.3.2) to return to the clinic.

[g] ECR Visit will occur 96 hours (± 24 hours) after the first dose of study drug. Procedures already completed as specified in protocol Sections 3.4.1.3 or 3.4.1.5 do not need to be repeated unless outside the ECR 96-hour (± 24 hours) window.

[h] 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.

[i] Clinical signs and symptoms of CABP will be assessed by the investigator using a 4-point severity scale (see in protocol Section 3.4.2.1).

[j] 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.

[k] Electrocardiograms will be performed at screening and if clinically indicated as determined by the investigator after screening.

[l] Targeted physical examinations will be performed during the study to assess changes from baseline parameters, adverse events, and other relevant safety information.

[m] Will be performed only in the event of lack of efficacy.

[n] 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.

[o] Pregnancy tests to be performed on women of childbearing potential only.

[p] Urinalysis and coagulation at screening only.

[q] 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. 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.

[r] 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. Rapid test for MRSA identification methods are acceptable to use if *S. aureus* is identified by the local/regional laboratory.

[s] Results are not required prior to dosing. Refer to the laboratory manual for detailed instructions on collection, processing and shipment.

[t] 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 ± 4 hours of the normally scheduled second dose. The every-12-hours (± 2 hours) dosing schedule is set after the first dose (or dose adjustment).

[u] 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.

[v] 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 protocol Section 3.4.1.8.1.

[w] Blood samples for PK analysis will be obtained from subjects at select sites on Day 3 (± 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 ± 10-minute window. Subjects do not need to be fasted before dosing or during PK sample collections.

[x] See protocol Section 3.4.3.12 for collection of concomitant medications at FU.

[y] Serious adverse events will be reported per protocol and recorded in the eCRF from the time subject provides informed consent through the FU visit.

4 STUDY OBJECTIVE AND DESIGN

4.1 Study Objectives

4.1.1 Primary Objectives

Table 4-1 Primary Objectives

The primary objective is:

FDA	EMA
To assess the clinical efficacy of 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 (± 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.

4.1.2 Secondary Objectives

Table 4-2 Secondary Objectives

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 (± 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 of respiratory pathogens.	To assess the microbiologic response to delafloxacin of respiratory pathogens in the ModMITT and ModME populations.
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 all-cause mortality in adult subjects with CABP on Day 28	To assess 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.

4.2 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, medical history, physical examination, clinical laboratory evaluations, and blood cultures within 24 hours before the first dose of study drug. Subjects may be pre-screened based on having a 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, culture, and, if possible, susceptibility testing, if positive. Blood samples for procalcitonin and serology will be obtained on Day 1, along with nasopharyngeal (NP) and oropharyngeal (OP) 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 any 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 BID IV infusions.

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 (± 24 hours) after the start of the first dose of study drug, End of Treatment (EOT), up to 28 hours after last dose, 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 (±2 days).

5 RANDOMIZATION

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 IXRS. The unblinded pharmacist or unblinded designee will obtain the treatment assignment from the IXRS as

described in the IXRS manual. A statistician from Firma Clinical Research 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 to no more than 25% of total randomized subjects.

6 SAMPLE SIZE

FDA	EMA
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 (α) of 0.025; (3) a noninferiority margin of 12.5%.	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 (α) of 0.025; (3) a noninferiority margin of 10%.

Since 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.

7 ANALYSIS POPULATIONS

Data analyses will be conducted on different analysis populations according to the purpose of the analysis (e.g., safety or efficacy). Within the efficacy analysis, different combinations of populations will be used for the clinical response and the microbiologic response. Generally, the analyses for clinical response will be 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 ModME populations for EMA. Only patients who received at least one dose of study medication and are in PORT Class III-V will be included in the modified populations. The CE/ModCE populations will be further classified by the type of assessment and timepoint of the response, as well as ME/ModME populations. The details will be introduced in the following sections for each of the populations.

Patients who receive both study therapies or receive less than 4 doses will be excluded from the CE/ModCE and ME/ModME populations. 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:

7.1 Safety Population

All randomized subjects who receive at least 1 dose of study drug, analyzed according to the treatment (delafloxacin or moxifloxacin) they received most often. If the duration of treatment is the same, then these patients will be summarized in the delafloxacin treatment group.

7.2 Intent-to-treat (ITT) Population

All randomized subjects with informed consent signed, analyzed according to treatment arm to which they were randomized.

7.3 Modified Intent to Treat (ModITT)

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

7.4 Microbiological ITT (MITT) Population

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

There will be 2 subgroups: MITT-1 and MITT-2:

- MITT-1: baseline pathogens detected by all methods, i.e. to include bacterial culture, serology, PCR, and urinary antigen. All microbiological analyses based on MITT-1 will be displayed for all pathogens, as well as definite and probable (see Table 12-1) pathogens.
- MITT-2: baseline pathogens isolated by bacterial culture only (blood or any respiratory source, including organisms cultured from NP or OP swab [*S. pneumoniae* or *M. pneumoniae*]). For *S. pneumoniae* from NP swabs, there must be a concomitant *lytA* PCR value of $\geq$1000 gene copies per mL.

7.5 Modified Microbiological ITT (ModMITT) Population

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

Two subgroups will be analyzed: ModMITT-1 and ModMITT-2.

- ModMITT-1: baseline pathogens detected by all methods, i.e. bacterial culture, serology, PCR, and urinary antigen. All analyses based on ModMITT-1 will be displayed for all pathogens, as well as definite and probable (see Table 12-1) pathogens.
- ModMITT-2: baseline pathogens isolated by bacterial culture only (blood or any respiratory source, including organisms cultured from NP or OP swab [*S. pneumoniae* or *M. pneumoniae*]). For *S. pneumoniae* from NP swabs, there must be a concomitant *lytA* PCR value of $\geq$1000 gene copies per mL.

7.6 Clinically Evaluable (CE) Populations

There will be 3 CE populations each based on the type of assessment (clinical response based on the results from clinical signs/symptoms of CABP and the investigator-assessed clinical

outcome) and timing of the assessment, including ECR (96 hours (± 24 hours)), EOT (same day or up to 28 hours after the last dose of study drug) and TOC (5 to 10 days after last dose of study drug) visits.

Patients in the CE populations will be analyzed according to the treatment they were assigned at randomization. Subjects must receive at least 4 doses of study drug by the end of Day 3 to be classified as a Clinical Failure/Nonresponder. Patients who receive both study therapies or receive less than 4 doses will be excluded from the CE populations. Patients with Indeterminate/Missing values will be excluded from the CE populations.

The evidence of acute onset of CABP in defining each CE population is as defined in the inclusion criteria as documented by the investigator.

7.6.1 Clinically Evaluable at 96 Hours (± 24 hours) for Early Clinical Response (CEECR) Population

The CE at 96 hours (± 24 hours) for early clinical response (CEECR) population will consist of all patients in the ITT population who met all the following criteria:

- Evidence of acute onset of CABP.
- Received the correct study drug based on the randomization assignment.
- Received at least 80% of the expected doses of study drug in the treatment period (see Section 15 for definition of expected dose).
- Had required early clinical response assessments (clinical signs/symptoms) of the CABP being treated within ECR window (see Section 8.5) after the initiation of treatment or the patient is a clinical failure (nonresponder); to be classified as a clinical failure (nonresponder), the patient must receive a minimum of 4 doses of study drug by the end of Day 3.
- Did not receive any potentially effective, concomitant, systemic antibacterial therapy prior to the ECR assessment except for lack of efficacy (LOE).
- Had no protocol deviations that would affect assessment of efficacy through the early clinical response time point.

7.6.2 Clinically Evaluable at EOT for Clinical Outcome (CEEOT) Population

The CE at EOT for investigator-assessed clinical outcome (CEEOT) population will consist of all patients in the ITT population who met all the following criteria:

- Evidence of acute onset of CABP.
- Received the correct study drug based on the randomization assignment
- Received at least 80% of the expected doses of study drug (see Section 15 for definition of expected doses)
- Had required clinical outcome assessments (success/failure) of the CABP being treated at EOT visit (same day of last dose day or up to 28 hours after last dose administration if the patient is a clinical success, or the patient is a clinical failure); to be classified as a clinical failure, the patient must receive a minimum of 4 doses of study drug by the end of Day 3.

- Did not receive any potentially effective concomitant, systemic antibacterial therapy prior to the EOT assessment except for LOE.
- Had no protocol deviations that would affect assessment of efficacy through the EOT visit.

7.6.3 Clinically Evaluable at TOC for Clinical Outcome (CETOC) Population

The CE at TOC for investigator-assessed clinical outcome (CETOC) population will consist of all patients in the ITT population who met all the following criteria:

- Evidence of acute onset of CABP.
- Received the correct study drug based on the randomization assignment
- Received at least 80% of the expected doses of study drug (see Section 15 for definition of expected doses)
- Had required clinical outcome assessments (success/failure) of the CABP being treated at TOC visit (5-10 days after last dose of study drug if the patient is a clinical success, or the patient is a clinical failure); to be classified as a clinical failure, the patient must receive a minimum of 4 doses of study drug by the end of Day 3.
- Did not receive any potentially effective concomitant, systemic antibacterial therapy prior to the TOC assessment except for LOE.
- Had no protocol deviations that would affect assessment of efficacy through the TOC visit.

7.7 Modified Clinically Evaluable Populations (ModCE)

For the EMA there will be 3 CE modified populations each based on the type of assessment (clinical response based on the results from clinical signs/symptoms of CABP and the investigator-assessed clinical outcome) and timing of the assessment, including ECR (96 hours ± 24 hours), EOT (same day or up to 28 after the last dose of study drug) and TOC (5 to 10 days after last dose of study drug) visits. Patients must be classified as baseline PORT class III-V to be included in the ModCE populations. ModCE patients will be analyzed according to the treatment they were assigned at randomization. Subjects must receive at least 4 doses of study drug by the end of Day 3 to be classified as a Clinical Failure/Nonresponder. Patients who receive both study therapies or receive less than 4 doses will be excluded from the ModCE populations. Patients with Indeterminate/Missing values will be excluded from the ModCE populations.

7.7.1 Modified Clinically Evaluable Population at 96 Hours (± 24 hours) for Early Clinical Response (ModCEECR) Population

The ModCE at 96 hours (± 24 hours) for early clinical response (ModCEECR) population will consist of all patients in the CEECR population who met all the criteria in Section 7.6.1 and are also classified as PORT Class III-V.

7.7.2 Modified Clinically Evaluable at EOT for Clinical Outcome (ModCEEOT)

The ModCE at EOT for investigator-assessed clinical outcome (ModCEEOT) population will consist of all patients in the CEEOT population who met all the criteria in Section 7.6.2 and are also classified as PORT Class III-V.

7.7.3 Modified Clinically Evaluable at TOC for Clinical Outcome (ModCETOC)

The ModCE at TOC for investigator-assessed clinical outcome (ModCETOC) population will consist of all patients in the CETOC population who met all the criteria in Section 7.6.3 and are also classified as PORT Class III-V.

7.8 Microbiologically Evaluable (ME) Populations

The ME populations will each consist of all patients in the MITT populations who also met the criteria for the corresponding CE (CEECR, CEEOT, CETOC) population as follows:

- MEECR: 96 hours (± 24 hours) for the early clinical response
- MEEOT: ME at EOT for clinical outcome
- METOC: ME at TOC for clinical outcome

There will be 2 subgroups for each of the MEECR, MEEOT, and METOC populations: ME-1 (ME-1ECR/ ME-1EOT/ ME-1TOC) and ME-2 (ME-2ECR/ ME-2EOT/ ME-2TOC):

- ME-1: MITT-1 population limited to patients meeting corresponding CE definition
- ME-2: MITT-2 population limited to patients meeting corresponding CE definition

Patients in the above 6 ME populations will be analyzed according to the treatment they were assigned at randomization. Patients who receive both study therapies or receive less than 4 doses by the end of Day 3 will be excluded from the ME populations. Patients with Indeterminate/ Missing values will be excluded from the ME populations.

7.9 Modified Microbiologically Evaluable (ModME) Population

The ModME populations (ModME-1 ECR/ModME-1 EOT/ModME-1 TOC/ModME-2 ECR/ModME-2 EOT/ModME-2 TOC) will each consist of all patients in the corresponding ME population and who are also classified as PORT Class III-V.

Patients in the ModME populations will be analyzed according to the treatment they were assigned at randomization. Patients who receive both study therapies or receive less than 4 doses will be excluded from the ModME populations.

7.10 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 (± 1 Day) and have at least one delafloxacin plasma concentration available. The PK population will be used for PK analyses.

