16.1.9 Statistical Analysis Plan and Associated Document

Statistical Analysis Plan: PTK0796-CABP-19302

Study Title:	A Phase 3b Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Moxifloxacin IV/PO for Treating Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP)
Study Number:	PTK0796-CABP-19302
Study Phase:	3b
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Confidentiality Statement

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACM	all-cause mortality
AE	adverse event
BMI	body mass index
CABP	community-acquired bacterial pneumonia
CE	clinically evaluable
CN	clinically notable
CT	computed tomography
CXR	chest X-ray
ECG	electrocardiogram
eCRF	electronic case report form
ECR	Early Clinical Response
EMA	European Medicines Agency
EOT	End of Treatment
FDA	Food and Drug Administration
IND	Investigational New Drug
IV	Intravenous
IxRS	Interactive Response System
lpf	Low Power Field
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MIC	minimum inhibitory concentration
MRSA	Methicillin-Resistant *Staphylococcus aureus*
NI	non-inferiority
PORT	Pneumonia Outcomes Research Team
PK	Pharmacokinetic
PO	Orally

PR	Interval from the P wave (atrial contraction or depolarization) to the onset of the Q wave in the measurement of electrical activity of the myocardium
PTE	post therapy evaluation
QTc	QT, corrected
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
spp	species (plural)
SIRS	Systemic Inflammatory Response Syndrome
TEAE	treatment emergent adverse event
UAT	urinary antigen test
ULN	upper limit of normal
US	United States

3 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the protocol PTK0796-CABP-19302, "A Phase 3b Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Moxifloxacin IV/PO for Treating Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP) Version 5.0 Dated 19-November-2020." The statistical plan described is an *a priori* plan and no analysis prior to the preparation of this plan has been conducted. This SAP summarizes the study design and objectives, and provides details of the outcome definitions and statistical methods that will be used to analyze the data from protocol PTK0796-CABP-19302.

The study has been designed to address both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory requirements; however, a separate SAP will be developed to address the different primary efficacy outcome and analyses for the EMA. While the EMA supports the assessment of clinical response by the Investigator at a Post Therapy Evaluation (PTE) visit (which is scheduled to occur 5 to 10 days after the last dose of test article) as the primary endpoint, the FDA guidelines require using an earlier primary endpoint (72-120 hours after the first dose of test article) based on improvement in pneumonia symptoms.

4 TRIAL OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is:

- To demonstrate that iv to po omadacycline is non-inferior to iv to po moxifloxacin in the treatment of adults with PORT Risk Class III and IV CABP.

4.2 Secondary Objectives

The secondary objectives are as follows:

- To evaluate the safety of omadacycline in the treatment of adult subjects with CABP in the Safety population.
- To evaluate the Clinical Response (Early Clinical Response [ECR] and investigator assessment of response) according to the identified causative pathogen.
- To evaluate the pharmacokinetics (PK) of omadacycline in adult subjects with CABP.

5 STUDY DESIGN CONSIDERATIONS

5.1 Study Design

This is a randomized (1:1), active comparator controlled, double-blind, Phase 3 study comparing omadacycline and moxifloxacin in the treatment of adults with CABP (PORT Risk Class III and IV). Both iv and po phases of the study will be double-blind. Approximately 670 subjects will be enrolled at approximately 75 sites globally.

Subjects will participate in the study for up to 37 days. Following a Screening period of up to 24 hours, eligible subjects will be randomized to receive treatment. Subjects will be stratified by PORT Risk Class (III or IV) at Screening.

Eligible subjects with a PORT Risk Class III or IV will be randomized to receive 7 to 10 days of iv treatment with the option to switch to po treatment beginning on Day 3. Subjects with bacteremia identified at Screening can receive up to 14 days of treatment.

Switch to po will NOT be permitted until after the subject has completed at least 2 days of iv treatment. The decision to switch to po treatment will be made by the investigator; the subject should be considered clinically stable and meet all criteria for transition to a po regimen. Specifically, the subject must meet the following requirements, and this should be noted in source documents and recorded on the electronic case report form (eCRF):

- Temperature ≤ 37.8°C (100°F)
- Heart rate ≤ 100 beats/minute
- Respiratory rate (RR) ≤ 24 breaths/minute
- Systolic blood pressure (SBP) ≥ 90 mm Hg
- Oxygen saturation ≥ 90% as measured by pulse oximetry or partial pressure of arterial oxygen (PaO_2) ≥ 60 mm Hg by arterial blood gas (ABG)
- Normal (“absence of confusion”) or return to baseline mental status
- Ability to maintain po intake.

Eligible subjects will be randomized to one of the following treatment groups:

Group	Test Article	Study Day 1	Study Day 2	Study Days 3 to 10[a]
1	Omadacycline	200 mg iv QD or 100 mg iv BID	100 mg iv	100 mg iv or 300 mg po
2	Moxifloxacin	400 mg iv	400 mg iv	400 mg iv or 400 mg po

BID = twice a day dosing, iv = intravenous, po = per oral, PORT = pneumonia patient outcomes research team, QD = once a day dosing.

[a] The total duration of treatment for subjects is 7-10 days, with up to 14 days of treatment for subjects with bacteremia.

Subjects will return to the study site for a Post Therapy Evaluation (PTE) 5 to 10 days after the last dose of test article. A Final Follow-up visit (Final Follow-up) will be conducted within 30 to 37 days following the first dose of test article. The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be Clinical Success in the opinion of the investigator at end of treatment (EOT) and PTE and had no adverse events (AEs) or clinically significant laboratory or electrocardiogram (ECG) abnormalities noted at or after the PTE visit.

Otherwise, this assessment is to be performed with an in-person study visit.

A detailed Schedule of Study Procedures is provided in Appendix 1.

5.1.1 Sample Size

Table 1 provides a summary of clinical success rates in the omadacycline CABP-1200 study at ECR and PTE in the PORT Risk Class III and IV subjects.

Table 1. Clinical Success Rates in CABP-1200 at ECR and PTE in PORT III and IV Subjects

Outcome	Omadacycline n/N1 (%)	Moxifloxacin n/N1 (%)
ECR Success - ITT	270/329 (82.1)	279/331 (84.3)
PTE Success - ITT	291/329 (88.4)	282/331 (85.2)
PTE Success - CE	273/295 (92.5)	268/296 (90.5)

CABP = community-acquired bacterial pneumonia, ECR = Early Clinical Response, PTE = post-therapy evaluation, ITT = Intent to treat, CE = Clinically evaluable.

The primary efficacy outcome for the FDA is ECR at 72-120 hours following the first dose of test article in the ITT population. An NI margin of 10% will be used for the analysis in the ITT population. The NI margin was based on an analysis of historical data regarding the treatment effect of antibiotics in pneumonia. Based on data from study CABP-1200, it is reasonable to assume the rate of ECR success will be approximately 80% in both treatment groups. With a NI margin of 10%, 1-sided alpha level of 0.025 and 90% power, and using the sample size determination method of Farrington and Manning, a total of 670 subjects are required.

For the Investigator's Assessment of Clinical Response at PTE endpoint (EMA co-primary endpoint) with 670 subjects in the ITT population, assuming an outcome rate of 85% in both treatment groups, NI margin of 10% and 1-sided alpha level of 0.025, there is 94.7% power to show NI. Assuming the evaluability rate for the CE population is 80%, an outcome rate of 89% in both treatment groups, NI margin of 10% and 1-sided alpha level of 0.025, there is 94.9% power to show NI in the CE population.

Thus, 670 subjects provide sufficient power for the primary efficacy analyses for both the FDA and EMA regulatory authorities. A summary of the sample size calculations and assumptions is provided in Table 2.

Table 2 Sample Size and Power Calculations

	Primary Outcome FDA (Early Clinical Response)	Primary Outcome EMA (Investigator's Assessment of Clinical Response at PTE)	
Population	ITT	ITT	CE
NI Margin	10%	10%	10%
Evaluability Rate	N/A	N/A	80%
Outcome Rate	80%	85%	89%
N	670	670	536
Power	89.6%	94.7%	94.9%

CE = clinically evaluable; ITT = intent-to-treat; N = number; N/A = not applicable; NI = non-inferiority; PTE = post-therapy evaluation.

Assuming the microbiological evaluability rate is 30%, a total of 201 subjects are expected to be in the microbiological intent-to-treat (micro-ITT) population.

5.1.2 Randomization and Masking

All eligible subjects will be randomized via an Interactive Response System (IxRS) that assigns them to 1 of the 2 treatment arms omadacycline or moxifloxacin (in a 1:1 ratio). The site delegate will contact the IxRS (via web) after confirming that the subject fulfills all the inclusion criteria and has none of the exclusion criteria. The IxRS will assign a test article to the subject based on a computer-generated randomization schedule. The randomization will be a blocked randomization sequence stratified by PORT Risk Class (III and IV) and receipt of an allowed antibacterial therapy in the 72 hours prior to study treatment (yes and no). Subjects randomized into the study will be assigned the treatment corresponding to the next available number in the respective stratum of the computer-generated randomization schedule. The subject is considered randomized when the IxRS provides the test article assignment (ie, completes a randomization transaction), regardless of whether the subject actually receives any medication. Randomization of subjects who have received an allowed antibacterial therapy in the 72 hours prior to study treatment will be capped at 25% of the total number of subjects randomized.

5.2 Efficacy Measures

5.2.1 Primary Efficacy Outcome

The primary efficacy outcome is the determination of the response to therapy at the Early Clinical Response (ECR) assessment (72 to 120 hours after administration of the first dose of test article) and will be determined programmatically using the investigator's assessment of the subject's symptoms associated with CABP entered into the electronic case report form (eCRF). The severity of the subject's CABP symptoms of cough, sputum production,

pleuritic chest pain, and dyspnea will be evaluated on a 4-point scale (absent, mild, moderate, or severe) based upon the Community-Acquired Bacterial Pneumonia Subject Symptom Severity Guidance Framework for Investigator Assessment in Table 3.

Table 3. Community-Acquired Bacterial Pneumonia Subject Symptom Severity Guidance Framework for Investigator Assessment

COUGH?	**Absent**	**Mild**	**Moderate**	**Severe**
	No cough or resolution (to pre-CABP Baseline)	Cough present but it does not interfere with subject's usual daily activities	Cough present, frequent and it does interfere with some of the subject's usual daily activities	Cough is present throughout the day and night; it limits most of the subjects' usual daily activities and sleep patterns
PLEURITIC CHEST PAIN?	**Absent**	**Mild**	**Moderate**	**Severe**
	No chest pain or resolution of chest pain related to CABP	Chest pain present occasionally with deep breathing but it does not interfere with subject's usual daily activities	Chest pain is present with normal breaths and it does interfere with the subject's usual daily activities	Chest pain is present at rest and/or with shallow breathing; it limits most of the subject's usual daily activities
SHORTNESS OF BREATH?	**Absent**	**Mild**	**Moderate**	**Severe**
	No shortness of breath or resolution (to pre-CABP Baseline)	Shortness of breath with strenuous activities only but it does not interfere with subject's usual daily activities	Shortness of breath with usual activities and it does interfere with the subject's usual daily activities	Shortness of breath with minimal exertion or at rest; it limits most of the subject's usual daily activities
PHLEGM/ SPUTUM PRODUCTION?	**Absent**	**Mild**	**Moderate**	**Severe**
	No coughing up of phlegm/sputum or resolution (to pre-CABP Baseline)	Subject coughs up a small amount of phlegm/sputum	Subject coughs up a moderate amount of phlegm/sputum	Subject coughs up a large amount of phlegm/sputum

The categories of Early Clinical Response are defined as follows:

Clinical Success: at the ECR assessment will be defined as survival with improvement of at least 1 level (ie, severe to moderate, moderate to mild, mild to absent) compared to baseline (Screening) in at least 2 CABP symptoms (cough, sputum production, pleuritic chest pain, and dyspnea) with no worsening by at least 1 level in the other CABP symptoms. In order for the subject to be considered a Clinical Success, the subject may not meet any criteria for Clinical Failure or Indeterminate ECR.

Clinical Failure: meeting any of the following criteria:

- There is no improvement by at least 1 level (ie, severe to moderate, moderate to mild, mild to absent) compared to baseline (Screening) in 2 CABP symptoms.

- Any of the 4 CABP symptoms is worse (by at least 1 level) compared to baseline (Screening).
- The subject requires alternative (rescue) antibacterial treatment for CABP prior to the ECR assessment related to either (a) progression or development of new symptoms attributable to CABP; (b) development of infectious complications of CABP (eg, empyema, lung abscess) or (c) discontinuation of study therapy due to an AE.
- The subject is receiving antibacterial therapy that may be effective for the infection under study for a different infection from the one under study.
- Death prior to the ECR assessment.

Indeterminate: the clinical response to test article could not be adequately inferred due to:

- Subject was not seen for the evaluation because s/he withdrew consent, or were lost to follow-up
- Other specified reason.

Assuming none of the above definitions of failure is met, the following cases will be considered an indeterminate response: Subjects with missing data such that an ECR Response cannot be determined; subjects who did not have at least 2 symptoms of CABP at baseline; subjects with an ECR assessment outside of the 72–120-time window. Since subjects with an indeterminate response are included in the denominator of the calculation of Clinical Success, these subjects are essentially Clinical Failures. For the ITT population, the proportion of ITT subjects with a Clinical Success is defined using the following formula:

Number of subjects with an Early Clinical Success
Number of subjects with an Early Clinical Failure + Number of subjects with a response of Indeterminate + Number of subjects with an Early Clinical Success

5.2.1.1 Estimand Framework

An addendum to ICH E9 introduces the concept of an estimand which translates the trial objective into a precise definition of the treatment effect that is to be estimated. The description of the estimand includes 4 attributes: the population, the variable (or endpoint) to be obtained for each subject, the specification of how to account for intercurrent events (ICE) and the population-level summary for the variable. These attributes are described below:

	Early Clinical Response
Population	ITT Population
Variable/Endpoint	Programmatic determination of early clinical success
Handling of intercurrent events	Composite estimand as the following ICE's are incorporated into the variable/endpoint: • Receipt of alternative (rescue) therapy (failure)

	• Receipt of antibiotic that may be effective for CABP for a different infection (failure) • Death (failure)
Population-level summary	Difference between treatment groups in percentage of subjects with an early clinical sucess

5.2.2 Secondary Efficacy Outcomes

5.2.2.1 Investigators Assessment of Clinical Response

The investigator will make an assessment of Clinical Response at the EOT and PTE Visits, based on the definitions below. The secondary efficacy outcome is clinical response at PTE based on the investigator assessments at the EOT and PTE Visits in the ITT and CE-PTE populations as defined in Table .

EOT Visit

At the EOT Visit (on the calendar day of, or within 2 days following the last dose of test article), the investigator will indicate the clinical status of the infection under study as detailed below.

Clinical Success:

- The subject is alive and the infection is sufficiently resolved such that further antibacterial therapy is not needed.
    - These subjects may have some residual findings related to infection (ie, cough) requiring ancillary (ie, non-antibiotic) treatment (eg, expectorant).
- In order for the subject to be considered a Clinical Success at EOT, the subject may not meet any criteria for Clinical Failure or Indeterminate at EOT.

Clinical Failure:

- The subject requires alternative antibacterial treatment for CABP prior to EOT related to either
    - progression or development of new symptoms to CABP, or
    - development of infectious complications of CABP (eg, empyema, lung abscess), or
    - subject developed an AE that required discontinuation of study therapy prior to the EOT.

Other reasons for clinical failure are:

- Subject is receiving antibacterial therapy that may be effective for the infection under study for a different infection from the one under study.
- Death prior to EOT.

Indeterminate:

- The clinical response to test article could not be adequately inferred due to:
    - Subjects were not seen for EOT evaluation because they withdrew consent, were lost to follow-up, other reason (specify).
    - Other specified reason.

PTE Visit

At the PTE Visit (5 to 10 days after the subject's last day of study therapy) the investigator will indicate one of the following outcomes relating to the primary infection under study:

Clinical Success:

- Survival after completion of a test article regimen without receiving any systemic antibacterial therapy other than test article;
- Resolution of signs and symptoms of the infection present at Screening with no new symptoms or complications attributable to CABP; and
- No need for further antibacterial therapy.

Clinical Failure:

- The subject requires alternative antibacterial treatment for CABP prior to PTE related to either:
    - progression or development of new symptoms of CABP, or
    - development of infectious complications of CABP (eg, empyema, lung abscess).

Other reasons for clinical failure are:

- The subject is receiving antibiotics that may be effective for the infection under study for a different infection from the one under study.
- Death prior to PTE.

Indeterminate:

- The clinical response to test article could not be adequately inferred due to:

- Subjects were not seen for PTE evaluation because they withdrew consent, were lost to follow-up, other (specify).
- Other specified reason.

The efficacy outcome of Clinical Response at PTE is determined as follows from the investigator's assessments at the EOT and PTE Visits:

Table 4. Investigator's Assessment of Clinical Response

EOT Visit	PTE Visit	Clinical Response at PTE Visit
Success	Success	Success
Success	Failure	Failure
Success	Indeterminate	Indeterminate
Failure	Success	Failure
Failure	Failure	Failure
Failure	Indeterminate	Failure
Indeterminate	Success	Indeterminate
Indeterminate	Failure	Failure
Indeterminate	Indeterminate	Indeterminate

Abbreviations: EOT = end of treatment; PTE = post-therapy evaluation.

For the ITT population, the proportion of ITT subjects with a Clinical Success is defined using the following formula (where the denominator adds to the total number of subjects in the ITT population):

$$\frac{\text{Number of subjects with Clinical Success}}{\text{(Number of subjects with Clinical Success + Number of subjects with a Clinical Failure + Number of subjects with an Indeterminate response)}}$$

By definition, subjects in the CE-EOT and CE-PTE populations cannot have an Indeterminate response. Thus, for the CE-EOT and CE-PTE populations, the proportion of subjects with a Clinical Success is defined using the following formula:

$$\frac{\text{Number of subjects with Clinical Success}}{\text{(Number of subjects with Clinical Success + Number of subjects with a Clinical Failure)}}$$

5.2.2.2 Estimand Framework for Investigators Assessment of Clinical Response

The four attributes of estimand are described below:

	Investigators Assessment of Clinical Response
Population	ITT and CE-PTE Populations
Variable/Endpoint	Investigator Assessment of Clinical Success
Handling of intercurrent events	Composite estimand as the following ICE's are incorporated into the variable/endpoint: • Receipt of alternative (rescue) therapy (failure)

	• Receipt of antibiotic that may be effective for CABP for a different infection (failure) • Death (failure)
Population-level summary	Difference between treatment groups in percentage of subjects with an investigators assessment clinical sucess

5.2.2.3 Microbiologic Outcomes

Microbiological response definitions for the evaluations performed at the EOT and PTE Visits and analyzed in the microITT and microbiologically evaluable (ME) populations are presented in the table below. Post-baseline microbiological samples will be collected only as clinically indicated. Atypical pathogens identified only by acute and convalescent serology or baseline urinary antigen tests (UAT), and *Streptococcus pneumoniae* identified only by baseline UAT can only have a presumed or indeterminate microbiologic response.

If a subject has the same pathogen (ie, same genus and species) identified from both a respiratory and blood specimen, a microbiological response is determined for each of the pathogens. The microbiologic response for the respiratory pathogen is based on the pathogen isolated from the EOT or PTE specimen, if a specimen was collected. The microbiologic response for the blood pathogen is based on the blood sample collected at EOT or PTE, or if a sample was not collected at the post-baseline visit, the blood sample collected prior to and closest to the visit. For the pathogen specific microbiologic response, the worst outcome for the pathogen should be summarized. If *Streptococcus pneumoniae* is identified from both a UAT and a culture, the culture should be used to determine microbiological response.

Table 5. Per-Pathogen Microbiological Response Definitions at the EOT and PTE Visits

Term	Definition
Eradication	The baseline pathogen based on culture was absent from repeat culture(s) of the same sample type (blood or respiratory specimen).
Presumed Eradication	No post-baseline source specimen to culture in a subject assessed with a clinical success by the Investigator
Persistence	The baseline pathogen based on culture was present in repeat culture(s) of the same sample type (blood or respiratory specimen).
Presumed Persistence	No post-baseline source specimen to culture in a subject assessed with a clinical failure by the Investigator
Indeterminate	The subject's clinical response is indeterminate or other circumstance that precludes a microbiological evaluation

Abbreviations: EOT = end of treatment; PTE = post-therapy evaluation.