8 GENERAL CONSIDERATIONS FOR STATISTICAL ANALYSIS

8.1 Interim Analyses, Final Analyses, and Unblinding

No interim analysis will be performed for this study.

Final analyses will be performed after the database is locked and the study is unblinded. Unblinding will take place after the final SAP is signed, the database is locked, and the patients in the populations are identified.

8.2 Pooling of Sites

This is a global multicenter study which will have approximately 150 sites enrolling patients.

The primary analysis of the primary endpoint will not be stratified by site.

8.3 Statistical Analysis Considerations

All analyses and summaries will be produced using SAS® software (SAS Institute, Inc, Cary, North Carolina) version 9.4 (or higher). The Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 will be used for coding adverse events and medical history. The prior and concomitant medication will be coded using the World Health Organization Drug Dictionary (WHO Drug) version March 2016.

8.3.1 Baseline

In general, baseline is defined as the last assessment prior to the first dose of study drug. For patients who were randomized but not treated, baseline is defined as the last assessment before or on the randomization date, unless otherwise specified. Unless otherwise specified, measurements that are obtained after the first dose of study drug will be considered post-baseline values. Unless otherwise specified, if measurement of a variable is not obtained from a patient prior to first dose of study drug, then that patient will be considered not having a baseline value for that variable.

For vital signs and signs and symptoms assessments, screening value is first considered as the baseline value. If there is no value collected at screening for subjects who received study drug, the last non-missing value prior to first dose date/time will be used as baseline. If there is no value collected at screening for randomized subjects who did not receive dose, the last non-missing value prior to randomization date will be used as baseline. If there is no non-missing record found before the first study drug administration, the first non-missing record collected within the first 2 hours after the first dose administration will be used as the baseline value.

For Procalcitonin, the last available data collected at Day 1 visit within 24 hours of first dose will be considered as baseline value.

For microbiologic assessments, including urine antigen, assessments up to 2 days after first dose will be considered as baseline. For randomized patients who did not take any dose, assessments up to 2 days after randomization date will be considered as baseline. Multiple pathogens may be identified from one or more baseline specimens. For serology testing, all pathogens identified will be considered as baseline pathogen.

For questionnaires including SF12-v2 and Quality of Life, non-missing data collected at nominal Day 1 visit should always be baseline, no matter whether before or after dosing. If a patient does not have available data on Day 1 for a question, the patient will be considered not having a baseline value for that question.

Change from baseline is defined as post dose and post-baseline assessment minus baseline assessment.

8.3.2 Study Day

Study day is calculated as assessment date minus date of first dose of study drug + 1 if the assessment occurred after the date of first dose of study drug. For assessments that occurred before the first dose of study drug, study day is calculated as assessment date minus date of first dose of study drug. Date of first dose is defined as study Day 1. For patients who were randomized but not treated, the randomization date will be used in place of first dose day for the calculation of study day.

8.4 Table, Listing, Figure Formatting

Post-text tables and listings will be prepared in accordance with the current ICH Guidelines. [1] [2] Continuous data will be described using descriptive statistics (i.e., n, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be described using the count and percentage in each category. For the summary statistics of all numerical variables, unless otherwise specified, minima and maxima will be displayed to the same level of precision as reported. Means, least square (LS) means, and medians will be displayed to 1 level of precision greater than the data collected. Standard deviations and standard errors will be displayed to 2 levels of precision greater than the data collected. P-values will be rounded to 4 decimal places using SAS standard pvalue format. If a p-value is less than 0.0001 it will be reported as "<.0001."

For most summary statistics, data will be analyzed and displayed by the order of the treatment groups of "Delafloxacin" and "Moxifloxacin". When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. Unless otherwise specified, the denominator for all percentages will be the number of patients in that treatment within the population of interest.

Measurements from patients excluded from the predefined populations or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables or figures unless otherwise specified, but will be included in patient listings.

Patients in all listings will be identified by the patient identification number concatenated with the site number. In addition, the PORT Risk Class at randomization will be presented in all listings to indicate if the subject is in the corresponding modified population.

In general, patient listings will be sorted by treatment group, patient number, assessment name, assessment date, and time if applicable.

Shift tables will be produced for selected safety assessments and will contain counts and percentages of patients in each cross-classification level of baseline versus post-baseline assessment. Only patients with a baseline assessment will be included in these tables, but a missing category will be permitted for post-baseline values. Shift tables will be produced for some efficacy assessments and will contain counts and percentages of patients in each cross-classification level of one of the time points versus another. In these tables, unless otherwise specified, all categories including missing, will be displayed.

8.5 Visit Window and Data Selection

For analyses of early clinical response using the signs and symptoms of CABP collected at ECR timepoint, the window of 96 hours (± 24 hours) after initiation of treatment will be considered. Due to the ±2-hour window for study drug administration, there will be an additional 2-hour window programmatically applied for the ECR timepoint, which is 70 hours to 122 hours after the start date/time of first IV infusion. Where it is specified, measurements collected before 70 hours or after 122 hours will not be used. For this endpoint at 96 hours (± 24 hours/± 2 hours) after initiation of treatment, the last measurement in this window will be used, regardless of the eCRF visit name. If time of assessment is not collected, then the date on or between the date of first dose + 70 hours and the date of first dose + 122 hours will be considered within window.

For analyses of the clinical and microbiological outcomes at EOT and TOC, the eCRF visit will be mainly used for EOT/TOC endpoints, and all other safety variables.

For ITT/ModITT, MITT/ModMITT populations, no windows will be derived for each visit and all analyses will be based on what was collected at each visit. For summaries and analyses at EOT and TOC using the CE/ModCE and ME/ModME populations, windows are defined as follows:

- EOT: same day or up to 24 hours (+4 hours) after the last dose of study drug, as only date is collected for clinical response, the EOT window for clinical response is same day or up to one day after last dose of study drug;
- TOC: 5 to 10 days after the last dose of study drug

If a patient's EOT/TOC eCRF visit is out of the respective window, or their response is Indeterminate/Missing, or they are excluded from the CE population for any other reason, this patient (and their EOT/TOC outcomes) will be excluded from the clinical outcome analyses in the CE/ModCE and ME/ModME analysis sets.

9 PATIENT DISPOSITION

There will be a summary of populations for all randomized patients by planned treatment groups and the overall. Reasons for exclusion from CE/ModCE population will be summarized for the ITT/ModITT population.

The numbers of patients who enter and complete the study will be summarized for the ITT, MITT, CETOC, and Safety populations and the respective Modified populations. Patients who do not complete the study and patients who prematurely discontinue study drug will be tabulated and categorized by primary reason for study termination (lack of effect, lost to follow-up, physician decision, subject withdrawal, adverse event, death and other).

Listings will be presented for the ITT population for patient randomization, populations, exclusion from populations, inclusion and exclusion criteria not met, and patient disposition.

10 PROTOCOL DEVIATIONS

A protocol deviation 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 sub-investigator. A significant deviation occurs when there is non-adherence to the protocol that results in a significant, additional risk to the patient when the patient, principal investigator or sub-investigator has failed to adhere to significant protocol requirements. Significant deviations can include non-adherence to inclusion or exclusion criteria, enrollment of the patient without sponsor approval, or non-adherence to FDA or other applicable regulations and/or ICH E6(R1) guidelines [3].

The criteria for identifying significant protocol deviations will be finalized as part of the final blinded data review before database lock. They will be categorized into general categories including:

- Informed consent
- Inclusion/Exclusion criteria
- Dosing errors
- Randomization errors (includes stratification errors)

- Procedural errors
- Excluded concomitant medication

Protocol deviations will be collected in a separate system. Before database lock and treatment unblinding of the study, the sponsor will review all protocol deviations and determine which category they fall in and whether they are significant protocol deviations. Significant protocol deviations will be summarized for the ITT and modified ITT populations, and protocol deviations that are significant and/or impact evaluability will be listed.

11 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

All summaries for demographic and other baseline characteristics will be presented for the ITT, Safety, MITT, CETOC, and corresponding Modified analysis populations to assess the comparability of the treatment groups. The listings will be for the ITT population unless otherwise specified.

11.1 Demographics and Baseline Characteristics

Descriptive statistics will be presented for the continuous variables age, height, weight, and body mass index (BMI) at study entry. Age in years as collected from the eCRF will be used in the analysis. The last measurement of height and weight before the first dose will be used to calculate baseline BMI as (weight in kg) / ((height in cm)/ 100) ^{2}. In addition, descriptive statistics will be presented for baseline Creatinine Clearance (CrCL) and PORT risk score.

Frequency and percentage of patients will be presented for categorical variables including sex, race, ethnicity, region, baseline CrCl group based on the Cockcroft gault formula (>30 mL/min /30->60 mL/min /60-<90 mL/min /≥90 mL/min), CURB-65 Score, PORT risk class, baseline pulse oximetry, medical history of COPD/asthma, baseline bacteremia, diabetes, at least one baseline adequate Gram stain (<10 squamous epithelial cells [SEC] and/or >25 polymorphonuclear neutrophils [PMNs]), baseline procalcitonin (≥0.15 ug/L /≥0.25 ug/L / ≥1 ug/L), baseline evidence of hepatitis B or C (Yes/No) (based upon subject data collected from medical history data) and prior antibiotic use. Patients with prior antibiotic use will be further categorized as patients with a documented failure prior to randomization and patients with a single dose/regimen of a prior antibiotic. Additionally, age groups (<65, ≥65, ≥75) and BMI categories (<30 and ≥30 kg/m^2) will be summarized.

11.2 Arterial Blood Gases at Baseline

As part of vital sign assessments, arterial blood gases can be obtained at Screening if clinically warranted. Partial pressure of arterial oxygen and partial pressure of carbon dioxide at baseline will be summarized for all available data.

By patient listings of these demographics including country and other baseline characteristics will be provided.

11.3 Chest Radiography

The assessments and results of chest radiography will be provided for the ITT and modITT population using the frequency count and percentages.

The type of image (X-Ray, CT or Other), the assessment results, the location of CABP, and the location of pleural effusion will be tabulated. The view of X-Ray (Posteroanterior, Lateral or

Posteroanterior and Lateral) will be further tabulated for the results of X-Ray. Patients with more than one lobe (multilobar disease) will be counted at baseline.

A by patient listing of radiography assessment will be provided for the ITT population.

12 MICROBIOLOGY ASSESSMENTS AND ANALYSIS OF MICROBIOLOGY AT BASELINE

Causative pathogens will be identified by isolation from a baseline culture specimen (either a respiratory specimen or blood), by urinary antigen, by serology, and/or by qPCR. Organisms will be identified to the genus and species level, except where reported by the Central Laboratory as a group or complex.

By-patient listings of all microbiological test results for each test method will be provided for the ITT analysis population.

12.1 Respiratory Culture

The collection of a sputum sample for Gram stain, culture, and susceptibility testing, as applicable, will be attempted in all subjects at baseline. Other sources of lower respiratory tract specimens, such as those obtained via bronchoalveolar lavage (BAL), protected specimen brush (PSB), endotracheal aspirate (ETA), and thoracentesis (pleural fluid), if available, are acceptable to submit for culture.

All sputum and ETA samples will be evaluated by Gram stain to determine specimen quality. An adequate sample is one with polymorphonuclear leukocytes but few (or no) squamous epithelial cells. All efforts will be made to obtain an adequate sputum or ETA specimen defined as having < 10 SECs and/or > 25 PMNs per low-power field (lpf); however, the local microbiology laboratory will perform routine culture of the respiratory sample regardless of specimen adequacy. Sputum and ETA sample adequacy will be confirmed by the central microbiology laboratory (either by re-reading the original Gram stain prepared by the local microbiology laboratory or by staining and reading the back-up Gram stain slide). Local laboratory Gram stain results will only be used in the analyses if Central laboratory Gram stain data are missing.

Isolates from positive respiratory cultures will be sent to the central microbiology laboratory for identity confirmation and antibiotic susceptibility testing, unless considered a contaminate or part of normal respiratory flora. All *S. pneumoniae* isolates will be submitted to a specialty laboratory (Emory) for serotyping.

Residual respiratory sample will be frozen and sent to a specialty microbiology laboratory (SPL) for legionella culture and identification, antibiotic susceptibility testing, and serotyping.

12.2 Blood Culture

Two sets (aerobic and anaerobic) of blood specimens for culture will be obtained at baseline from different anatomic 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. Cultures will be performed at a local or regional laboratory, as applicable. Isolates from positive blood samples will be sent to the central microbiology laboratory for identity confirmation and antibiotic susceptibility testing. All *S. pneumoniae* isolates will be submitted to a specialty laboratory (Emory) for serotyping.

12.3 Urine Antigen Testing

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

12.4 Nasopharyngeal and Oropharyngeal Swab Testing

A nasopharyngeal swab will be obtained at baseline and forwarded to a specialty laboratory (Emory) for *S. pneumoniae* culture and qPCR analysis, and serotyping. All *S. pneumoniae* isolates will be submitted to the central microbiology laboratory for antibiotic susceptibility testing. Oropharyngeal swabs will be obtained at baseline and forwarded to a specialty laboratory (UAB) for *M. pneumoniae* culture and qPCR analysis, and antibiotic susceptibility testing.

12.5 Serology

Serum samples will be collected at baseline (acute sample) and TOC or FU (convalescent sample) and forwarded to the central laboratory for serology testing (detection of serum antibodies to atypical pathogens: *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila*). Development of a positive antibody titer post-baseline (seroconversion) is considered evidence of recent infection.

12.6 Pathogen Identification and Level of Microbiological Evidence of CABP by Detection Method

Table 12-1 below lists the various bacterial detection methods used in this study as well as whether the pathogen is considered "definitive" or "probable" based on the method of detection. If a pathogen is detected or identified from multiple sources and there is at least one definitive diagnosis, the pathogen will be considered as 'Definitive'; if all diagnoses are 'Probable', then the pathogen is considered as 'Probable'. Patients with at least one definitive diagnosis will be considered as having a "Definitive" microbiological diagnosis, and if all of the diagnoses are "Probable", the patient will be categorized as having a "Probable" microbiological diagnosis.

Table 12-1: Pathogen Identification and Level of Microbiological Evidence of CABP by Detection Method

Pathogen	Specimen Type	Method of Detection	Definitive	Probable
S. pneumoniae	Sputum, ETA	Culture and Gram stain	Positive culture with Gram-stain of <10 SECs and/or >25 PMN/lpf	Positive culture *without* Gram-stain of <10 SECs and/or >25 PMN/lpf
	Lavage fluid (BAL, mini-BAL), PSB, pleural fluid and blood	Culture	Positive culture	
	NP swab	PCR		Positive *lytA* PCR (≥1000 gene copies/mL)
	NP swab	Culture and PCR	Positive culture only with *lytA* PCR ≥1000 gene copies/mL (CFU/mL)[b]	
	Urine	Urinary Antigen	Positive Urinary Antigen	
M. pneumoniae	OP swab	Culture[c]	Positive culture	

Pathogen	Specimen Type	Method of Detection	Definitive	Probable
	Serum	Serology[d]	4-fold increase in titer reaching ≥160	
L. pneumophila	Sputum, lavage fluid (BAL, mini-BAL), PSB, pleural fluid	Culture	Positive Culture	
	Urine	Urinary Antigen	Positive Urinary Antigen	
	Serum	Serology[d]	4-fold increase in titer reaching ≥128	
C. pneumoniae	Serum	Serology[d]	4-fold increase to ≥64	
Other CABP pathogens[a]	Sputum, ETA	Culture and Gram stain	Positive culture with Gram-stain of <10 SECs and/or >25 PMN/lpf	Positive culture *without* Gram-stain of <10 SECs and/or >25 PMN/lpf
	Lavage fluid (BAL, mini-BAL), PSB, pleural fluid and blood	Culture	Positive Culture	

a) Other organisms recovered by culture will be reviewed on a case-by-case basis by the Sponsor to determine eligibility as a CABP pathogen.
b) For subjects that are NP culture positive with corresponding *lytA* PCR <1000 copies per mL, these subjects are considered carriers of *S. pneumoniae,* unless *S. pneumoniae* was detected by another method.
c) Quantitative PCR (qPCR) is performed to distinguish between growth of *M. pneumoniae* versus other species of mycoplasma considered to be normal oral flora.
d) For Serology testing, any 4-fold increase between subsequent visits will be considered as having a positive baseline pathogen, even if the 4-fold increase is between two post-baseline visits.

In vitro susceptibility of pathogens to delafloxacin and moxifloxacin will be determined at the central laboratory (Covance) and reference laboratories (SPL for legionella susceptibility and UAB for mycoplasma susceptibility) 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 comparator antibiotics will also be evaluated.

For *Haemophilus influenzae* and *Haemophilus parainfluenzae,* minimum inhibitory concentration (MIC) interpretations for moxifloxacin, levofloxacin, and azithromycin (CLSI test methodology) will be derived according to CLSI guidelines [4] as shown in Table 12-2.

Table 12-2: *Haemophilus influenzae* and *Haemophilus parainfluenzae*: Susceptibility Interpretive Criteria for Moxifloxacin, Levofloxacin, and Azithromycin

	MIC Interpretive Criteria (µg/mL)	
	Susceptible	**Non-susceptible**
Moxifloxacin	≤ 1	≥ 2
Levofloxacin	≤ 2	≥ 4
Azithromycin	≤ 4	≥ 8

For the organisms listed in Table 12-3, delafloxacin MIC and zone diameter values will be interpreted based on FDA-established breakpoints [5].

Table 12-3: Susceptibility Test Interpretive Criteria for Delafloxacin

Organisms[a]	MIC (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus	≤ 0.25	0.5	≥ 1	≥ 23	20-22	≤ 19
Staphylococcus haemolyticus	≤ 0.25	0.5	≥ 1	≥ 24	21-23	≤ 20
Streptococcus pyogenes[b]	≤ 0.06	-	-	≥ 20	-	-
Streptococcus agalactiae	≤ 0.06	0.12	≥ 0.25		-	
Enterococcus faecalis	≤ 0.12	0.25	≥ 0.5	≥ 21	19-20	≤ 18
Enterobacteriaceae[c]	≤ 0.25	0.5	≥ 1	≥ 22	19-21	≤ 18
Pseudomonas aeruginosa	≤ 0.5	1	≥ 2	≥ 23	20-22	≤ 19

S = susceptible; I = intermediate; R = resistant

a) Select organisms from the FDA-approved Baxdela (delafloxacin) label for acute bacterial skin and skin structure infections (ABSSSI), for which MIC data will be available.
b) Isolates yielding MIC results other than "susceptible" will be considered "non-susceptible"
c) *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* complex only

12.7 Analysis of Microbiology at Baseline

Number and percentage of subjects with a respiratory specimen obtained, the total number of respiratory specimens obtained, and the number and frequency of each specimen type will be summarized for the ITT/ModITT populations. The microbiological yield of each respiratory specimen type at baseline will also be summarized for the ITT/ModITT populations. Based on the level of microbiological evidence of CABP described in section 12.6, the number and frequency of each baseline pathogen (definitive, probable, and total) will be summaried by treatment group and overall for the MITT-1/ModMITT-1 populations. The number and frequency of baseline pathogens will be summarized by treatment group, by test method, across all geographic regions and by geographic region (Europe, Latin American, United States, and South Africa) for the MITT-1, MITT-2, ME-1 TOC, ME-2 TOC and the corresponding modified populations.

In all microbiology summaries and analyses, the following apply:

- If the same pathogen is detected from multiple methods, it will only be counted once.
- *Staphylococcus aureus* will be summarized as a distinct pathogen with MRSA and MSSA summarized separately and considered distinct pathogens. Likewise, *Streptococcus pneumoniae* will be summarized as a distinct pathogen. Also, PRSP/PISP/PSSP will be considered as distinct pathogens, as well as MRSP/non-MRSP and MDRSP/non-MDRSP. PRSP/PISP/PSSP, MRSP and MDRSP will be summarized separately. A *S. pneumoniae* pathogen will be considered multiple drug resistant if susceptibility testing shows resistance to three or more of the classes of antibiotics.
- A patient with both MRSA and MSSA at baseline will be counted once in the overall *S. aureus* category. A patient with any combination of PSSP, PISP, and PRSP will be counted once in the overall *S. pneumoniae* category.
- When summarizing pathogens by method of detection, if *S. pneumoniae* is detected by NP swab PCR ≥1000 (probable diagnosis) and not by NP swab culture, the method of detection will be NP swab PCR; however, if *S. pneumoniae* is detected by NP swab culture and PCR ≥1000, the detection method will be NP swab culture/PCR, and the probable PCR diagnosis will be ignored in this case.

A by-patient listing of each pathogen detected, analysis visit, specimen source, method of diagnosis, associated Gram stain results (where applicable), and level of diagnostic evidence (definitive/probable) will be provided for the MITT-1 population.

12.8 Organisms Classifications

Organism classifications (Aerobe/Anaerobe, Gram-positive/ Gram-negative/ Atypical) for culture identified organisms will be reported by the central and/or specialty microbiology laboratories. However, missing organisms classifications (for organisms identified by urinary antigen tests, serology, or qPCR) will be derived as follows:

Table 12-4: Organisms Classifications

Organisms	Aerotolerance	Gram Classification
Chlamydia pneumoniae	NA	Atypical
Legionella pneumophila	Aerobe	Atypical
Mycoplasma pneumoniae	Aerobe	Atypical
Streptococcus pneumoniae	Aerobe	Gram-positive

13 PRIOR, CONCOMITANT AND POSTTREATMENT MEDICATIONS

All medications will be coded according to the WHO Drug, version March 2016.

Prior Medications: All medications taken once or more in the 14 days before Screening, including nonprescription medications and dietary supplements, will be recorded. Prior antibacterials taken up to 30 days before the first dose of study drug will also be collected.

Concomitant Medications: All concomitant medications will be recorded from the time the subject signs the informed consent through the EOT. Nonprescription medications, medications given at the time of any surgical procedure, and dietary supplements will be included.

Posttreatment Medications: Any antibiotics taken after EOT are entered 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 FU Visit. All medications collected in the eCRF, including nonprescription medications and dietary supplements, taken once or more from the EOT through the FU Visit will be defined as post treatment medication.

Medication start and end dates will be compared with the start date of study drug infusion as well as the EOT date and classified as noted in Table 13-1.

Table 13-1: Classification of Prior, Concomitant and Posttreatment medications

End Date/time / Start Date/time	Before start of study drug administration	On or after start of study drug administration but before EOT	After EOT	Missing
Before start of study drug administration	Prior	Concomitant	Concomitant	Concomitant
On or after start of	–	Concomitant	Concomitant	Concomitant

End Date/time / Start Date/time	Before start of study drug administration	On or after start of study drug administration but before EOT	After EOT	Missing
study drug administration but before EOT				
After EOT	–	–	Posttreatment	Posttreatment
Missing	Prior	Concomitant	Concomitant	Concomitant

For randomized subjects who do not take study drug, if any medication is collected, it will be considered as prior.

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 medication will be considered prior. 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 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 whether the medication is prior or concomitant. If the medication stopped before Day 1 of the study, then it will be considered prior. If the end date is on or after Day 1 of the study, the medication will be considered concomitant.
- 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 medication will be considered concomitant.
- If the month/year of the onset date is later than the month/year of Day 1 of the study and on or before the month/year of EOT, the medication will be considered concomitant. If the month/year of the onset date is after the month/year of EOT, the medication will be considered posttreatment.

Medications with completely missing stop dates and start dates will be considered concomitant medications.

All prior, concomitant, and post-treatment medications will be summarized by treatment group for Anatomical Therapeutic Chemical (ATC) levels (4th level: Chemical Subgroup) and preferred terms according to drug class using WHO Drug. The number and percentage of patients reporting each medication will be provided for each treatment group. At each level of summarization, a patient will only be counted once per drug class or preferred term. For example, if a patient reports multiple medications with the same drug class, then that drug class will only be incremented by one. As with the drug class, if a patient reports multiple medications with the same preferred term, then that preferred term will only be incremented by one since patient counts will be presented.

Summaries will be provided for prior non-antibacterial medications for the ITT/ModITT population and for non-antibacterial medications received on after the first dose of study drug through the Follow-up for the ITT/ModITT population.

Summaries will be provided for prior antibacterial medications for the ITT/ModITT population. A similar summary will be provided for antibacterial medications received on or after the first

dose of study drug through the EOT visit and those received after the EOT visit for the ITT/ModITT population.

All non-antibacterial medications data and all antibacterial medications data will be provided in separate listings.

14 MEDICAL HISTORY

14.1 General Medical and Surgical History

Medical and surgical history is recorded at screening and includes clinically significant medical illnesses, surgical procedures, or underlying/accompanying diseases (excluding pulmonary conditions) existing 2 years prior to or on entry to the trial. It will be summarized overall and for each system organ class (SOC) and each preferred terms (PT) for the ITT/ModITT population. Number and percentage of subjects with medical and surgical history will be presented, as well as number and percentage of subjects hospitalized for more than 2 days within the last 90 days.

SOC and PT will be coded term using MedDRA version 19.1.

Data related to the current infection under study will be recorded under CABP signs and symptoms pages of the eCRF.

Medical history and surgical history will be presented in a listing for the ITT population.