Microbiological outcomes are further categorized as favorable, unfavorable, and indeterminate. Favorable microbiological outcomes are defined as eradication or presumed eradication. Unfavorable microbiological outcomes are defined as persistence or presumed persistence. Microbiological response will be derived using electronic microbiology data from the central laboratory and from pathogen determination provided by the Sponsor for each baseline isolate.

Overall microbiological response at PTE is determined as follows from the microbiological responses at the EOT and PTE Visits:

Table 6. Per-Pathogen Microbiologic Response

EOT Visit	PTE Visit	Overall Microbiologic Response at PTE
Favorable	Favorable	Favorable
Favorable	Unfavorable	Unfavorable
Favorable	Indeterminate	Indeterminate
Unfavorable	Favorable	Unfavorable
Unfavorable	Unfavorable	Unfavorable
Unfavorable	Indeterminate	Unfavorable
Indeterminate	Favorable	Indeterminate
Indeterminate	Unfavorable	Unfavorable
Indeterminate	Indeterminate	Indeterminate

Abbreviations: EOT = end of treatment; PTE = post-therapy evaluation.
Note: Favorable is defined as eradication or presumed eradication. Unfavorable is defined as persistence or presumed persistence.

Per-subject responses will be based on per-pathogen responses. To have an overall per-subject favorable microbiologic response, the outcome for each baseline pathogen must be favorable (eradicated or presumed eradicated). If the outcome for any pathogen is unfavorable (persistence or presumed persistence), the subject will be considered to have an unfavorable per-subject microbiologic response. Subjects with an indeterminate response for all pathogens will be considered to have an indeterminate per-subject microbiologic response. If the same pathogen is isolated from multiple sample types (blood, respiratory, urine), the worst outcome will be used to determine per-subject microbiologic response. Superinfections will not be considered in the microbiological response. Microbiological response from worst to best are as follows: persistence, presumed persistence, indeterminate, presumed eradication, and eradication.

The overall per-subject microbiologic response at PTE is determined from the per-subject microbiologic responses at the EOT and PTE Visits in the same manner as the per-pathogen microbiologic response in Table 6. For subjects with a per-subject favorable response at the EOT Visit, the overall microbiologic response at PTE of eradication, presumed eradication, persistence, and presumed persistence are based on the response at the PTE Visit. For subjects with a per-subject unfavorable response at the EOT Visit, the overall microbiologic response at PTE of persistence and presumed persistence are based on the response at the EOT Visit except for when the response at the PTE Visit is unfavorable. In this case, the

overall microbiologic response at PTE of persistence and presumed persistence are based on the response at the PTE Visit. For subjects with a per-subject indeterminate response at the EOT Visit and unfavorable at the PTE Visit, the overall microbiologic response at PTE of persistence and presumed persistence are based on the response at the PTE Visit.

For the microITT population, the proportion of subjects with a favorable microbiological response is defined using the following formula (where the denominator adds to the total number of subjects in the microITT population):

$$\frac{\text{Number of subjects with eradication + Number of subjects with presumed eradication}}{\text{(Number of subjects with eradication + Number of subjects with presumed eradication + Number of subjects with persistence + Number of subjects with presumed persistence + Number of subjects with indeterminate response)}}$$

By definition, the ME populations (ME-EOT and ME-PTE) must have sufficient information to determine the outcome and thus, excludes subjects with indeterminate responses. For the ME populations, the proportion of subjects with a microbiological response is defined using the following formula:

$$\frac{\text{Number of subjects with eradication + Number of subjects with presumed eradication}}{\text{(Number of subjects with eradication + Number of subjects with presumed eradication + Number of subjects with persistence + Number of subjects with presumed persistence)}}$$

Microbiological response definitions of superinfection and new infection are presented in Table 7 below:

Table 7. Microbiological Response Definitions: Superinfection or New Infection

Term	Definition
Superinfection	Isolation of a non-baseline pathogen from blood or respiratory cultures while the subject is on test article and the subject shows progression or development of new symptoms of CABP or development of infectious complications of CABP (ie, the subject is deemed a clinical failure by the investigator at the EOT Visit)
New infection	Isolation of a non-baseline pathogen from a post-treatment culture of a blood or respiratory specimen and the subject shows progression or development of new symptoms of CABP or development of infectious complications of CABP (ie, the subject is deemed a clinical failure by the investigator at the PTE Visit)

Abbreviations: CABP = community-acquired bacterial pneumonia.

For subjects with multiple microbiological samples taken either while the subject is on test article (for determination of superinfection) or post-treatment (for determination of new infection) all cultures will be used in the analysis.

5.3 Safety Measures

The safety parameters include AEs, clinical laboratory evaluations, vital signs, and electrocardiogram (ECG) findings. AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA, Version to be delineated in the CSR) to the System Organ Class and Preferred Term levels.

5.4 Pharmacokinetic Parameters

The concentration of omadacycline will be obtained from plasma samples. Refer to the pharmacokinetic analysis plan for further details.

6 ANALYSIS POPULATIONS

6.1 Analysis Populations

6.1.1 Intent-to-Treat (ITT) Population

The ITT population will consist of all randomized subjects regardless of whether or not the subject received test article. A subject is considered randomized when the IxRS provides the test article assignment (ie, completes a randomization transaction).

6.1.2 Safety Population

The Safety population will consist of all randomized subjects who receive test article (either active or placebo). All safety analyses will be conducted in this population.

6.1.3 Microbiological Intent-to-Treat (microITT) Population

The microITT population will consist of all subjects in the ITT population who have at least one causative bacterial pathogen identified from a culture of a respiratory specimen (eg, respiratory fluid obtained by bronchoalveolar lavage [BAL] or bronchoscopy; pleural fluid obtained by thoracentesis; or expectorated or induced sputum meeting adequacy criteria as defined by the Gram stain results), culture of blood or from a culture-independent method (eg, positive urinary antigen test for *Streptococcus pneumoniae* or *Legionella pneumophila*, or positive serology for *Legionella pneumophila*, *Mycoplasma pneumoniae,* or *Chlamydophila pneumoniae*) at baseline.

Pathogen determination of typical bacteria is based on the genus and species identification from the central laboratory. If the local laboratory grows an acceptable pathogen but the central laboratory is not able to grow the isolate, if isolates are lost during transportation or storage, or there are major discrepancies between the local and central laboratory in the identification of species, the central laboratory or other Sponsor designee will request that the local laboratory resend the isolate. If the central laboratory cannot determine the genus and species of the isolate for any reason, the local laboratory determination of genus and species will be used for pathogen identification. The central laboratory identification of genus and species is used for analysis unless no central determination exists in which case the local laboratory determination is used.

In general, baseline is defined as the 24-hour period prior to the administration of the first dose of test article. However, if the subject is unable to produce a sputum sample at baseline or the sputum sample is not adequate based on the Gram stain criteria, a specimen obtained within 24 hours after the first dose of test article may be considered a baseline sample. If the sputum sample collected in the 24-hour period prior to the administration of the first dose of test article is not adequate based on the Gram stain criteria and the sputum sample obtained within 24 hours after the first dose of test article is not adequate based on the Gram stain criteria, only the sputum sample collected in the 24-hour period prior to administration of the first dose of test article will be considered baseline. UAT samples up through 24 hours after the first dose of test article may be considered the baseline sample, if a previous sample was

not taken or was found to be negative. Blood samples up through 24 hours after the first dose of test article may be considered the baseline sample, if a previous sample was not taken or was found not to have a pathogen.

The following isolates will always be considered a pathogen:

Streptococcus pneumoniae

- Positive BAL, bronchoscopy, pleural fluid, or blood culture; or
- Positive sputum culture in the presence of an adequate Gram stain defined as having > 25 polymorphonuclear neutrophils (PMNs)/Low Power Field (LPF) and < 10 Squamous Epithelial Cells (SECs)/LPF; or
- Positive urinary antigen test

Haemophilus influenzae

- Positive BAL, bronchoscopy, pleural fluid, or blood culture; or
- Positive sputum culture in the presence of an adequate Gram stain (> 25 PMNs/LPF and < 10 SECs/LPF)

Staphylococcus aureus

- Positive BAL, bronchoscopy, pleural fluid, or blood culture
- Positive sputum culture in the presence of an adequate Gram stain (> 25 PMNs/LPF and < 10 SECs/LPF)

Moraxella catarrhalis

- Positive BAL, bronchoscopy, pleural fluid, or blood culture; or
- Positive sputum culture in the presence of an adequate Gram stain (>25 PMNs/LPF and < 10 SECs/LPF)

Legionella pneumophila

- Positive BAL, bronchoscopy, pleural fluid, or blood culture; or
- Positive sputum culture, regardless of Gram stain findings; or
- Positive or borderline acute (baseline) or positive or borderline convalescent (PTE) IgM (Euroimmun IgM ELISA IgM ≥0.80 ratio).
- Negative acute (baseline) and positive or borderline convalescent (PTE) IgG (Euroimmun IgG ELISA IgG ≥16 RE/mL).

- A positive urine antigen test

Mycoplasma pneumoniae

- Positive or borderline acute (Baseline) or positive or borderline convalescent (PTE) IgM (Euroimmun IgM ELISA IgM ≥0.80 ratio).
- Negative acute (Baseline) and positive or borderline convalescent (PTE) IgG (Euroimmun IgG ELISA IgG ≥16 RE/mL).

Chlamydophila pneumoniae

- Positive or borderline acute (Baseline) or positive or borderline convalescent (PTE) IgM (Euroimmun IgM ELISA IgM ≥0.80 ratio)
- Negative acute (Baseline) and positive or borderline convalescent (PTE) IgG (Euroimmun IgG ELISA IgG ≥16 RE/mL)

The following isolates are considered as contaminants from respiratory specimens rather than pathogens of CABP: *Candida* spp. and other fungi, *Enterococcus* spp., viridans streptococci, coagulase-negative staphylococci, *Micrococcus* spp., *Neisseria* spp. other than *N. meningitidis*, *Corynebacterium* spp. and other coryneforms, *Lactobacillus* spp., *Vibrio* spp., *Capnocytophaga* spp., *Cardiobacterium* spp., *Flavobacterium* spp, *Staphylococcus lugdunensis, Staphylococcus capitis, Staphylococcus caprae , Staphylococcus chine, Staphylococcus condiment, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus saprophyticus, Staphylococcus sciuri, Staphylococcus simulans, Streptococcus epidermidis, Streptococcus viridans, Staphylococcus warneri, Staphylococcus xylosus*

Other isolates identified from culture of blood and respiratory specimens will be reviewed in a blinded manner by the Sponsor on a case-by-case basis for determination of whether the organism is a pathogen for CABP.

Staphylococcus aureus will be considered a distinct pathogen with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* considered distinct pathogens. Likewise, *Streptococcus pneumoniae* will be a distinct pathogen with penicillin-nonsusceptible *Streptococcus pneumoniae*, penicillin-susceptible *Streptococcus pneumoniae*, macrolide-resistant *Streptococcus pneumoniae,* quinolone-resistant *Streptococcus pneumoniae,* and multiple drug resistant *Streptococcus pneumoniae* each considered distinct pathogens. A pathogen will be considered multiple drug resistant if susceptibility testing shows resistance to one drug in 3 or more of the classes of antibiotics provided below except in the case of MRSA where penicillin and cephalosporin are due to a single mechanism in which case 2 non-β-lactam resistances in addition to oxacillin, will be considered multi-drug resistant. *Streptococcus* spp. and *Staphylococcus* spp., isolates resistant to macrolides but susceptible to lincosamides and D-test positive (> 4/0.5 ug/ml) will be considered resistant to both macrolides and lincosamides. Susceptibility will be based on the most current CLSI guidelines for each antibiotic or if unavailable, on FDA

labeled susceptibility criteria. Antibiotics that define resistance for the class are listed as follows:

- Penicillins – penicillin
- Fluoroquinolones – moxifloxacin
- Cephalosporins – ceftriaxone
- Lincosamides – clindamycin
- Macrolides – azithromycin or erythromycin
- Tetracyclines – tetracycline or doxycycline
- Folate Pathway Inhibitors – Trimethoprim/sulfamethoxazole
- Glycopeptides – vancomycin
- Oxazolidinone – linezolid

If there are multiple specimens (of the same testing modality) from the same time-point where the same pathogen is isolated, only the pathogen with the highest MIC to the test article received will be used. If the pathogens have the same MIC to the test article received, the pathogen with the lowest accession number will be used. The Gram stain associated with the selected pathogen will be utilized for analysis.

If the same pathogen is identified from the blood and respiratory sample, for tables providing MIC or disk diffusion data, the pathogen with the highest MIC to the test article received will be used.

6.1.4 Clinically Evaluable (CE) Populations

Two CE populations will be defined: the CE-EOT and the CE-PTE. Subjects will be *included* in or *excluded* from the CE analysis sets based on the criteria listed below.

6.1.4.1 Diagnosis of CABP

To be included in the CE-EOT and CE-PTE populations, subjects must meet the following protocol defined inclusion criteria that describe the CABP:

Inclusion Criterion 3: Has at least 3 of the following symptoms:

- Cough
- Production of purulent sputum
- Dyspnea (shortness of breath)
- Pleuritic chest pain.

Inclusion Criterion 4: Has at least 2 of the following abnormal vital signs:

- Fever or hypothermia documented by the investigator (po or rectal temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
- Hypotension with systolic blood pressure (SBP) < 90 mmHg
- Heart rate > 90 bpm
- Respiratory rate (RR) > 20 breaths/minute.

Inclusion Criterion 5: Has at least 1 clinical sign or laboratory finding associated with CABP:

- Hypoxemia Partial pressure of arterial oxygen (PaO_2) < 60 mmHg by arterial blood gas (ABG)
- Physical examination findings of pulmonary consolidation (dullness on percussion, bronchial breath sounds, egophony, rales, rhonchi, or decreased breath sounds)
- An elevated total white blood cell (WBC) count (> 12,000 cells/mm^3) ***or*** leucopenia (WBC < 4,000 cells/mm^3) ***or*** elevated immature neutrophils (> 15% band forms regardless of total peripheral WBC count).

Inclusion Criterion 6: Has disease categorized as being PORT III or IV at Screening

Inclusion Criterion 7: Radiographically-confirmed pneumonia, ie, new or progressive pulmonary infiltrate(s) on chest X-ray (CXR) or chest computed tomography (CT) scan consistent with acute bacterial pneumonia within 48 hours prior to the first dose of test article.

The Sponsor Medical Monitor will also review those subjects with a concomitant illness identified after baseline that could have presented at baseline as pneumonia, including COVID-19. If it is determined that the subject does not have pneumonia but had another condition such as lung cancer or COVID-19 at baseline, the subject will not be evaluable for the CE populations. Any subject who is confirmed or suspected to have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection based on local standard-of-care assessments during the post-randomization period may be excluded from the CE populations based on Sponsor review.

6.1.4.2 Prior Antibiotic Therapy

Subjects will be excluded from the CE populations if they meet the prior antibiotic exclusion criteria:

Exclusion Criterion 1: Has received 1 or more dose(s) of a potentially effective systemic antibacterial treatment within the 72 hours prior to the first dose of test article (a subject will be considered to have received a potentially effective systemic antibacterial treatment if the pathogen identified as causing infection is shown to be susceptible to the antibacterial given or, in the circumstance where a pathogen is not identified, if the antibacterial agent is approved for treatment of pneumonia or is known to have activity against any of the leading

causes of CABP [eg, *Streptococcus pneumoniae, Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus, Legionella pneumophila*]). EXCEPTION: Subjects (not exceeding 25% of the total study population) may be eligible despite prior antibacterial therapy if they have been treated with a single dose of a short-acting antibacterial (ie, an antibacterial whose standard dosing regimen is more frequent than once per day, see Appendix 4 of the protocol).

6.1.4.3 Concomitant Antibiotic Therapy

Subjects who receive any systemic concomitant antibiotic therapy from the time of the first dose of test article through the time of the last dose of test article at EOT and through the PTE Visit with a spectrum of activity against the known or potential infecting pathogen(s) responsible for the CABP under study will be excluded from the CE-EOT and CE-PTE populations, respectively, unless the subject receives the antibiotic therapy for treatment of the CABP due to insufficient therapeutic effect of the test article (ie, for progression or development of new symptoms of CABP or development of infectious complications of CABP).

Subjects who receive a systemic concomitant antibiotic that is not effective against the baseline pathogen, or if no pathogen is isolated, and the antibiotic does not have activity against CABP pathogens, will be included in the CE-EOT and CE-PTE populations.

6.1.4.4 Test Article Therapy

Subjects must meet all of the following to be included in the CE populations:

- Received at least 1 dose of active test article and the correct test article based on the randomization assignment.
- Study personnel involved in the assessment of efficacy remained blinded to study treatment, unless a treatment limiting adverse event (AE) occurred which required emergency unblinding.
- Evaluable failure: The subject received the first 2 doses (if receiving 200 mg iv QD on Day 1) or 3 doses (if receiving 100 mg iv on Day 1) of active test article (omadacycline group) or first 2 doses of active test article (moxifloxacin group) and the investigator classifies the subject as a Clinical Failure at the EOT Visit (CE-EOT population) or the overall Clinical Response (based on the investigator's assessment) at the PTE Visit (CE-PTE population) is Clinical Failure.
- Evaluable success: The subject received the first 3 doses (if receiving 200 mg iv QD on Day 1) or 4 doses (if receiving 100 mg iv on Day 1) of active test article (omadacycline group) or the first 3 doses of active test article (moxifloxacin group) and the investigator classifies the subject as a Clinical Success at the EOT Visit (CE-EOT population) or the overall Clinical Response (based on the investigator's assessment) at the PTE Visit (CE-PTE population) is Clinical Success.

6.1.4.5 Clinical Outcome Assessment

Subjects must meet the following to be included in the CE populations:

- For the CE-EOT population:
  - Completed the investigator's assessment of clinical response (ie, was not deemed an indeterminate outcome) at the EOT Visit, and
  - The EOT Visit occurred on the day of, or within 2 days following the last dose of test article.

- For the CE-PTE population:
  - The overall Clinical Response (based on the investigator's assessment) at the PTE Visit is not Indeterminate.
  - The PTE Visit occurred 5 to 10 days after the last dose of test article, unless the subject was considered to be a Clinical Failure based on the investigator's assessment at the EOT Visit or the patient died after EOT and before PTE.

6.1.4.6 Baseline Medical Events

Subjects will be excluded from the CE populations if the investigator has documented in the eCRF that they meet any one of the following protocol-defined exclusion criteria at baseline (ie, prior to randomization):

Exclusion Criterion 2: Is known or suspected to have CABP caused by a pathogen that may be resistant to either test article (eg, , *Pseudomonas aeruginosa*, *Proteus* spp., *Morganella morganii*, *Providencia* spp. *Pneumocystis jiroveci*, obligate anaerobes, mycobacteria, fungal pathogens).

Exclusion Criterion 3: Suspected or confirmed empyema (a parapneumonic pleural effusion is not an exclusion criteria) or lung abscess.

Exclusion Criterion 5: Subjects who reside in a long-term care or subacute/intermediate healthcare facility (eg, nursing home) or a subject admitted with pneumonia following a recent hospitalization (overnight admission within 90 days prior to current admission.

Exclusion Criterion 12: Requires acute pharmacologic intervention to stabilize blood pressure (BP) and/or adequate tissue perfusion, OR meets septic shock criteria (meets ALL of the following):

- Meets at least 2 criteria for sepsis as defined by the quick Sequential Organ Failure Assessment (qSOFA) score: (a) Altered mental status with Glasgow Coma Scale (GCS) < 15, (b) RR ≥ 22 breaths per minute, and (c) SBP ≤ 100 mmHg
- Despite adequate fluid resuscitation, persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mmHg.
- Serum lactate ≥ 2 mmol/L (serum lactate measurement is not required at

Screening if any of the above septic shock criteria are not met)

Exclusion Criterion 13: PORT Risk Class I, II and V patients.

1. Exclusion Criterion 14; Requires or expected to require Intensive Care Unit (ICU) admittance or invasive or non-invasive ventilation.

Exclusion Criterion 15: Known or suspected primary or metastatic neoplastic lung disease, aspiration pneumonia, active tuberculosis, cystic fibrosis, bronchiectasis, bronchial obstruction (eg, post-obstructive pneumonia), chronic neurological disorder preventing clearance of pulmonary secretions, or severe chronic obstructive pulmonary disease (COPD) (severe COPD is defined as known forced expiratory volume in 1 second [FEV_1] < 50% of predicted in a patient with FEV_1/forced vital capacity [FVC] < 70%; note that spirometry or pulmonary function testing is not required during Screening).