14.2 Pulmonary Disease History

Pulmonary disease history is also recorded at screening. It includes oxygen therapy prior to enrollment for a condition other than this episode of pneumonia and any pulmonary illnesses or underlying/accompanying pulmonary diseases existing 2 years prior to or on entry to the trial.

A summary of pulmonary disease history will be provided for ITT/ModITT population. Subjects who received oxygen prior to enrollment for a condition other than this episode of pneumonia, along with methods of administration will be tabulated. The number and percentage of subjects who had a history of pulmonary disease in the last two years, and the number and percentage of subjects hospitalized for each pre-existing pulmonary conditions for more than 2 days within the last 90 days will be presented as well.

A by subject listing of pulmonary disease history will be provided for all ITT subjects.

14.3 Risk Factors for Pneumonia

Smoking history, and vaccination history data are collected at screening. The smoking status for each subject, whether the subject had a pneumococcal vaccination against pneumococci during the last 5 years or a flu vaccine during the current year, and the type of vaccine will be summarized for ITT/ModITT population.

A by subject listing of risk factors for pneumonia will be provided for all subjects in ITT population.

15 STUDY DRUG EXPOSURE AND COMPLIANCE

The following analyses will be provided for the ITT/ModITT and safety populations.

A dosing summary by treatment group will be presented. Duration of study drug exposure in days will be defined as (start date of last dose – start date of first dose + 1). If the date of either the first or last dose is unknown, duration of exposure to study drug will be calculated using all

available information. For example, if a patient is missing the stop date for the last day of his dosing on day 6 and has the start and stop dates for dosing on days 1-5, his duration of exposure is 6 days. The number and percentage of patients by the total number of days on therapy, defined as 24 hour periods on study drug therapy (0, 0.5 to 4, >4 to 8, >8 to 10, >10 days) in each treatment group will be presented as well as descriptive statistics for total days on therapy.

In addition, descriptive statistics for total days on oral and total days on IV therapy will be provided as well.

For summarization, a partial dose will be treated as a full dose. The descriptive statistics of the total number of IV doses in each treatment group will also be presented.

The number and percentage of patients who received linezolid or linezolid placebo by the total number of days on therapy, defined as 24 hour periods on study drug therapy (0 to 2, 3 to 5, 6 to 8, 9 to 10, >10) in each treatment group will be presented as well as descriptive statistics for total days on therapy.

There will be summaries of the number and percentage of patients for whom at least 1 infusion is interrupted or not completed.

Specific dosing regimens by treatment group are summarized in Table 15-1.

Table 15-1 Treatment Regimens

	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/placebo 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 a partial switch back to IV applies	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 and continue oral placebo delafloxacin twice daily

All placebo will be counted for number of doses on both IV therapy and oral therapy; If some dose administration data are missing for a patient, but there are data showing a dose was

administered to the patient, the dose will be considered administered for calculation of compliance.

Percent compliance at EOT and TOC:

In general, the percent compliance for each subject in the treatment period will be determined as the number of doses received divided by the expected number of doses multiplied by 100%. The expected number of doses will be the summation of the expected number of doses in each treatment period.

For subjects who never took a study drug, the percent compliance at EOT and TOC will be considered as 0.

Number of doses:

The count for the IV dosing data will be used to determine the number of study drug doses received for IV treatment. The sum of the number of capsules/tablets taken collected in the 'Oral Dosing' eCRF,will be calculated for the number of doses on oral therapy. For subjects who never took a study drug, the number of doses will be considered as 0.

The calculation of the expected number of doses may be based on one to three treatment periods, depending on the actual received treatment for each subject.

Treatment period and Expected number of daily dose:

If a patient is randomized to delafloxacin treatment group, the expected number of daily doses varies in the following periods:

- IV Period – Patient will receive 2 IV delafloxacin daily doses. Expected daily dose=2;
- IV Period with MRSA Treatment Initiated – Patient will receive 2 IV delafloxacin doses. Expected daily dose=2;
- Oral Period – Patient will receive 2 oral delafloxacin doses and 1 oral placebo moxifloxacin dose. Expected daily dose=3;
- Oral Period with MRSA Treatment Initiated – Patient will receive 2 oral delafloxacin doses and 2 IV placebo linezolid doses. Expected daily dose=4;

If a patient is randomized to moxifloxacin treatment group, the expected number of daily doses varies in the following periods:

- IV Period – Patient will receive 1 IV moxifloxacin dose and 1 IV placebo moxifloxacin dose. Expected daily dose=2;
- IV Period with MRSA Treatment Initiated – Patient will receive 2 IV linezolid doses. Expected daily dose=2;
- Oral Period – Patient will receive 2 oral placebo delafloxacin doses and 1 oral moxifloxacin dose. Expected daily dose=3;
- Oral Period with MRSA Treatment Initiated – Patient will receive 2 oral placebo delafloxacin doses and 2 IV linezolid doses. Expected daily dose=4;

Each patient will not undergo all of these 4 treatment periods. A patient may stay on IV treatment throughout the study, or never be identified with MRSA. A patient may skip the oral

period if the MRSA is identified before the oral switch. IV Period with either Delafloxacin or Moxifloxacin as first administration should always be the first treatment period.

Cut-off dates and duration in treatment:

If a patient never switched to oral, the duration in treatment period can be determined using the treatment day and first/second dose collected in the eCRF:

First, duration in IV treatment is calculated by last treatment day – first treatment day + 1, Then, if the last IV dose is the first dose in that treatment day, substract duration by 0.5 day.

If a patient switched to oral, the first date of MRSA and the first date of oral dosing will be the cut-off dates for different treatment periods, wherever applicable.

The duration for each treatment period is first calculated as: period end date – period start date + 1. For the oral period, if the start time is in PM, then the duration – 0.5, meanwhile, if the end time is in AM, the duration – 0.5. If a patient initiated MRSA treatment after switching to oral dose, the later end date between MRSA treatment and oral treatment will be used to calculate the treatment duration.

For subjects who never took a study drug, the duration in treatment will be considered as 0.

Expected number of doses in treatment:

The expected number of doses in each treatment period will be calculated as follows:

Number of doses in the first day of each treatment period + Number of doses in the last day of each treatment period + [Expected number of daily dose × (last day of each treatment period − first day of each treatment period − 1)].

For subjects who never took a study drug, the expected number of doses will be considered as 0.

Percent compliance at ECR timepoint:

All dose(s), including IV, oral doses and placebo that are administered before the date of last available data in eCRF page 'Clinical Signs/Symptoms of CABP' before 122 hours will be considered when determining the compliance rate at ECR.

If subjects do not have signs/symptoms of CABP assessed at ECR timepoint at all, then 122 hours after first dose administration will be used to identify which dosing data to be included for compliance rate calculation at ECR.

If a patient switched to oral on or before having ECR assessment, or the patient switched to oral on or before the date of first dose/time + 122 hours if the patient does not have ECR assessment, the oral end time before ECR timepoint will be considered as 'PM'.

After selecting the dosing data, the algorithm used for EOT/TOC will be applied to calculate the compliance rate at ECR. In this case, the date/time of last available data in eCRF page 'Clinical Signs/Symptoms of CABP' before 122 hours will be used as the last period end date/time in the formula for compliance rate calculation at ECR timepoint. If the patient does not have ECR assessment, first dose date/time + 122 hours will be used as the last period end date/time in the formula for compliance rate calculation at ECR timepoint.

For subjects who never took a study drug, the percent compliance at ECR timepoint will be considered as 0.

Descriptive statistics of compliance at EOT and TOC for the study will be presented by treatment group as well as the proportion of patients with at least 80% compliance.

Study drug administration for each patient will be presented in two separate listings (IV and Oral). Dosing date and time, dose amount and dose unit, treatment day, which infusion of the day (First/Second) or timing of oral dose (AM/PM), whether the treatment is used for MRSA infection or not, IV interrupted or incomplete and other administration related information will be included.

Number of doses, expected doses and compliance rate for each patient will be presented in a listing named "Study Drug Compliance".

The IV drug preparation date and time, drug prepared, and other preparation related information will be provided in a listing named "IV Drug Preparation".

16 ANALYSIS OF EFFICACY

The efficacy endpoint definitions for clinical response are based on FDA and EMA guidance and recommendations. Efficacy will be evaluated via the investigators'assessments of signs and symptoms of infection. Summaries will be presented by the randomized treatment group.

16.1 Efficacy Endpoints Definitions

16.1.1 Early Clinical Response

Symptoms for the Early Clinical Response will be evaluated by the investigator on a four-point scale (absent, mild, moderate, severe) with improvement defined as at least a 1-point improvement (decrease) from baseline to the assessment performed 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 21.7 for definitions of symptom intensity. Due to the 2-hour window for study drug administration, there will be an additional 2-hour window programmatically applied for the ECR timepoint, which is 70 hours to 122 hours after the start date/time of first IV infusion. See section 8.5 for selection of ECR assessment.

Responders: Improvement at 96 hours (± 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.

Nonresponders: Improvement is not achieved at 96 hours (± 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 worsening of a CABP symptom; 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 from the current CABP infection. Indeterminate/missing assessments will be mapped to nonresponders in the statistical analysis of the ITT/ModITT Population.

16.1.2 Clinical Outcome at EOT and TOC

The 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 eligible 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 analyses in the ITT/ModITT populations and will be excluded from analyses in the CE/ModCE and ME/ModME populations.

16.1.3 Microbiologic Response

By-patient microbiological responses at TOC will be determined by consideration of the microbiological response(s) for each baseline pathogen at TOC. By-patient microbiological success is defined as eradication or presumed eradication of all baseline pathogens. By-patient microbiological responses for subjects in the MITT-1/ModMITT-1 and ME-1 TOC/ModME-1 TOC sets will be based on by-pathogen microbiological responses of baseline pathogens identified by all test methods. By-patient microbiological responses for subjects in the MITT-2/ModMITT-2 and ME-2 TOC/ModME-2 TOC analysis sets will be based on by-pathogen microbiological responses of baseline pathogens identified by culture methods.

By-pathogen microbiological responses will be based on follow up cultures performed at TOC that document eradication or persistence of pathogens detected at baseline. When post-baseline culture results are missing, the clinical outcome assigned by the investigator will be considered. Pathogens identified at baseline by a test method other than routine culture of a blood or lower respiratory tract sample (ie, sputum, ETA, pleural fluid, PSB, or lavage fluid) can only have a presumed or indeterminate microbiologic response, unless persistence is demonstrated by culture.

If a patient received a non-study antibiotic prior to a TOC microbiological sample collection, and the TOC culture shows no growth, normal respiratory flora, or is positive for "new" isolates only (different from the baseline pathogen), then the pathogen-level micro response at TOC will be based on clinical response at TOC.

The following by-pathogen microbiological responses will be considered for baseline pathogens:

Eradication: The respiratory and/or blood specimen at the TOC Visit shows the pathogen(s) present at enrollment was eradicated and there was no use of additional antimicrobial therapy for the current infection. Investigator-assessed clinical outcome is not considered a determining factor for this microbiologic response definition.

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 the causative pathogen(s) present at enrollment. Persistence of the baseline pathogen at EOT is carried forward to TOC. Investigator-assessed clinical outcome is not considered a determining factor for this microbiologic response definition.

Presumed Persistence: No respiratory and/or blood specimen was available for a case classified as clinical failure (including failures carried forward to TOC visit.)

Indeterminate/missing: No respiratory and/or blood specimen was available at TOC with a clinical assessment of Indeterminate/missing, unless there was evidence of persistence of the baseline pathogen at EOT (carried forward to TOC).

The following categorizations will be analyzed for new post-baseline pathogens:

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

New infection: A culture taken after 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.

16.2 Endpoints

For FDA, the primary endpoint of the ECR defined as improvement at 96 hours (± 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 the other symptoms in the ITT population will be tested for noninferiority (NI). If the NI of delafloxacin is declared in the primary analysis, the secondary endpoints will be tested for superiority using a fixed sequential (hierarchical) testing procedure.

For the EMA, the primary endpoint is the clinical outcome at TOC 5-10 days after the first dose of study drug. All the primary and secondary endpoints for EMA will be analyzed for noninferiority with the possibility to switch to superiority.

Primary Endpoints:

FDA	EMA
The ECR defined as improvement at 96 hours (± 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 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 ModCETOC populations.