6.1.5 Microbiologically Evaluable (ME) Populations

The ME-EOT and ME-PTE populations will consist of all subjects in both the microITT and the CE-EOT and CE-PTE populations, respectively.

6.2 Evaluability Review Team

6.2.1 Membership and Responsibilities

The Evaluability Review Team (ERT) will review both clinical and microbiological data for determination of criteria used to assess inclusion in the analysis populations and for determination of baseline and post-baseline pathogens. ERT members will be blinded to treatment assignment and will review the data concurrent with the conduct of the study. The ERT will be conducted in accordance with the ERT Process Document.

6.2.2 Process for Determining Inclusion in Populations

Inclusion into the ITT and Safety populations will be determined programmatically from the eCRF data. Inclusion into the CE populations will be determined programmatically from the eCRF data and the manual review conducted by the ERT. The ERT may review subject data to confirm that population criteria are satisfied.

Inclusion into the microITT population will be determined programmatically by incorporating the outcome of the review of the isolates by the ERT. The ERT will determine whether each isolate (baseline and post-baseline) is considered a pathogen based on a review of information from baseline samples including Gram stain results, and local and central laboratory genus and species identification. Inclusion into the ME populations will be determined programmatically.

Review of data, Sponsor determination of evaluability, and final subject population classification will be performed in a blinded manner prior to database lock and unblinding with the exception of those criteria requiring the subject's actual treatment assignment (for example, the requirement for the subject to have received the correct test article per the randomization assignment). For the criteria requiring the subject's actual treatment assignment, population determination will be completed programmatically.

6.3 Subgroups

Analyses will be conducted (as described in Section 9) for subgroups defined by the randomization stratification factors: PORT Risk Class (III and IV) and receipt of an allowed antibacterial therapy in the 72 hours prior to study treatment (yes vs no). Analyses of ECR (in the ITT population) and clinical response at the PTE visit (in the ITT and CE-PTE populations) will also be conducted in the following subgroups: bacteremic subjects, defined as subjects with a positive blood culture at baseline (microITT population), by CURB-65 Score, and subjects meeting the systemic inflammatory response syndrome (SIRS) criteria at baseline. CURB-65 Score is derived from the eCRF data and ranges from 0-5 where 1 point is given for each of the following at baseline: confusion, blood urea nitrogen > 19 mg/dL (urea > 6.8 mmol/L), respiratory rate ≥ 30 breaths/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years. Confusion is defined as altered mental status as recorded on the PORT Risk Class Determination eCRF. SIRS is defined as having 2 or more of the following criteria: temperature < 36°C or > 38°C (oral or oral equivalent), heart rate > 90 bpm, respiratory rate > 20 breaths/min, or WBC count < 4000 cells/mm^3 or > 12,000 cells/mm^3 or > 10% bands.

Exploratory analyses in other subgroups may also be conducted.

7 OVERALL STATISTICAL CONSIDERATIONS

7.1 General Conventions

The following general comments apply to all statistical analyses and data presentations:

- Summaries will include frequency and percentages for categorical data; frequency and median for ordinal data; and frequency, mean, standard deviation, and median, minimum, and maximum for quantitative data.
- Duration variables will be calculated using the general formula (end date − start date) +1.
- Change from baseline will be calculated for each subject at the specified time point as the value at the specified time point minus the baseline value.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (eg, a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as '< 10' or '≤ 5' will be treated as '10' or '5' respectively, and a value such as '> 100' will be treated as '100.' However, the actual values as reported in the database will be presented in data listings. Data will be reviewed on an ongoing basis in a blinded manner to assess the frequency of occurrence of laboratory parameters reported as a character string.
- Individual subject listings of all data represented on the eCRFs will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety parameters.
- Version 9.3 (or higher) of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

7.2 Baseline Definition

In general, baseline is defined as the value closest to but prior to the initiation of test article administration. If no test article is received, baseline is defined as the value closest to but prior to randomization.

For pathogen determination, baseline is defined as either Day –1 or 1 (the 24-hour period prior to the administration of the first dose of test article) or if the subject is unable to produce a sputum sample at baseline or the sputum sample does not have an adequate Gram stain, a specimen obtained within 24 hours after the first dose of test article may be used as baseline. If no test article is received, for pathogen determination, Study Day is defined based on date of randomization.

For analyses of vital signs and ECGs, if no value is available prior to the initiation of test article administration, a value within 2 hours after initiation of test article administration can be used as baseline.

7.3 Handling of Missing Data

Missing data will be handled as outlined below:

- All missing and partial dates for AEs or for medications received after randomization will be queried for a value. If no value can be obtained, substitutions will be made as detailed in Appendix 3. These substitutions will be used in calculations; however, the actual value recorded on the eCRF will be used in all listings.
- Missing start and stop times for prior and concomitant antibiotics will be queried for a value. If no value can be obtained but the site indicates the antibiotic was received (onset time) prior to the first dose of test article, 00:01 will be used for the onset time. If the site also indicates that the end time was prior to the first dose of test article, 00:01 will be used for end time. The actual value (blank) will be recorded on the eCRF and will be used in the listings.
- Missing times for assessments of CABP symptoms will be queried for a value. If minutes are not available, the time will be recorded to the closest hour.
- If no value can be obtained for all other times for events and assessments occurring after randomization, the time will not be imputed but will remain missing.
- The severity and causality assessment for AEs cannot be missing. Missing data will be queried for a value.
- If the time of administration of the first dose of test article is missing, it will be set to 1 minute after midnight (00:01)

For clinical and microbiological response, missing data will be handled as follows:

- For the primary outcome measure (ECR at 72 to 120 hours after administration of the first dose of test article):
  - The subject will be considered to have missing data if an assessment of all of the CABP symptoms (cough, sputum production, pleuritic chest pain, and dyspnea) is not made from 72 to 120 hours after the administration of the first dose of test article, unless the subject is considered a Clinical Failure for another reason. Subjects who do not have at least 2 symptoms of CABP at baseline will also be considered to have missing data unless the subject is considered a Clinical Failure for another reason. Subjects with missing data will be defined as an Indeterminate response which is essentially a Clinical Failure for the primary analysis in the ITT population.

- For the secondary outcome measures (investigator's assessment of Clinical Response at the EOT and PTE Visits):
  - Subjects will be defined as an Indeterminate if the investigator cannot determine whether the subject is a Clinical Success or Failure at the EOT or PTE Visits or the subject has a missing response Table 4. By definition, subjects with an Indeterminate response are included in the denominator for analyses in the ITT and microITT populations, and thus, are considered Clinical Failures. Subjects with an

Indeterminate response are excluded from the CE-EOT, CE-PTE, ME-EOT and ME-PTE populations.

- For microbiologic response:
  - If no post-baseline source specimen is obtained and the subject has an investigator's assessment of Clinical Response, the per-pathogen microbiological response is based on the investigator's assessment of Clinical Response (ie, the response is a presumed response). A per-pathogen microbiological response at the EOT Visit or PTE Visit will be considered Indeterminate only if the Clinical Response at EOT or PTE is also Indeterminate.
- Missing values for other individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.
- Where individual data points are missing, categorical data will be summarized based on reduced denominators (ie, only subjects with available data will be included in the denominators).

7.4 Interim Analysis

An interim analysis to assess efficacy is not planned. However, a Data and Safety Monitoring Committee (DSMC) will review safety data (eg, AEs and serious adverse events [SAEs], laboratory data, ECG and vital signs assessments) by unblinded (treatment A and treatment B) treatment assignment at regular time points while the study is ongoing. However the DSMC can convene unscheduled meetings as necessary. A detailed DSMC charter outlines the responsibilities of the DSMC, format and frequency of the meetings, methods of providing data to and from the DSMC, statistical issues, documentation of the meeting outcomes, and communication pathways.

7.5 Pooling Strategy for Study Sites

Data will be pooled across sites and geographic regions.. Due to the large number of sites and the small number of subjects per site, no analyses by site will be conducted

7.6 Visit Windows/Unscheduled Visits

For the primary efficacy outcome, if more than one complete assessment of the symptoms of CABP is done in the ECR assessment window of 72 to 120 hours after administration of the first dose of test article, the latest will be used. For secondary and additional efficacy outcomes, the data collected at the EOT and PTE Visits, regardless of when these occur will be utilized in the ITT and microITT analyses. The CE and ME populations exclude subjects with a visit occurring outside the window allowed per protocol.

For each safety outcome, analyses will utilize assessments occurring during the scheduled visit windows (provided in Table 8). Thus, if a subject has a visit outside the scheduled visit window, for example, a PTE Visit occurred 20 days after the subject's last day of therapy, the assessment will not be summarized with the PTE Visit but will be considered an unscheduled

assessment. If a subject does not have an assessment at a scheduled visit and an unscheduled assessment was taken within the window for the time point (for example, 5 to 10 days after the subject's last day of therapy for PTE), these assessments will be summarized in the by time point analyses. If more than one measurement is taken during the visit window, the value taken on the scheduled visit will be utilized or if no scheduled visit was done, the first (earliest) measurement in the visit window will be used. If more than one measurement is taken on the same day, the assessment closest to the start of the dose will be used for on treatment values and the last measurement on the day will be used for post-treatment values. For worst overall post-baseline analyses, all assessments including those obtained from unscheduled visits will be included.

Table 8. Scheduled Study Visits

Study Visit	Study Day	Notes
Baseline	Day -1 or Day 1	Except where indicated, last measurement prior to the first dose of test article. Screening assessments are to be taken within 24 hours prior to the first dose of test article. If no test article is taken, the date and time of randomization is used in place of the first dose of test article.
On Treatment	Day 1-Day 10	Visits occur on Days 1,2,3,4 to 6 (ECR). Visits will occur on Days 8 to 10 if treatment extends beyond 7 days. Subjects with bacteremia identified at Screening may have visits up to Day 14. For subjects that have been switched to po treatment and were discharged from the hospital prior to Day 4, only 1 visit is required between Study Days 4 to 6.
EOT		Within 2 days following the last dose of test article
PTE		5-10 days after the subject's last day of therapy
Final Follow-up	Day 30-37	30-37 days after the start of the first infusion of test article

Study Day is calculated relative to the first dose of test article (Day 1); there is no Day 0 – the day prior to the first dose of test article is Day -1. If no test article is taken, Study Day is calculated relative to the date of randomization.

8 STATISTICAL ANALYSIS METHODS

8.1 Subject Disposition

The number of Screen Failures and reason for screen failure will be presented. A listing, grouped by randomization stratum (PORT Risk Class and receipt of prior antibiotics), will be provided that indicates the subject's date and time of randomization, randomized treatment assignment, and randomization number.

The number of subjects included in each of the analysis populations (ie, ITT, Safety, microITT, CE-EOT, CE-PTE, ME-EOT, and ME-PTE) will be summarized by treatment group and country. A table will summarize the reasons for exclusion from each population and a listing will be provided that indicates each subject's inclusion in/exclusion from the populations and the reason for exclusion from each of the populations.

A listing will be provided of randomized subjects who did not meet all inclusion/exclusion criteria, and which criteria were not met. The number and percentage of subjects completing the study (defined as receiving at least 1 dose of test article and returning for all of the EOT, PTE, and Follow-up Visits), not completing the study, missing each of the EOT and PTE Visits, and prematurely discontinuing from test article (including due to COVID-19) will be presented for each treatment group and overall for the ITT, microITT, and CE-PTE populations (by definition, a subject in the CE-PTE population cannot have missed the PTE Visit, unless the subject was a clinical failure at the EOT Visit). Reasons for premature discontinuation of test article, not completing the study, and for missing each of the visits (including due to COVID-19), as recorded on the eCRF will be summarized (number and percentage) by treatment group for the ITT, microITT, and CE-PTE populations. Percentages of subjects discontinued from test article and not completing the study will be compared between treatment groups using Fisher's exact test. A listing of all subjects who prematurely discontinued from test article or not completing the study will be presented, and the primary reason for discontinuation of test article or not completing the study, as well as the visit(s) missed and the reason for missing the visit(s), will be provided.

8.2 Demographics and Baseline Characteristics

Except where indicated, demographic data and baseline characteristics will be presented by treatment group for the ITT, Safety, microITT, and CE-PTE populations. A table will present the subject demographics (eg, gender, age, ethnicity, and race) and baseline characteristics (height, weight, body mass index (BMI), and creatinine clearance categorized as severe renal impairment [< 30 mL/min], moderate renal impairment [30-50 mL/min], mild renal impairment [> 50-80 mL/min], and normal renal function [> 80 mL/min]) collected before the start of test article. . Age will be summarized as a continuous variable and in the categories, 18-45 years, > 45-65 years and > 65 years. The number and percentage of subjects > 75 years of age will also be provided. Creatinine clearance will be calculated from the local laboratory data since these data were used for determination of the inclusion and exclusion criteria and will be determined from the Cockcroft-Gault equation:

$$\frac{(140\text{-age[yrs]})*\text{weight [kg]}*(Z)}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Z = 1.0, if Male
Z = 0.85, if Female

Differences between treatment groups will be analyzed using Fisher's exact test for dichotomous variables (gender and ethnicity), Chi-squared test for categorical variables (age category and race) and the Wilcoxon Rank Sum test for continuous variables (age, height, weight, and BMI).

A table will provide the frequency counts and percentages by treatment group for subjects who received prior antibiotics (as randomized), PORT Risk Class (from the eCRF and as randomized), CURB-65 Score, subjects meeting the modified American Thoracic Society (ATS) severity criteria, and subjects meeting the SIRS criteria for the ITT, microITT and CE-PTE populations. PORT score will also be summarized as a continuous variable. CURB-65 score is derived from the eCRF data and ranges from 0-5 where 1 point is given for each of the following at baseline: confusion, blood urea nitrogen > 19 mg/dL (urea > 6.8 mmol/L), respiratory rate ≥ 30 breaths/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years. Confusion is defined as altered mental status as recorded on the PORT Risk Class Determination eCRF. Modified ATS severity and SIRS criteria are derived from the eCRF data. Modified ATS severity criteria is defined as presence of ≥ 3 of the following 9 criteria at baseline: respiratory rate ≥ 30 breaths/min, O_2 saturation < 90% or PaO_2 < 60 mmHg, blood urea nitrogen ≥ 20 mg/dL, WBC < 4000 cells/mm^3, confusion, multilobar infiltrates, platelets < 100,000 cells/mm^3, temperature < 36°C, and systolic blood pressure < 90 mmHg. SIRS criteria is defined as having 2 or more of the following 4 symptoms at baseline: temperature < 36°C or > 38°C (oral or oral equivalent), heart rate > 90 bpm, respiratory rate > 20 breaths/min, WBC < 4000 cells/mm^3 or WBC > 12,000 cells/mm^3, or bands > 10%. Differences between treatment groups will be tested using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables.

By-subject listings of the modified ATS severity criteria and SIRS criteria will be provided. A listing of subjects with discrepancies between the PORT Risk Class to which they were randomized and their true PORT Risk class as captured in the clinical database will also be provided.

Baseline assessments of clinical symptoms, clinical signs, abnormal vital signs, and abnormal laboratory signs of CABP will be presented for the ITT, Safety, microITT, and CE-PTE populations. The number and percentage of subjects with each of the CABP symptoms (cough, pleuritic chest pain, dyspnea, and phlegm/sputum production) by severity (absent, mild, moderate, severe) will be presented by treatment group. The number and percentage of subjects with the presence by severity (ie, absent, mild, moderate, severe) of the following clinical signs will be provided by treatment group: rales, rhonchi, dullness on percussion, bronchial breath sounds, wheezing, decreased breath sounds, and egophony. The number and percentage of subjects with fever (defined as body temperature > 38°C [100.4°F] oral or rectal), hypothermia (defined as body temperature < 36°C [95.5°F] oral or rectal), hypotension with systolic blood pressure < 90 mmHg, heart rate > 90 bpm, respiratory rate > 20 breaths/min, hypoxemia (defined as PaO_2 < 60 mmHg by arterial blood gas or

oxygen saturation < 90% by pulse oximetry), elevated total WBC count (> 12,000 cells/mm^3), leucopenia (WBC < 4,000 cells/mm^3), elevated immature neutrophils (> 15% band forms regardless of total peripheral WBC count) and any of elevated total WBC count, leucopenia or elevated immature neutrophils will be summarized by treatment group. Differences between treatment groups will be tested for statistical significance using Fisher's exact test.

Risk factors for CABP will be presented by treatment group for the ITT, Safety, microITT, and CE-PTE populations. Risk factors include smoking (current, past, and descriptive statistics of the number of years since quitting for those subjects who were previous smokers), receipt of pneumococcal vaccine, prior lung infection, whether the subject had mild to moderate COPD, symptomatic asthma with wheezing, and chronic cough with or without sputum production. Differences between treatment groups will be tested for statistical significance using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Other medical and surgical history will be summarized based on MedDRA system organ class by treatment group for the ITT and Safety populations.

Readings of baseline chest radiographs, including the type of assessment (CXR or CT scan), presence of pleural effusion, whether the pleural effusion is unilateral or bilateral, whether the pulmonary infiltrate was uni- or multi-lobar and the location of the pulmonary infiltrate (combining left upper lobe and lingula) will be summarized by treatment group for all subjects in the ITT, Safety, microITT, and CE-PTE populations. Differences between treatment groups will be tested for statistical significance using Fisher's exact test.

8.2.1 Microbiology

Findings from the local laboratory assessment of the Gram-stained respiratory specimens (SECs [< 10, 10-25, > 25], PMNs [< 10, 10-24, ≥ 25], combinations of the bacteria found [monomicrobial Gram negative only, polymicrobial Gram negative only, monomicrobial gram positive only, polymicrobial Gram positive only, any Gram negative and Gram positive, and other] and whether or not a culture was performed) will be tabulated by treatment group for all subjects in the ITT, microITT, and ME-PTE populations.

If a subject has more than one baseline respiratory specimen, the best will be summarized. The best respiratory specimens include deep respiratory samples (eg, bronchoalveolar lavage [BAL], bronchoscopy) or pleural fluid cultures. Sputum adequacy criteria do not apply to these types of specimens.

If no deep respiratory or pleural fluid specimens are available, expectorated sputum will be assessed using Gram stain criteria. Best sputum samples are defined based on the PMNs and SECs as follows (ranked best to worst):

1. > 25 PMNs and < 10 SECs
2. 10-25 PMNs and < 10 SECs
3. < 10 PMNs and < 10 SECs
4. >25 PMNs and 10-25 SECs

5. 10-25 PMNs and 10-25 SECs
6. < 10 PMNs and 10-25 SECs
7. > 25 PMNs and > 25 SECs
8. 10-25 PMNs and > 25 SECs
9. < 10 PMNs and > 25 SECs

The number and percentage of subjects with a qualifying Gram-stain (ie, ≥ 25 PMNs and < 10 SECs) will also be presented.

The pathogenic organisms identified from the baseline blood culture, culture of the respiratory specimen, UAT, and serology will be presented by genus and species and by testing modality (ie, culture, UAT, serology) for *Streptococcus pneumoniae* and *Legionella pneumophila*, for the microITT, ME-EOT, and ME-PTE populations. The same pathogen identified from multiple testing modalities will be counted only once in the summary at the genus and species level. The pathogenic organisms identified from the baseline blood culture, culture of the respiratory specimen, UAT, and serology will also be presented by country in the microITT population. The number and percentage of subjects with CABP caused by monomicrobial and polymicrobial Gram-positive or Gram-negative pathogens, only atypical pathogens (ie, *Legionella pneumophila*, *Mycoplasma pneumoniae,* or *Chlamydophila pneumoniae*), a mixture of both Gram-positive and Gram-negative pathogens, a mixture of Gram-positive and atypical pathogen, or a mixture of Gram-negative and atypical pathogens will be summarized by treatment group overall (microITT and ME-PTE populations) and by PORT Risk Class and country for the microITT and ME-PTE populations.

The number and percentage of subjects with a positive blood culture by pathogenic organism will be provided for the microITT and ME populations. The number and percentage of subjects with a Gram-positive organism (aerobes and anaerobes) and with a Gram-negative organism (aerobes and anaerobes) will be presented by genus and species. The percentage of subjects with a positive blood culture by pathogenic organism will be provided for the microITT population by geographic region.

A listing will be provided that includes all baseline and post-baseline isolates obtained from the blood, respiratory specimen, UAT, and serology and will indicate the type of specimen, testing modality, and pathogenic organism.