Secondary Endpoints:

FDA	EMA
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 (± 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 any of the other symptoms in the ModITT and ModCEECR populations
Clinical Outcome at TOC (CETOC 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 ModCEECR populations
Clinical Outcome at the EOT (ITT and CEEOT)	Clinical Outcome at EOT (ModITT and ModCEEOT)
ECR in the MITT-1 and MITT-2 population	Clinical Outcome at TOC in the ModMITT-1, ModMITT-2, ModME-1 TOC, and ModME-2 TOC populations
Microbiologic Response (MITT-1, MITT-2, ME-1-TOC and ME-2-TOC)	Microbiologic response at TOC (ModMITT-1, ModMITT-2, ModME-1-TOC and ModME-2-TOC)
All-cause mortality (ITT and Safety)	All-cause mortality (ModITT and Safety)

16.3 Primary and Secondary Efficacy Analyses Specific for FDA

16.3.1 Primary Efficacy Analyses for FDA

The primary efficacy endpoint for FDA is the Early Clinical Response defined as improvement at 96 hours (± 24 hours), which is 70 hours to 122 hours after the start date/time of first IV infusion due to the 2-hour window for study drug administration, 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 any of the other symptoms in the ITT population.

Each treatment group's response rate will be defined as:

(# Responders) / (# Responders+ # Non-responders).

Primary Hypothesis for FDA

The null (H_0) and alternative (H_a) hypotheses to be tested to establish the non-inferiority of delafloxacin are:

$$H_0: P_d - P_m \leq -0.125$$
$$H_a: P_d - P_m > -0.125$$

where P_d and P_m are the probabilities of the ECR for delafloxacin and moxifloxacin, respectively.

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.

An indeterminate/missing response will be classified as Nonresponders for purposes of the primary analysis for FDA.

The number and percentage of patients in each response category (responder and nonresponder) will be summarized by treatment group. The reasons for clinical non-response at ECR will be summarized for the ITT population.

Forest plots of the difference (defined as the delafloxacin treatment group minus the moxifloxacin treatment group) between treatment groups for the primary endpoint will be produced for the ITT population.

16.3.2 Sensitivity Analyses for FDA

Sensitivity analyses of the primary FDA endpoints will be performed to investigate the robustness of the primary efficacy results. 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 single dose/regimen systemic antimicrobial use using the same Miettinen-Nurminen test.
- The primary analysis performed on the MITT-1/MITT-2, CEECR, and ME-1ECR/ME-2ECR analysis populations.

16.3.3 Subgroup Analyses for FDA

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 with respect to these subgroups, further exploration will be performed as an adjusted analysis of the primary outcome.

- Demographic subgroups: age categories (age <65, ≥65, ≥75), sex, BMI categories (BMI < 30 and ≥30), baseline PORT score (I, II, III, IV, or V), baseline CURB-65 Score (0-5), ethnicity (Hispanic or Latino, Not Hispanic or Latino, or Not Applicable), region (Europe, Latin America, North America, and South Africa), and race categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Applicable, or Other).
- Prior systemic antibiotic use, and the further subcategories of patients with documented failure prior to randomization and patients with a single dose/regimen of a prior antibiotic.
- Presence or absence of: baseline bacteremia, multilobar pneumonia, diabetes, history of COPD/asthma, history of infectious hepatitis, renal impairment/disease based on CrCl, baseline nursing home status/hospitalization in last 90 days, and baseline Gram stain adequacy (Yes/No)
- Baseline procalcitonin category (≥0.15 ug/L /≥0.25 ug/L / ≥1 ug/L)
- Baseline pathogen by any diagnostic method and by diagnostic method

- Monomicrobial versus polymicrobial infection
- System Organ Class (SOC) of Cardiac Disease
- SOC of Vascular Disease
- SOC of Cardiac or Vascular Disease

These subgroup analyses will be performed using the ITT and CEECR populations for the primary FDA efficacy endpoint except as follows: analysis of ECR by adequate Gram stain (Yes/No) and baseline procalcitonin level will additionally be performed in the MITT-1 population. Analysis of ECR by pathogen, and by monomicrobial/polymicrobial infections will be performed for the MITT-1, MITT-2, ME-1 ECR and ME-2 ECR populations. Analysis of ECR by pathogen by diagnostic method will be performed in the MITT-1 and ME-1 ECR populations.

Additional subgroup analyses may be performed if deemed necessary.

16.3.4 Secondary Efficacy Analyses for FDA

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 16.2 Unless specified otherwise in the endpoint definition, the testing will be performed in the ITT analysis population.

Hypotheses for Superiority Analysis

The null (H_o) and alternative (H_a) hypotheses to establish superiority of delafloxacin in the clinical response or clinical outcome can be written as:

$H_o: P_d - P_m \leq 0$

$H_a: P_d - P_m > 0$

A two-sided 95% CI for superiority testing will be computed based on the difference in sample responder rates for delafloxacin and moxifloxacin at ECR, EOT and TOC after initiation of treatment using both stratified and non-stratified method proposed by Miettinen and Nurminen 1985 [6], details in Appendix (Section 21.1).

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 of the 95% CI exceeds 0, it will be concluded that delafloxacin is superior to moxifloxacin for treating patients with CABP.

16.3.4.1 Early Clinical Response with the Addition of Improvement in Vital Signs Required as Response

In addition to meeting the criteria for the primary signs and symptoms-based endpoint, to be considered a responder for this secondary endpoint subjects were required at the ECR visit to show improvement or no worsening in all vital signs assessments. If a patient had abnormal vital signs at baseline, that abnormal vital sign has to be normal at ECR. If a vital sign was normal at baseline, then it could not have worsened (ie, be abnormal) at ECR.

The abnormal vital signs were defined as following:

a) Fever: body temperature > Upper Limit of Normal (ULN)

Temperature Method	ULN
Oral	38°C/100.4°F
Tympanic	38.5°C/101.3°F
Rectal	39°C/102.2°F
Axillary, Forehead	37.5°C/99.5°F

Temperature collected through other methods will be assessed at the study end and before the study unblind.

b) Hypotension - systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg

c) Tachycardia (heart rate >100 beats per minute)

d) Tachypnea (respiratory rate >18 breaths/minute).

If multiple results were collected in the ECR window, the latest results within the ECR window will be used for the analysis.

The treatment difference (delafloxacin – moxifloxacin) and the superiority testing using the 2-sided 95% CI on the difference from the Miettinen-Nurminen test, without stratification, of ECR with the addition of Improvement in vital signs and no worsening of the 4 symptoms required as response will be presented. 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 0, it will be concluded that delafloxacin is superior to moxifloxacin for treating patients with CABP.

This analysis will be performed using the ITT and CEECR population.

16.3.4.2 Clinical Outcome at EOT and TOC

The difference (delafloxacin – moxifloxacin) in response rates and the superiority testing of two treatment comparison using the 2-sided 95% CI from Miettinen-Nurminen test, without stratification, on the difference in response rates will be presented.

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 of the 95% CI exceeds 0, it will be concluded that delafloxacin is superior to moxifloxacin for treating patients with CABP.

The analysis of clinical outcome at EOT and TOC will be performed using the ITT, and respective CE analysis populations.

In addition, the analysis of clinical outcome at TOC will be performed using the MITT-1, MITT-2, ME-1 TOC and ME-2 TOC analysis populations.

An indeterminate/missing response will be classified as failure for purposes of the primary ITT and MITT analyses, but will be excluded from the analyses of CE and ME populations.

For the assessment of Clinical Outcome at EOT and TOC, each treatment group's Clinical Outcome rate will be defined as: (# Success) / (#Success+#Failure).

The assessment of Clinical Outcome at TOC will also be performed stratified by baseline PORT classification, medical history of COPD/asthma and prior receipt of systemic antimicrobials. In addition, subgroup analyses listed in Section 16.3.3 will also be performed for the assessment of

Clinical Outcome at the TOC. These subgroup analyses will be performed using the ITT and CE TOC populations except as follows: analysis of Clinical Outcome at TOC by adequate Gram stain (Yes/No) and baseline procalcitonin level will additionally be performed in the MITT-1 analysis population. Analysis of Clinical Outcome at TOC by pathogen (by any diagnostic method and by each diagnostic method) and by monomicrobial/polymicrobial infections will be performed using the MITT-1/ME-1 populations. Analysis of Clinical Outcome at TOC by monomicrobial/polymicrobial infections will additionally be presented for the MITT-2 and ME-2 populations

The clinical outcome assessed by the investigator at each visit will be provided in a listing along with the reason for failure/indeterminate/missing.

Forest plots for secondary endponts will display the difference between treatment groups for each population and selected subgroup analyses.

16.3.4.3 Early Clinical Response for Subjects in the MITT Population

The treatment difference (delafloxacin – moxifloxacin) of ECR for patients in the MITT-1 and MITT-2 populations 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.

16.4 Primary and Secondary Efficacy Analyses Specific for EMA

16.4.1 Primary Efficacy Analyses for EMA

The primary efficacy endpoint for EMA is the Clinical Outcome at TOC.

For the assessment of Clinical Outcome at TOC, each treatment group's Clinical Outcome rate will be defined as:

(# Success) / (# Success+ # Failure).

Primary Hypothesis for EMA

The null (H_0) and alternative (H_a) hypotheses to be tested to establish the non-inferiority of delafloxacin are:

$$H_0: P_d - P_m \leq -0.1$$
$$H_a: P_d - P_m > -0.1$$

where P_d and P_m are the probabilities of the Clinical Outcome rates for delafloxacin and moxifloxacin, respectively.

The difference (delafloxacin – moxifloxacin) in response rate and the treatment comparison using the 2-sided 95% confidence interval (CI) on the difference in response rate stratified by baseline PORT classification, medical history of COPD and asthma, and prior receipt of systemic antimicrobials using the Miettinen- Nurminen test will be presented. This analysis will be performed using the ModITT/ModCETOC population.

An indeterminate/missing response will be classified as Failure for purposes of the primary analysis for EMA in the ModITT analysis and excluded from the ModCETOC analysis.

The number and percentage of patients in each outcome category (success and failure) will be summarized by treatment group. The reasons for failure at TOC will be summarized for the ModITT population.

Forest plots of the difference (delafloxacin – moxifloxacin) between treatment groups for the primary endpoint will be produced for the ModITT/ModCETOC population.

16.4.2 Sensitivity Analyses for EMA

Sensitivity analyses of the primary EMA endpoints for will be performed to investigate the robustness of the primary efficacy results. The following sensitivity analyses for the primary endpoint will be performed

- The primary analysis without stratification using the same Miettinen- Nurminen test.
- The primary analysis, without stratification, performed on the ModMITT and ModMETOC analysis populations.
- To control the possible influence of age on the clinical evaluation, the primary endpoint will be assessed using age categories, defined as Age < 65 and Age ≥ 65, as an additional factor in the model.

16.4.3 Subgroup Analyses for 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. If there are large imbalances between treatment groups in these subgroups, further exploration will be performed 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 score (I, II, III, IV, or V), baseline CURB-65 Score (0-5), ethnicity (Hispanic or Latino, Not Hispanic or Latino, or Not Applicable), region (Europe, Latin America, North America, and South Africa), and race categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Applicable, or Other).
- Prior systemic antibiotic use, and the further subcategories of patients with a documented failure prior to randomization and patients with a single dose/regimen of a prior antibiotic (Yes/No).
- Presence or absence of: baseline bacteremia, multilobar pneumonia, diabetes, history of COPD/asthma, history of infectious hepatitis, renal impairment/disease based on CrCL, baseline nursing home status/hospitalization in last 90 days, baseline adequate Gram stain (Yes/No), and by pathogen.
- Baseline procalcitonin category (≥0.15 ug/L /≥0.25 ug/L / ≥1 ug/L)
- Baseline pathogen by any diagnostic method and by diagnostic method
- Monomicrobial versus polymicrobial infection
- SOC of Cardiac Disease
- SOC of Vascular Disease
- SOC of Cardiac or Vascular Disease

These subgroup analyses will be performed using the ModITT and ModCE TOC populations for the primary EMA efficacy endpoint except as follows: analysis of Clinical Outcome at TOC by adequate Gram stain (Yes/No) and baseline procalcitonin level will additionally be performed in the ModMITT-1 analysis population. Analysis of Clinical Outcome at TOC by pathogen (by any diagnostic method and by each diagnostic method) and by monomicrobial/polymicrobial

infections will be performed using the ModMITT-1/ModME-1 populations. Analysis of Clinical Outcome at TOC by monomicrobial/polymicrobial infections will additionally be presented for the ModMITT-2 and ModME-2 populations.

Additional subgroup analyses may be performed if deemed necessary.

16.4.4 Secondary Efficacy Analyses for EMA

For EMA submissions, if noninferiority of delafloxacin is declared in the primary analysis, the secondary endpoints will be tested for NI, with the possibility of establishing to switch to superiority in the ModITT/ModCE and ModMITT/ModME analysis populations.

Hypotheses for NI analysis

The hypotheses for NI in the secondary efficacy analysis for EMA will be similar to those for the primary efficacy analyses for EMA.

Hypotheses for Superiority Analysis

The null (H_o) and alternative (H_a) hypotheses to establish superiority of delafloxacin in the clinical response or clinical outcome can be written as:

$$H_o: P_d - P_m \leq 0$$
$$H_a: P_d - P_m > 0$$

A two-sided 95% CI for superiority testing will be computed based on the difference in sample responder rates for delafloxacin and moxifloxacin at ECR, EOT and TOC after initiation of treatment using non-stratified method proposed by Miettinen and Nurminen 1985, details in Appendix (Section 21.1).

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 of the 95% CI exceeds 0, it will be concluded that delafloxacin is superior to moxifloxacin for treating patients with CABP.

The ECR related endpoints and analyses defined for FDA submission will also be performed as additional sensitivity analyses for EMA submission.

16.4.4.1 Early Clinical Response in the ModITT and ModCE Population

The primary efficacy endpoint for FDA is the Early Clinical Response defined as improvement at 96 hours (± 24 hours) 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 any of the other symptoms in the ITT population. For EMA, assessment of early clinical response will be performed in the ModITT and ModCE-ECR populations and is considered a secondary endpoint.

16.4.4.2 Early Clinical Response with the Addition of Improvement in Vital Signs Required as Response

In addition to meeting the criteria for the primary signs and symptoms-based endpoint, to be considered a responder for this secondary endpoint subjects were required at the ECR visit to show improvement or no worsening in all vital signs assessments. If a patient had abnormal vital signs at baseline, that abnormal vital sign has to be normal at ECR. If a vital sign was normal at baseline, then it could not have worsened (ie, be abnormal) at ECR.

The abnormal vital signs were defined as following:

a) Fever: body temperature > Upper Limit of Normal (ULN)

Temperature Method	ULN
Oral	38°C/100.4°F
Tympanic	38.5°C/101.3°F
Rectal	39°C/102.2°F
Axillary, Forehead	37.5°C/99.5°F

Temperature collected through other methods will be assessed at the study end and before the study unblind.

b) Hypotension - systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg

c) Tachycardia (heart rate >100 beats per minute)

d) Tachypnea (respiratory rate >18 breaths/minute).

If multiple results were collected in the ECR window, the latest results within the ECR window will be used for the analysis.

The superiority testing of 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. 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.

This analysis will be performed using the ModITT and ModCE-ECR populations.

16.4.4.3 Clinical Outcome at EOT

The testing of 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 ModITT and ModCEEOT analysis populations.

An indeterminate/missing response will be classified as failure for purposes of the primary ModITT analysis. For the assessment of Clinical Outcome at EOT, each treatment group's Clinical Outcome rate will be defined as: (# Success) / (#Success+#Failure).

In addition, this analysis will be performed on the ModMITT-1 analysis population.

16.4.4.4 Clinical Outcome at TOC in the ModMITT and ModME Populations

The primary EMA endpoint, without stratification, will also be analyzed using the ModMITT, ModME-1TOC and ModME-2TOC analysis populations. An indeterminate/missing response will be classified as failure for purposes of the ModMITT analysis; but will be excluded from ModME analysis populations.

16.5 Other Secondary Efficacy Analyses for both FDA and EMA

16.5.1 Microbiological Response Analyses for both FDA and EMA

The secondary endpoints of microbiological response (documented eradicated, presumed eradicated, documented persisted, presumed persisted, indeterminate/missing) will be determined at the patient and pathogen level for the MITT-1, MITT-2, ME-1TOC and ME-2TOC populations for FDA; and for the ModMITT-1, ModMITT-2, ModME-1TOC and ModME-2TOC populations for EMA. The treatment difference (delafloxacin – moxifloxacin) in microbiologic success rates and a comparison using the 2-sided 95% CI around the difference in microbiologic success rates from the Miettinen-Nurminen test, without stratification, will be presented. By patient microbiologic responses will be summaried by definitive vs probable microbiologic diagnosis patient subgroup in the MITT-1and ME-1TOC populations for FDA; and in the ModMITT-1, and ModME-1TOC populations for EMA.

Per-pathogen microbiologic responses will be summarized in the MITT-1, MITT-2, ME-1TOC and ME-2TOC for FDA; and ModMITT-1, ModMITT-2, ModME-1TOC and ModME-2TOC populations for EMA. Per-pathogen microbiologic responses will be summarized by definitive vs probable baseline pathogenin the MITT-1and ME-1TOC populations for FDA; and ModMITT-1and ModME-1TOC populations for EMA. Microbiological outcomes will be summarized for *Staphylococcus aureus* and separately for MRSA and MSSA. Microbiological outcomes will be summarized for *Streptococcus pneumoniae* (SP) and separately for PSSP, PISP, and PRSP and MDRSP. Patients with both MRSA and MSSA, or with any combination of PSSP/PISP/PRSP, will be counted once in the overall organism group.

A by-patient listing of all baseline pathogens including patient-level and pathogen-level microbiological responses for the MITT-1 and MITT-2 will be generated for the ITT population.

In addition, per-patient microbiological response at TOC by monomicrobial (Gram-positive, Gram-negative, Atypical), polymicrobial/mixed microbial infection subgroup will be presented by treatment group in the MITT-1, MITT-2, ME-1TOC and ME-2TOC for FDA; and ModMITT-1, ModMITT-2, ModME-1TOC and ModME-2TOC populations for EMA. The treatment difference (delafloxacin – moxifloxacin) in microbiologic success rates and a comparison using the 2-sided 95% CI around the difference in microbiologic success rates from the Miettinen-Nurminen test, without stratification, will be presented.

The number and frequency of superinfections, new infections, and colonization/contamination with a pathogen not present at baseline will be determined for the ITT, MITT-1 and ModMITT-1 populations. A by-patient listing of all pathogens associated with superinfection, new infection, or colonization/contamination will be provided.

16.5.2 All-Cause Mortality

All-cause mortality in adult subjects with CABP on Day 28 (±2 days) 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 (±2 days). Patients who do not die will be censored at the end of study participation date. Randomized patients who did not take study drug at all will be censored at Day 1. 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 baseline covariates, including 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/ModITT/Safety populations.

16.6 Exploratory Analyses for both FDA and EMA

As exploratory analyses, the sensitivity analyses for each secondary analysis that used non-stratified Miettinen-Nurminen CIs may be repeated using the same method but stratified by PORT score, medical history of COPD/asthma, and prior systemic antimicrobial use.

In addition, the following shift analyses will be performed as exploratory:

- Shift of outcomes from the Early Clinical Response to the Clinical Outcome at EOT in ITT/ModITT, and CE ECR analysis populations
- Shift of outcomes from the Early Clinical Response to the Clinical Outcome at TOC in ITT/ModITT, and CE ECR analysis populations
- Shift of outcomes from the Clinical Outcome at EOT to the Clinical Outcome at TOC in ITT/ModITT, and CE EOT analysis populations

Accounting for the correlation between the Response/Outcome at earlier timepoint and the later timepoint, the Likelihood Ratio Chi-Square Test [7] will be used, assuming the Response at earlier Timepoint is fixed.

- Change in individual signs and symptoms.

The severity scale for the individual signs and symptoms will be treated as continuous values and Mixed Effect Model Repeated Measure (MMRM) will be used for the change from baseline analyses at each post dose visit. This analysis will be performed in ITT/ModITT and CE TOC/ ModCE TOC analysis populations

16.7 Health-Related Quality-of-Life Analyses

Within each treatment group, the following health-related quality-of-life scores will be compared between baseline and EOT and between baseline and TOC 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 (PORT Class, medical history of chronic obstructive pulmonary disease (COPD)/asthma, and prior systemic antimicrobial use).

16.7.1 SF-12v2® domain scores and the component scores

The SF-12v2 is a 12-item questionnaire. Eight domains make up the SF-12v2: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. In addition, the physical functioning, role-physical, bodily pain, and general health domains will be combined to obtain the Physical Health Component Score (PCS); the vitality, social functioning, role-emotional, and mental health domains will be combined to obtain the Mental Health Component Score (MCS). The scores for each domain, the PCS and the MCS range from 0 to 100, where zero indicates the lowest level of health by the scales and 100 indicates the highest level of health.

Summary scores for PCS and MCS for each patient will be computed using published algorithms [8]. Each summary measure is scored and standardized using a t-score transformation, such that a higher score represents better health status, with a mean score of 50 and a standard deviation of 10 in the general population. Missing data on the SF-12v2 will be handled as follows: domain scores will not be calculated for domains in which data are missing. Subsequently, component scores in which domain scores are missing will not be calculated.

16.7.2 Subject's ability to work and earn income

The extent to which patients had difficulty (1-5) doing their job (work, childcare, housework, etc.) and earning their income will be analyzed. If a subject checked "No" for the question "Have you had any difficulty doing the following activities?" then the result will be treated as 0. "Illegible", "Not Applicable", "Not Done" and Missing results will all be treated as missing.

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

16.7.3 Time to oral switch

If a patient does not have oral switch occurred during the treatment period, the patient will be censored at the last dose date. If randomized subjects do not take study drug, the patient will be censored at Day 1.

16.7.4 Time to hospital discharge

If a patient does not discharge from hospital during the study, the patient will be censored at date of completion/withdrawal from the study. If randomized subjects do not take study drug, the patient will be censored at Day 1.

The probabilities of the above two measurements (time to oral switch and time to hospital discharge) at each day with associated standard error and 95% CIs will be presented. The log-rank test will be used to compare time to oral switch and hospital discharge 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/ModITT population.

17 ANALYSIS OF SUSCEPTIBILITY DATA

Unless otherwise specified, the following analyses will be provided for the MITT-2, ME-2TOC and the companion modified analysis sets. As indicated, some analyses will only include *target* pathogens; target pathogens include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter cloacae* complex, *Pseudomonas aeruginosa*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*, and any pathogen that is present at baseline in at least 8 subjects in the delafloxacin treatment group.

17.1 Selection of a Representative Isolate

A patient may have more than one pathogen (e.g., *S. pneumoniae*) from the same or different sources (blood, sputum, NP swab). For each distinct pathogen identified for a patient, if the same pathogen (genus and species) is isolated more than once in a given visit window (e.g., *S. pneumoniae* isolated at baseline from blood and respiratory samples), a representative isolate will be selected for use in all MIC/zone diameter-related analyses. If the levels of diagnostic evidence are different, the isolate with the 'definitive' level of diagnosis will be selected. If the levels of diagnosis are the same, the isolate with the highest MIC to delafloxacin will be selected. If the isolates have the same MIC to delafloxacin, or MIC results are not available, the isolate with the lowest delafloxacin zone diameter will be selected. If the isolates have the same delafloxacin MIC and zone diameters, the isolate with the lowest isolate accession number will be selected. For *S. pneumoniae*, susceptibility data from nasopharyngeal isolates will only be selected if susceptibility data are not available from other sources.

If a patient has a combination of MRSA and MSSA, or any combination of PSSP/PISP/PRSP, and only one of these *distinct* pathogens demonstrates microbiological persistence, the corresponding baseline isolate will be selected for use in all MIC/zone diameter-related analyses.