Several tables providing the minimum inhibitory concentration (MIC) data for the pathogens identified from the baseline blood and respiratory cultures will be provided for the microITT and ME populations:

- The MIC distribution to omadacycline and moxifloxacin, across treatment groups
- The MIC distribution to the test article received, by treatment group

  MIC summary statistics (ie, range, MIC_{50} and MIC_{90}) to the test article received. The MIC range will be provided for all baseline pathogens. The MIC_{50} and MIC_{90} will be provided only for those pathogens isolated at least 10 times in a treatment group.
  - Susceptibility (susceptible, intermediate or resistant) to the test article received will be summarized by pathogen.

8.3 Treatment Compliance and Exposure

Exposure summary by treatment group will be presented for the Safety, microITT, and CE-PTE populations. The distribution of subjects by the total number of days on therapy (0, 1-3, 4-6, 7-10, 11-14, and > 14 days), the number of days on iv infusion (0, 1-2, 3-6, 7-10, 11-14, and > 14 days), the number of days of oral test article (0, 1-4, 5-7, 8-11, and > 11 days) and the number of days of oral switch (1-2, 3-5, 6-7, ≥8) will be presented. A summary of the number of days of iv therapy prior to oral switch defined as 24-hour periods (ie, time to oral switch), the day of oral switch, and the criteria for iv to oral switch will be presented by treatment group. For the Safety population, the summary of test article exposure will be based on the actual treatment received whereas for all other analysis sets, the summary will be based on the randomized treatment.

Treatment compliance is defined as the number of iv doses (including partial doses, active and placebo) and oral doses actually received divided by the number of doses expected (× 100) over the time period defined by the first infusion date and the last dose date. Descriptive statistics for treatment compliance and the number and percentage of subjects at least 80% compliant will be presented by treatment group for the ITT, Safety, and CE-PTE populations.

9 EFFICACY PARAMETERS

For all efficacy analyses, subjects will be analyzed in the group to which they were randomized. Subjects who receive the wrong test article are not included in the CE-EOT, CE-PTE, ME-EOT, and ME-PTE populations. Subjects who are randomized to the wrong PORT Risk Class or prior antibiotic stratum will be analyzed in the stratum to which they were randomized, unless otherwise stated. A summary of the efficacy analyses is provided in Appendix 2.

Subjects who miss the efficacy assessment due to COVID-19 will have an indeterminate response and the number and percentage of subjects with an indeterminate response due to COVID-19 will be summarized. Depending on the number of subjects in the study diagnosed with COVID-19, primary efficacy outcome may be analyzed in patients with and without COVID-19 and additional sensitivity analyses may be included to treat indeterminates in various ways.

9.1 Primary Analysis

The primary efficacy analyses will be based on the ITT population. The non-inferiority test will be a 1-sided hypothesis test performed at the 2.5% level of significance. This non-inferiority test will be based on the lower limit of the 2-sided 95% confidence interval (CI). The primary efficacy outcome is the percentage of subjects with a Clinical Success at the ECR Assessment (72 to 120 hours after the first infusion of test article).

The number and percentage of subjects in each treatment group defined as an ECR Clinical Success, Clinical Failure and Indeterminate (subjects with missing data or who are lost to follow-up) will be tabulated, as will the overall category combining Clinical Failure and Indeterminate. The null and alternative hypotheses are as follows:

$$H_0 : p_1 - p_2 \leq -\Delta \text{ and } H_1 : p_1 - p_2 > -\Delta,$$

where p_1 is the primary efficacy success rate in the omadacycline treatment group, p_2 is the primary efficacy success rate in the moxifloxacin treatment group, and Δ is the non-inferiority margin of 10%.

To test the null hypothesis, a 2-sided 95% CI for the observed difference in primary outcome rates (omadacycline treatment group minus moxifloxacin treatment group) will be calculated for the ITT population. If the lower limit of the 95% CI for the difference in the ITT population exceeds –10%, then the null hypothesis will be rejected and the non-inferiority of omadacycline to moxifloxacin will be declared.

The 2-sided 95% CI for non-inferiority testing based on the difference of ECR Clinical Success rates at the ECR assessment (72 to 120 hours after the first infusion of test article), will be computed using the method proposed without stratification by Miettinen and

Nurminen (1985). For notation purposes, assume 1 represents the omadacycline group (Group 1) and 2 represents the moxifloxacin group (Group 2).

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

$$\chi_\alpha^2 = \frac{(\hat{p}_1 - \hat{p}_2 - RD)^2}{V}$$

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

$$V = \left[\frac{\tilde{p}_1(1-\tilde{p}_1)}{n_1} + \frac{\tilde{p}_2(1-\tilde{p}_2)}{n_2} \right] \frac{n_1 + n_2}{n_1 + n_2 - 1}$$

where n_1 = number of subjects in Group 1; n_2 = number of subjects in Group 2; $\tilde{p}_1 = \tilde{p}_2 + RD$; 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 2-sided 95% CI for the difference in rates is given by the roots for $RD = p_1 - p_2$ from the equation above, but this equation does not allow for explicit solution for RD . Therefore, a numerical algorithm will be used to obtain the 2 roots (CI) for RD . This CI approach corresponds to the non-inferiority test (a p-value approach) proposed by Farrington and Manning (1990).

The reasons for Clinical Failure and reasons for Indeterminate response will be summarized by treatment group.

9.2 Sensitivity and Additional Analyses of the Primary Efficacy Outcome

If the null hypothesis of inferiority is rejected for ECR in the ITT population and the observed Clinical Success proportion for omadacycline is larger than the observed proportion for moxifloxacin, a formal statistical analysis of superiority will be conducted. If the lower limit of the 95% 2-sided CI for the treatment difference is greater than 0.00, omadacycline will be considered superior to moxifloxacin.

Sensitivity analyses of the primary outcome include:

- Determination of the 95% CI adjusted for PORT Risk Class (III and IV) and prior use of antibiotics (yes and no). If there are < 20 subjects within a stratum and treatment group or there is a 0 count within a stratum for a treatment group and outcome, the receipt of prior antibiotics (yes vs no) will be combined. The 95% CI interval will be computed using

the stratified methodology of Miettinen and Nurminen (1985). Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI as follows, where n_{1i} = number of subjects in Group 1 in the ith stratum; n_{2i} = number of subjects in Group 2 in the ith stratum:

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

- The second sensitivity analysis of the primary outcome will consider all subjects who are lost to follow up prior to having an ECR assessment or have missing data, as a Clinical Success (these subjects are considered Indeterminates and analyzed as Clinical Failures in the primary analysis).

9.3 Secondary Analysis

The number and percentage of subjects in each treatment group with a Clinical Success, Clinical Failure, and Indeterminate for the assessment of Clinical Response at the PTE Visit (based on the investigator's assessment) will be reported for the ITT, CE-PTE, and ME-PTE populations (by definition CE-PTE and ME-PTE subjects cannot have a response of Indeterminate). Two-sided- 95% CIs will be constructed for the observed differences in the Clinical Success rate using the method of Miettinen and Nurminen (1985) without stratification. The 95% CIs are for descriptive purposes only and no conclusion of NI will be made. The reasons for Clinical Failure and Indeterminate will be summarized by treatment group.

The number and percentage of subjects in each treatment group in each response category for ECR will be presented for the microITT populations. The number and percentage of subjects who are classified as a Clinical Success and Clinical Failure based on the assessment of Clinical Response at the PTE Visit (based on the investigator's assessment) in the ME-PTE population will be calculated. Two-sided 95% CIs without stratification will be constructed for the observed difference in the Clinical Success rates in the microITT, and ME-PTE populations using the method of Miettinen and Nurminen (1985).

Early Clinical Response and the assessment of Clinical Response at the PTE Visit by baseline pathogen will be determined as the proportion of subjects with a Clinical Success, for each pathogen isolated at baseline. The number and percentage of subjects in each treatment group with a Clinical Success (based on ECR and investigator's assessment of response) will be tabulated per pathogen for the microITT, and ME-PTE (for Investigators assessment only).

All-cause mortality (ACM) at 15 and 30 days after the first dose of test article will be summarized in the ITT population. Subjects who are lost to follow-up will be considered deceased for this analysis (ie, included in the numerator and denominator of the calculation) but will be presented separately on the summary table. An additional analysis in the ITT population of ACM will be completed that includes only those subjects whose status is known at 15 and 30 days after the first dose of study drug.

9.4 Additional Analyses

Additional efficacy analyses will be conducted to support the efficacy findings of the primary and secondary outcomes. CIs will be determined for descriptive purposes, but no conclusions of NI will be made.

Clinical Outcomes

The number and percentage of subjects classified as a Clinical Success, Clinical Failure, and Indeterminate by the Investigator's Assessment at EOT in the ITT and CE-EOT populations (by definition subjects with an Indeterminate response are excluded from the CE-EOT population) will be calculated. The number and percentage of subjects in each response category for the assessment of Clinical response at PTE (based on the investigator's assessment) in the microITT population will also be provided. Two-sided unadjusted 95% CIs will be constructed for the observed difference in the Clinical Success rate using the method of Miettinen and Nurminen (1985).

The number and percentage of subjects with stabilization of all vital signs associated with CABP at 72 to 120 hours post first dose of test article will be presented by treatment group in the ITT population as will the number and percentage of subjects with stabilization of each vital sign. These include temperature (no fever or hypothermia), SBP (> 90 mmHg), heart rate (< 90 bpm), RR (< 20 breaths/minutes), and PaO_2 (> 60 mmHg by pulse oximetry or ABG). WBC count (< 12,000 cells/mm^3 or ≥ 4,000 cells/mm^3) and immature neutrophils (< 15%).

A summary (number and percentage of subjects) of the assessment of clinical symptoms of CABP at each time point throughout the study will be presented by treatment group in the ITT population. Clinical symptoms of CABP (cough, pleuritic chest pain, dyspnea, and phlegm/sputum production) will be summarized as shift tables of score (absent, mild, moderate, and severe) as compared with baseline. Percentages for clinical symptoms will be based on the number of subjects with a baseline and post-baseline evaluation at the time point of the specific clinical symptom. The number and percentage of subjects with resolution of all symptoms present at baseline (back to pre-CABP status) will also be provided by study visit in the ITT population. The number and percentage of subjects with no worsening of clinical symptoms of CABP and with the absence of new symptoms of CABP will also be provided by treatment group and study visit in the ITT population.