This selection of a "representative" isolate will be applied to the following analysis:

i) Baseline by-pathogen MIC distribution and summary statistics (MIC_{50}, MIC_{90}, Range)

ii) Baseline by-pathogen disk diffusion zone diameter distribution and summary statistics (mean, median, range)

iii) Percent non-susceptible by baseline pathogen (where resistance rates for each drug tested are presented)

iv) Microbiologic Response by MIC/zone diameter

17.2 Analysis of Baseline Susceptibility

In addition to the baseline microbiology analyses described in Section 12.7, the following baseline susceptibility analyses will be conducted in the MITT-2, ModMITT-2, ME-2TOC, and ModME-2TOC analysis populations:

- Frequency distribution of the MIC values of delafloxacin by treatment group and for the treatment groups combined for all target pathogens (all regions combined and by geographic region).
- Frequency distribution of the MIC values of moxifloxacin by treatment group and for the treatment groups combined for all target pathogens (all regions combined and by geographic region).
- Frequency distribution of the MIC values of linezolid by treatment group and for the treatment groups combined for *S. aureus* (all regions combined and by geographic region).
- MIC summary statistics (MIC_{50}, MIC_{90}, and range) of delafloxacin by treatment group and for the treatment groups combined for all target pathogens (all regions combined and by geographic region). When there are fewer than 10 results for a pathogen, only the

number, minimum and maximum (range) will be presented. Additionally, MIC summary statistics will be provided for the following pathogen subgroups:

  - For *S. aureus*: MRSA, MSSA, PVL-positive, PVL-negative
  - For *H. influenzae, H. parainfluenzae*: β-lactamase-positive, β-lactamase-negative
  - All target pathogens: fluoroquinolone susceptible/non-susceptible
  - For *S. pneumoniae*: PSSP, PISP, PRSP, MDRSP
  - For *Streptococci*, *Haemophilus*, *Legionella*, *Mycoplasma* spp.: macrolide susceptible/non-susceptible
  - For all target Gram-negative pathogens: ESBL-positive, ESBL-negative

- MIC summary statistics (MIC_{50}, MIC_{90}, and range) of moxifloxacin by treatment group and for the treatment groups combined for all target pathogens (all regions combined and by geographic region). When there are fewer than 10 results for a pathogen, only the number, minimum and maximum (range) will be presented.
- MIC summary statistics (MIC_{50}, MIC_{90}, and range) of levofloxacin by treatment group and for the treatment groups combined for all target pathogens (all regions combined and by geographic region). When there are fewer than 10 results for a pathogen, only the number, minimum and maximum (range) will be presented.
- MIC summary statistics (MIC_{50}, MIC_{90}, and range) of linezolid by treatment group and for the treatment groups combined for *S. aureus* (all regions combined and by geographic region). When there are fewer than 10 results for a pathogen, only the number, minimum and maximum (range) will be presented.
- Percent non-susceptible (non-susceptible, intermediate, or resistant) to each antibiotic tested by treatment group and for the treatment groups combined for all target pathogens.
- Frequency distribution of disk diffusion zone diameters of delafloxacin by treatment group and for the treatment groups combined for all target pathogens (all regions combined and by geographic region).
- Disk diffusion zone diameter summary statistics (MIC_{50}, MIC_{90}, and range) of delafloxacin by treatment group and for the treatment groups combined for all target pathogens (all regions combined and by geographic region). When there are fewer than 10 results for a pathogen, only the number, minimum and maximum (range) will be presented.

For susceptibility analyses the following apply:

- If a pathogen is susceptible to levofloxacin or ciprofloxacin, the pathogen will be considered as fluoroquinolone susceptible; if a pathogen is intermediate, resistant, or non-susceptible to levofloxacin or ciprofloxacin, the pathogen will be considered as fluoroquinolone non-susceptible.
- If a pathogen resistant to three or more antibiotic classes, the pathogen is considered multi-drug resistant.

- If a pathogen is susceptible to azithromycin or erythromycin, the pathogen will be considered as macrolide susceptible; if a pathogen is intermediate, resistant, or non-susceptible to azithromycin or erythromycin, the pathogen will be considered as macrolide non-susceptible.

17.3 Additional By-Pathogen Microbiological Response Analyses

The following microbiological response by study drug MIC and zone diameter analyses will be conducted in the MITT-2, ModMITT-2, ME-2TOC, and ModME-2TOC analysis populations:

- Per-pathogen microbiological responses for target pathogens, at TOC will be summarized for delafloxacin treatment group by baseline delafloxacin MIC values, across all geographic regions, by geographic region and definite and probable diagnosis criteria as defined in Section 12.6. Additionally, microbiological responses by delafloxacin MIC value will be provided for the following pathogen subgroups:
    - For *S. aureus*: MRSA, MSSA, PVL-positive, PVL-negative
    - For *H. influenzae, H. parainfluenzae*: β-lactamase-positive, β-lactamase-negative
    - All target pathogens: fluoroquinolone susceptible/non-susceptible
    - For *S. pneumoniae*: PSSP, PISP, PRSP, MDRSP
    - For *Streptococci, Haemophilus, Legionella, Mycoplasma* spp.: macrolide susceptible/non-susceptible
    - For all target Gram-negative pathogens: ESBL-positive, ESBL-negative
- Per-pathogen microbiological responses for target pathogens at TOC will be summarized for moxifloxacin treatment group by baseline moxifloxacin MIC values, across all geographic regions, by geographic region and definite and probable diagnosis criteria as defined in Section 12.6.
- Per-pathogen microbiological responses for target pathogens at TOC will be summarized for delafloxacin treatment group by baseline delafloxacin zone diameters, across all geographic regions, by geographic region and definite and probable diagnosis criteria as defined in Section 12.6. Additionally, microbiological responses by delafloxacin zone diameter value will be provided for the following pathogen subgroups:
    - For *S. aureus*: MRSA, MSSA, PVL-positive, PVL-negative
    - For *H. influenzae, H. parainfluenzae*: β-lactamase-positive, β-lactamase-negative
    - All target pathogens: fluoroquinolone susceptible/non-susceptible
    - For *S. pneumoniae*: PSSP, PISP, PRSP, MDRSP
    - For *Streptococci, Haemophilus* spp.: macrolide susceptible/non-susceptible
    - For all target Gram-negative pathogens: ESBL-positive, ESBL-negative

17.4 Microbiology Listings

The following microbiological listings will be provided for the ITT analysis population:

- Serology test results for *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*

- Urine antigen test results (*S. pneumoniae* UAT, *L. pneumophila* UAT)
- Nasopharyngeal and oropharyngeal swabs culture and qPCR test results
- Blood culture results
- Respiratory specimen culture results
- Gram stain results for all Gram-stained respiratory specimens by treatment group
- Microbiological responses, including patient-level and pathogen-level microbiological responses separately for the MITT-1 and MITT-2 (described in Section 16.5.1)
- Patients with superinfection, new infection, or colonization/contamination

The following microbiological listings will be provided for the MITT-1 analysis population:

- MIC and Disk Diffusion Testing results for each patient, each pathogen and each drug.
- Definitive and Probable Pathogens by patient (described in Section 12.7)
- Clinical and microbiological responses by pathogen and patient with study drug MIC. This listing will display serotype for *S. pneumoniae* isolates, PVL status for *S. aureus* isolates, methicillin susceptibility for *S. aureus*, fluoroquinolone susceptibility, penicillin suscepibility, macrolide susceptibility, β-lactamase status for *Haemophilus* spp., and ESBL status (as applicable).
- All pathogens associated with microbiological failure with MICs of study drug received
- All pathogens associated with microbiological failure with zone diameters of study drug received [Note: zone diameters will be available for delafloxacin only.]
- Patients with a pathogen showing decreased susceptibility (≥4-fold increase in MIC from baseline) including type of specimen, pathogen, and MIC value
- Listing of *S. aureus* (MRSA and MSSA) and *mecA* status

The above listings will be generated separately using susceptibility test results obtained using CLSI methodology (for FDA analyses) and EUCAST methodology (for EMA analyses), except where EUCAST methodology does not exist for certain organisms. Susceptibility data in all listings will be based on CLSI methodology for *M. pneumoniae* and *L. pneumophila*.

In addition, a microbiological data listing will be provided for the microbiologic reviewer's guide. All pathogens for each patient and their pathogen-level and subject-level microbiological response data (MITT-1 and MITT-2), clinical response data, CLSI/EUCAST susceptibility test results, QRDR genotype data (if available) will be combined and displayed all together.

Additional listings may be generated, including presentation of QRDR data.

18 ANALYSIS OF SAFETY

The safety and tolerability of the study drug will be assessed using:

- Adverse events (AEs) including SAEs
- Vital signs measurements (Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Respiratory Rate, Pulse Oximetry, and Body Temperature)
- Clinical laboratory test results (Serum Chemistry, Procalcitonin, C-Reactive Protein, Hematology, Coagulation, Urinalysis
- Pregnancy Tests
- 12-lead electrocardiograms (ECGs) assessments (if clinically indicated)
- Physical examination (PEs) findings

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

18.1 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. And related TEAE is defined as TEAE with at least possibly related to the study drug.

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, TEAEs of special interest, 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 case of missing severity, the AE will be considered as 'Severe'. Similarly, if an AE has missing relationship to the study drug, the AE will be considered 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.

The following analyses of adverse events will be provided:

- All TEAEs for the Safety population
- SAEs for the Safety population
- TESAEs for the Safety population
- TEAEs by maximum severity for the safety population
- Related TEAEs
- TEAEs leading to deaths for the Safety population
- Related leading to deaths for the Safety population
- TEAE special interest for the safety population
- Related special interest for the safety population
- TEAEs resulting in discontinuation of study drug for the safety population
- Related resulting in discontinuation of study drug for the safety population
- TEAEs resulting in premature study discontinuation for the safety population

- Related resulting in premature study discontinuation for the safety population
- TEAEs by preferred term with incidence ≥5% in descending order
- TEAEs by preferred term with incidence ≥2% in descending order

The following listings of adverse events for all subjects will be provided:

- All AEs
- SAEs
- Deaths
- AE special interest
- AEs resulting in discontinuation of study drug
- AEs resulting in premature study discontinuation
- Pre-treatment SAEs

18.1.1 Subgroup Analyses of Adverse Events

Subgroups for adverse event analyses will be defined as follows:

- Age: based on the age at screening
    - Age < 65 years
    - Age ≥ 65 years
- Gender:
    - Male
    - Female
- Race category: the following standard categories for the U.S. Federal Office of Management and Budget (OMB)
    - American Indian or Alaska Native
    - Asian
    - Black or African American
    - Native Hawaiian or Other Pacific Islander
    - White
    - Other
- Ethnicity: the following standard OMB categories
    - Hispanic or Latino
    - Not Hispanic or Latino
- BMI:
    - BMI <30
    - BMI ≥30
- Diabetes:
    - Yes
    - No
- Patients with baseline Creatinine clearance of less than 90 mL/min
- Patients with history of infectious hepatitis
- SOC of Cardiac Disease
- SOC of Vascular Disease
- SOC of Cardiac or Vascular Disease

For safety analyses set, the above subgroup variables will be used for the following analyses:

- Overview summary of TEAEs
- Summary of TEAEs
- Summary of TEAEs by maximum severity
- Summary of TEAEs by relationship to study drug

Additional subgroup analyses may be performed if deemed necessary.

18.1.2 Treatment-Emergent Adverse Events of Special Interest

For safety analysis set, TEAEs and related TEAEs included in the categories of special interest listed in Table 18-1 will be summarized for each treatment group by each medical topic and PT, separately.

In addition, number of TEAEs included in the categories of special interest listed in Table 18-1 with longer than 30 days' duration will be summarized for each treatment group by each medical topic and PT.

Table 18-1 AE of Special Interest

Medical Topics	Potential SMQ	Search Criteria
Potential Myopathy	Rhabdomyolysis/ Myopathy SMQ	Rhabdomyolysis/ myopathy SMQ Broad
C. difficile diarrhea	Pseudomembranous colitis SMQ	Pseudomembranous colitis SMQ narrow
Convulsions	Convulsions SMQ	Convulsion SMQ narrow
Potential Peripheral Neuropathy	Peripheral neuropathy SMQ	Peripheral neuropathy SMQ broad
Potential Tendon Disorder	NA	HLT tendon disorders
Potential QT prolongation	Torsade de pointes/QT prolongation SMQ	Torsade de pointes/QT prolongation SMQ broad
Potential Phototoxicity	NA	Preferred term Photosensitivity reaction
Potential Allergic reactions	Hypersensitivity SMQ	Hypersensitivity SMQ, narrow
Hyperglycemia	Hyperglycemia SMQ	Use narrow SMQ "hyperglycemia/new onset diabetes"
Hypoglycemia	NA	Use HLT "hypoglycemic conditions NEC" plus preferred terms "blood glucose abnormal" and "blood glucose fluctuation"

Hepatic related events	Sub SMQ-Drug related hepatic disorders comprehensive	Use SMQ "cholestasis and jaundice of hepatic origin, narrow" and SMQ "hepatic failure, fibrosis and cirrhosis and other liver damage related conditions, narrow" and SMQ "Hepatitis, non-infectious, narrow" and SMQ "Liver related investigators, signs and symptoms, narrow"

Source: Review of MedDRA Introductory Guide for SMQs Version 19.1; HLT: [MedDRA] high level term; NEC: not elsewhere classified; SMQ: Standardized MedDRA Queries

18.2 Vital Signs and Body Temperature

Vital sign measurements (systolic and diastolic blood pressure [mmHg], heart rate [beats/minute], respiration rate [breaths/minute], oxygen saturation [%], 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.

A by patient listing will be provided for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and body temperature.

18.3 Clinical Laboratory Evaluation

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.

Laboratory values presented will include Serum Chemistry, Other Chemistry (Procalcitonin) , Hematology, Coagulation, and Urinalysis. Descriptive statistics (number of patients with a reported value, mean, SD, median, minimum, and maximum) will be presented for quantitative laboratory parameters and, for qualitative laboratory parameters, tables will display the number of patients with a reported value and percentage in each category. Quantitative laboratory parameters will be assessed for change from baseline by visit.

The changes from baseline will be calculated using the baseline values defined in Section 8. Patients with missing data for a given visit will not contribute to the summary statistics for that visit.

Laboratory results will be classified as low (L), normal (N), or high (H) according to the laboratory-supplied reference ranges. For hematology and serum chemistry laboratory test results, shift tables will be presented for each laboratory test at the EOT and TOC visits.

The number and percentage of patients with newly notable laboratory abnormalities will be summarized. A newly notable laboratory abnormality is defined as an abnormality observed post baseline that meets the notable criteria in Table 18-2 and that did not exist at baseline. Notable laboratory abnormalities are based on upper limit of normal (ULN) and lower limit of normal (LLN). Patients can still meet the criteria for a newly notable laboratory abnormality if the baseline value is missing. Table 18-2 displays the general variables and thresholds of interest. A

patient is considered to have a notable laboratory abnormality if his/her value falls within the specified definitions at least once during the treatment period.

Table 18-2 Notable Criteria for Laboratory Data

Laboratory Variable	SI Units
AST	>2 x ULN >3 x ULN >5 x ULN
ALT	>2 x ULN >3 x ULN >5 x ULN
Total Bilirubin	>2 x ULN
Serum Creatinine	>2 x ULN >3 x ULN
Glucose	<2.22 mmol/L

The number and percentage of subjects who meet potential Hy's Law criteria will be summarized. These criteria are defined as any elevated ALT and/or AST > 3 x ULN value that is associated with both an ALP less than 2 × ULN and an increase in bilirubin level of at least 2 × ULN.

There will be separate data listings for each lab category test results. Patients with values above or below the reference range, regardless of clinical significance, will be identified in the data listings with flags for high and low values.

18.4 Pregnancy Tests

A listing of serum pregnancy tests results will also be provided.

18.5 Electrocardiograms (ECGs)

A 12-lead ECG will be performed at Screening, and if clinically indicated after Screening. A single ECG will be recorded after the patient has been in a supine position and at rest for at least 3 minutes.

All ECG data will be provided in a data listing.

18.6 Physical Examination Findings

Physical examination data for each body system are collected at screening. If improved at post baseline timepoint, physical examination data are also collected at ECR, EOT, TOC and unscheduled visits. The summary for the improved results (normal, abnormal) will be produced for each body system.

All physical examination findings will be provided in a listing.

19 PHARMACOKINETIC ANALYSES

Serial blood samples for PK analysis will be obtained at select investigative sites on Day 3 (± 1 day) of treatment within the 30 minutes before study drug administration and at 1.5 and 3 hours after the start of dosing. All time points will have a ± 10-minute window. Subjects should have

received a minimum of 3 consecutive doses of study drug prior to the start of PK blood collection.

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 for each planned timepoint regardless which study day the sample was collected.

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

20 MISSING DATA AND HANDLING OF MISSING VALUES AND OUTLIERS

Every effort will be made to minimize missing data for the safety and efficacy assessments during the conduct of the trial. Missing data will result in a reduced sample size for some analyses.

Missing values for safety data (except for dates) will not be imputed. Missing or partial dates will be imputed as described in the corresponding section. Since the safety analyses will be predominantly presentations in tables and individual data listings, those displays will include patients having data at the relevant visits. A patient who withdraws prior to the last planned observation in a study period will be included in the safety analyses up to the time of discontinuation.

For efficacy, the following rules will be used for handling missing data:

1. Missing data for ECR will be considered nonresponders.
2. Missing data for Clinical Outcome based on the investigator assessment of signs and symptoms of pneumonia will be considered a Failure in the primary ITT and ModITT analyses.
3. For each secondary and exploratory efficacy end points, 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 Nonresponders in the ITT and ModITT analysis.

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.

21 APPENDIX

21.1 Miettinen and Nurminen Confidence Intervals

Some two-sided 95% CI will be computed using the method proposed for stratified designs by Miettinen and Nurminen (1985). For notation purposes, assume 1 indicates the delafloxacin group (Group 1), 2 the moxifloxacin group (Group 2), and i the ith stratum. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation for the CI as follows:

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

Based on Miettinen and Nurminen 1985, the two-sided 95% CI is given by the roots for $RD = p_1 - p_2$ of the following equation:

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

where χ_α^2 is the cut point (upper quantile) of size α from the central chi-square distribution with degree of freedom = 1 (χ_α^2 =3.84 for two-sided 95% CI); RD is the difference between the two population rates ($RD = p_1 - p_2$); $\hat{p}_1$ = the observed weighted average (across the strata using the W_i and then normalized) proportion in Group 1; $\hat{p}_2$ = the observed weighted average (across the strata using the W_i and then normalized) proportion in Group 2; and

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

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

As stated above, the two-sided 95% CI bounds for the difference in rates are given by the roots for $RD = p_1 - p_2$ from the equation above. This equation does not provide an analytic solution for RD . Therefore, a numerical algorithm will be used to obtain the two roots (CI bounds) for RD . This CI approach corresponds to the NI test (a p-value approach) proposed by Farrington and Manning.

If any stratifications result in sample sizes too small to allow the CIs to be calculable, strata will be combined such that so as to make the combined strata are as equal in size as possible.

21.2 CURB-65

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

CURB-65	
Symptom	**Points**
Confusion*	1
Urea > 7 mmol/L or BUN > 19 mg/dL	1
Respiratory Rate ≥ 30 breaths/min	1
Blood Pressure (S**B**P < 90 mmHG, D**B**P ≤ 60 mmHg)	1
Age ≥ **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.

21.3 Child-Pugh Classification of Severity of Liver Disease

Clinical and Biochemical Measurements for Child-Pugh Classification of Severity of Liver Disease[a,b,c]	Points Scored for Increasing Abnormality		
	1	**2**	**3**
Hepatic encephalopathy (grade[d])	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate[e]
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[f]			
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.

[a] Pugh RN, Murray-Lyon IM, Dawson JL, et al. Brit J Surg. 1973;60(8):646-9.

[b] Lucey MR, Brown KA, Everson GT, et al. Liver Transpl Surg. 1997;3(6)628-37.

[c] 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.

[d] Grading from Trey C, Burns DG, Saunders SJ. N Engl J Med. 1966;274(9):473-81.

[e] Moderate or controlled by diuretics.

[f] 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.

21.4 Cockcroft-Gault Formula

The Cockcroft-Gault formula for estimating CrCl:

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

CrCl (mL/min) = {(140 – age) × weight (kg)} / 72 × SCr in mg/dL (× 0.85 if subject is female)

- When SCr is measured in µmol/L:

CrCl (mL/min) = {(140 – age) × weight (kg) × [1 – (0.15 × sex)]} / (0.814 × SCr),

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

21.5 SF-12v2® 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:**

HS-1

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

	Yes, limited a lot	Yes, limited a little	No, not limited at all
HS-2 <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
HS-3 Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

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
HS-4 a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
HS-5 b. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 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
HS-6 a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
HS-7 b. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

HS-8 **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
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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
HS-9	a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
HS-10	b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
HS-11	c. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

HS-12 **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
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

6. These questions are about how you feel and how things have been with you <u>during the past week</u>. 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 <u>past week</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
HS-9 a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
HS-10 b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
HS-11 c. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

HS-12

7. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> 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
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Creating SF-12v2 Summary PCS and MCS Scores

Step 1. Item Recoding

If HS-1 = 1, then HS_1R = 5.0.
If HS-1 = 2, then HS_1R = 4.4.
If HS-1 = 3, then HS_1R = 3.4.
If HS-1 = 4, then HS_1R = 2.0.
If HS-1 = 5, then HS_1R = 1.0.
Else, HS_1R = missing.

If HS-2 = 1, 2, or 3, then HS_2aR = HS-2.
Else HS_2aR = missing.

If HS-3 = 1, 2, or 3, then HS_2bR = HS-3.
Else HS_2bR = missing.

If HS-4 = 1, 2, 3, 4, or 5, then HS_3aR = HS-4.
Else HS_3aR = missing.

If HS-5 = 1, 2, 3, 4, or 5, then HS_3bR = HS-5.
Else HS_3bR = missing.

If HS-6 = 1, 2, 3, 4, or 5, then HS_4aR = HS-6.
Else HS_4aR = missing.

If HS-7 = 1, 2, 3, 4, or 5, then HS_4bR = HS-7.
Else HS_4bR = missing.

If HS-8 = 1, then HS_5R = 5.
If HS-8 = 2, then HS_5R = 4.
If HS-8 = 3, then HS_5R = 3.
If HS-8 = 4, then HS_5R = 2.
If HS-8 = 5, then HS_5R = 1.
Else, HS_5R = missing.

If HS-9 = 1, then HS_6aR = 5.
If HS-9 = 2, then HS_6aR = 4.
If HS-9 = 3, then HS_6aR = 3.
If HS-9 = 4, then HS_6aR = 2.
If HS-9 = 5, then HS_6aR = 1.
Else, HS_6aR = missing.

If HS-10 = 1, then HS_6bR = 5.
If HS-10 = 2, then HS_6bR = 4.
If HS-10 = 3, then HS_6bR = 3.

If HS-10 = 4, then HS_6bR = 2.
If HS-10 = 5, then HS_6bR = 1.
Else, HS_6bR = missing.

If HS-11 = 1, 2, 3, 4, or 5 then HS_6cR = HS-11.
Else HS_6cR = missing.

If HS-12 = 1, 2, 3, 4, or 5 then HS_7R = HS-12.
Else HS_7R = missing.

If a beneficiary has a missing value for HS_1R, HS_2aR, HS_2bR, HS_3aR, HS_3bR, HS_4aR, HS_4bR, HS_5R, HS_6aR, HS_6bR, HS_6cR, or HS_7R, set any remaining derived variables equal to missing. Do **NOT** perform calculations below if any recoded values have been set to missing. (Missing values will be imputed later. Scale scores and corresponding transformed and standardized scores cannot be calculated for missing data.)

Step 2. Creating Scale Scores

PF = HS_2aR + HS_2bR

RP = HS_3aR + HS_3bR

BP = HS_5R

GH = HS_1R

VT = HS_6bR

SF = HS_7R

RE = HS_4aR + HS_4bR

MH = HS_6aR + HS_6cR

Step 3. Transformation of Scale Scores

PF_Trans = [(PF – 2) / 4] * 100

RP_Trans = [(RP – 2) / 8] * 100

BP_Trans = [(BP – 1) / 4] * 100

GH_Trans = [(GH – 1) / 4] * 100

VT_Trans = [(VT – 1) / 4] * 100

SF_Trans = [(SF – 1) / 4] * 100

RE_Trans = [(RE – 2) / 8] * 100

MH_Trans = [(MH – 2) / 8] * 100

Step 4. Standardization of Scale Scores

PF_Z = (PF_Trans – 81.18122) / 29.10558

RP_Z = (RP_Trans – 80.52856) / 27.13526

BP_Z = (BP_Trans – 81.74015) / 24.53019

GH_Z = (GH_Trans – 72.19795) / 23.19041

VT_Z = (VT_Trans – 55.59090) / 24.84380

SF_Z = (SF_Trans – 83.73973) / 24.75775

RE_Z = (RE_Trans – 86.41051) / 22.35543

MH_Z = (MH_Trans – 70.18217) / 20.50597

Step 5. Aggregation of Scale Scores

AGG_PHYS = (PF_Z * 0.42402) + (RP_Z * 0.35119) + (BP_Z * 0.31754) + (GH_Z * 0.24954) + (VT_Z * 0.02877) + (SF_Z * -0.00753) + (RE_Z * -0.19206) + (MH_Z * -0.22069)

AGG_MENT = (PF_Z * -0.22999) + (RP_Z * -0.12329) + (BP_Z * -0.09731) + (GH_Z * -0.01571) + (VT_Z * 0.23534) + (SF_Z * 0.26876) + (RE_Z * 0.43407) + (MH_Z * 0.48581)

Step 6. Transformation of Summary Scores

PCS = 50 + (AGG_PHYS * 10)

MCS = 50 + (AGG_MENT * 10)

21.6 Quality-of-Life Questions

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

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

	Have you had difficulty doing the following activities? (check one)	To what extent have you had difficulty? (1 = little difficulty to 5 = tremendous difficulty).
Doing your job (work, childcare, housework, etc.)	[ ] yes [ ] no	1 2 3 4 5
Earning an income	[ ] yes [ ] no [ ] not applicable (I do not work)	1 2 3 4 5

21.7 Definitions of Symptom Intensity

Symptom	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Cough	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
Dyspnea/Shortness of Breath	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
Chest Pain due to Pneumonia	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
Sputum Production	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

22 REFERENCES

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