The number and percentage of subjects with an ECR Clinical Success (microITT population) with an assessment of Clinical Success (based on the investigator's assessment) at the EOT Visit (microITT and ME-EOT populations), and with an assessment of Clinical Success at the PTE Visit (based on investigator's assessment, for the microITT and ME-PTE populations), will be tabulated by baseline MIC to omadacycline and moxifloxacin by pathogen (for those pathogens occurring at least 5 times in one of the treatment groups) and treatment group.

At Screening and Final Follow-up visits, the subject will complete a SF-36v2® Health Survey (Medical Outcomes Trust, Optum™). The SF-36v2® Health Survey has 8 subscales: physical

functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue and general health perceptions. It also has a single item that provides an indication of perceived change in health. Physical and mental health composite scores (PCS and MCS) are computed and range from 0 (lowest level of health measured by the scales) to 100 (highest level of health). Descriptive statistics for the subscales, PCS and MCS will be provided at Screening, the Final Follow-up Visit and the change from baseline by treatment group in the ITT Analysis Sets.

Microbiological Outcomes

The per-subject microbiological response at the EOT and PTE Visits in the microITT, ME-EOT (EOT Visit only), and ME-PTE (PTE-Visit only) populations will be determined to support the clinical findings. The number and percentage of subjects classified with a favorable (eradication and presumed eradication) and unfavorable (persistence, presumed persistence) and indeterminate microbiological response (by definition, indeterminates are excluded from the ME populations) will be tabulated for both treatment groups. A 2-sided 95% CI without stratification will be constructed for the observed difference in the per-subject favorable microbiological response rate between the omadacycline and moxifloxacin groups using the method of Miettinen and Nurminen (1985).

Per-subject microbiological response at the PTE Visit in the microITT and ME-PTE populations will also be provided for infections caused by monomicrobial and polymicrobial Gram-positive or Gram-negative pathogens, only atypical pathogens, a mixture of both Gram-positive and Gram-negative pathogens, a mixture of Gram-positive and atypical pathogens, or a mixture of Gram-negative and atypical pathogens.

Microbiologic response by baseline pathogen will be determined as the proportion of subjects with a favorable microbiological response (eradication or presumed eradication) at the EOT and PTE Visits for each pathogen isolated at baseline. The number and percentage of subjects in each treatment group with a microbiologically favorable outcome will be tabulated for the microITT, ME-EOT (EOT Visit), and ME-PTE (PTE Visit) populations. Favorable microbiologic response by baseline pathogen will also be summarized separately for pathogens obtained from the blood culture (ie, for bacteremic subjects) for the microITT population.

Microbiological categories for pathogens identified after baseline assessment are superinfection and new infection. The number and percentage of subjects with a superinfection or new infection will be presented by treatment group. A listing will be provided that presents the subjects with a superinfection and new infection including the type of specimen and pathogen.

Decreasing susceptibility of a pathogen is defined as >4-fold increase from baseline to any subsequent study time point in the MIC of the test article received. The number and percentage of subjects in the microITT population with a pathogen showing decreasing susceptibility will be tabulated for each treatment group. In addition, a table will list all subjects in each treatment group with a pathogen showing decreasing susceptibility,

including the type of specimen, pathogen, and MIC values. Additional exploratory microbiological analyses may be conducted.

Health Surveyl Outcomes

At Screening and Final Follow-up visits, the subject will complete a SF-36v2® Health Survey (Medical Outcomes Trust, Optum™). The SF-36v2® Health Survey has 8 subscales: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue and general health perceptions. It also has a single item that provides an indication of perceived change in health. Physical and mental health composite scores (PCS and MCS) are computed and range from 0 (lowest level of health measured by the scales) to 100 (highest level of health).

The eight SF-36 subscales, PCS, and MCS will be derived in accordance with established norm-based standards for the survey using the software provided by the Medical Outcomes Trust, Optum™. Descriptive statistics for the eight subscales, PCS and MCS will be provided at Screening, the Final Follow-up Visit and the change from baseline by treatment group in the ITT Population.

The change from baseline for each of the eight subscale, PCS, and MCS scores will be analyzed using an analysis of covariance model with treatment group as a fixed effect and baseline scaled score as a covariate. Least-squares mean differences, corresponding 95% confidence intervals, and *P*-values were obtained using this model.

9.5 Interim Analysis

No interim analysis of efficacy is planned.

9.6 Subgroup Analyses

The primary analysis (ECR) results will be assessed separately across PORT Risk Class and use of prior antibiotics by treatment group for both the as randomized strata and the actual strata as indicated on the eCRF. For each PORT Risk Class stratum– and prior antibiotic stratum, a 2-sided 95% CI for the observed difference in the Early Clinical Success rates will be calculated for the ITT population.

Results of the assessment of Clinical Response at the PTE Visit (based on the investigator's assessment at the EOT and PTE Visits) will also be assessed across PORT Risk Class and use of prior antibiotics by treatment group for both the as randomized strata and the actual strata as indicated on the eCRF. Separately for each PORT Risk Class stratum and use of prior antibiotics stratum, 2-sided 95% CIs for the observed difference in clinical response in the ITT and CE-PTE populations will be calculated.

10 SAFETY AND TOLERABILITY

All safety analyses will be conducted in the Safety population. Subjects who receive the wrong test article for their entire course of treatment will be analyzed in the group based on the drug received. If a subject receives both omadacycline and moxifloxacin, the subject will be analyzed in the omadacycline arm regardless of the amount of omadacycline received or the randomized treatment assignment. Safety parameters include AEs, vital signs, electrocardiogram (ECG) parameters, and clinical laboratory parameters.

10.1 Adverse Events

Verbatim descriptions of AEs will be coded using MedDRA (Version to be delineated in the CSR). Summary tables will be provided for all treatment-emergent adverse events (TEAEs) but all AEs will be provided in a listing. A treatment-emergent AE is defined as any AE that newly appeared, increased in frequency, or worsened in severity on or after the initiation of active test article. An AE is considered treatment emergent if the AE start date and time is on or after the start date and time of the first infusion of active test article. If time of the AE is missing and it occurred on the same date as the first infusion of active test article, the AE will be defined as treatment emergent. If the start date of the AE is partial or missing and it cannot be determined if the AE occurred prior to or after the first dose of test article, the AE should be defined as treatment emergent.

An overall summary of AEs will include the number of subjects who experienced at least one AE of the following categories: any AE, any TEAE, any drug-related TEAE, any severe TEAE, any serious TEAE, any drug-related SAE, any serious TEAE leading to death, any TEAE leading to premature discontinuation of test article, any TEAE leading to premature discontinuation from the study, any TEAE leading to dose interruption of test article, and any serious TEAE leading to premature discontinuation of test article.

The number and percentage of subjects reporting a TEAE in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity (mild, moderate, and severe); and by system organ class, preferred term, and relationship (unrelated or related to test article). The incidence of TEAEs will be summarized by preferred term and treatment group, sorted by decreasing frequency in the omadacycline group, for all TEAEs, related TEAEs, serious TEAEs, and TEAEs leading to study drug discontinuation. The number and percentage of subjects reporting a TEAEs representing administration/infusion site reaction (based on the appropriate MedDRA higher level term) will be tabulated by treatment group, preferred term and severity (mild, moderate, and severe). The incidence of serious TEAEs, TEAEs leading to premature discontinuation of test article, and TEAEs leading to a dose interruption of test article will be summarized by system organ class and preferred term. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to test article.

TEAEs occurring (ie, with a start date and time) during the time period subjects are on treatment, and separately for the time period subjects are on iv and po test article will be summarized by system organ class and preferred term.

In addition, all AEs (including non-TEAEs), serious TEAEs, TEAEs leading to discontinuation of test article, and TEAEs leading to dose interruption of test article will be provided in listings by treatment group, study site, subject, verbatim term, MedDRA system organ class and preferred term, start and end date, seriousness flag, severity, relationship to test article, relationship to study protocol, action taken with test article, non-test article action taken and outcome.

10.2 Vital Signs

Blood pressure (systolic and diastolic), respiratory rate, temperature, and pulse/heart rate will be summarized using descriptive statistics at the following time points: Day 1 to Day 14,, ECR Visit, EOT Visit, PTE Visit, and highest and lowest post-baseline value. Heart rate and blood pressure will also be summarized for the following additional time points: 30 minutes before and approximately 1 hour after the completion of the infusions on Day 1 and Day 2. Descriptive statistics of the change from baseline to each post-baseline time point and the highest and lowest post-baseline value will also be provided. Baseline is defined as the value closest to but prior to the initiation of test article administration. If no value is available prior to the initiation of test article administration, a value within 2 hours after initiation of test article administration.

Post-baseline vital signs will be defined as clinically notable (CN) if they meet the criterion value or both the criterion value and the change from baseline criterion listed in Table 9. The incidence of CN vital signs will be summarized by time point and treatment group and will be listed and flagged in by-subject listings. The overall post-baseline incidence of CN values for each vital sign parameter, which includes values from unscheduled post-baseline visits, will also be summarized. A listing will also be provided of subjects with a CN vital sign and will list all values for a vital sign noted as CN.

Table 9. Criteria for Treatment Emergent Clinically Notable Vital Signs

Vital Sign Parameter	Flag	Criterion Value	Change from Baseline
Systolic Blood Pressure (mmHg)	High (CH)	≥ 180	Increase of ≥ 20 mmHg
	Low (CL)	≤ 90	Decrease of ≥ 20 mmHg
Diastolic Blood Pressure (mmHg)	High (CH)	≥ 105	Increase of ≥ 15 mmHg
	Low (CL)	≤ 50	Decrease of ≥ 15 mmHg
Heart Rate (bpm)	High (CH)	≥ 120	Increase of ≥ 15 bpm
	Low (CL)	≤ 50	Decrease of ≥ 15 bpm
Temperature (^{o}C)	Low (CL)	<36.0	NA
	High (CH)	>38.0	NA

10.3 Electrocardiogram

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QT corrected (QTc) interval at baseline and at the EOT Visit, and the change from baseline will be presented by treatment group. The QTc interval will be presented by both the Bazett ($QTcB = QT/(RR)^{1/2}$) and the Fridericia ($QTcF = QT/(RR)^{1/3}$)

corrections. The change from baseline to the minimum and maximum post-baseline values will also be summarized by treatment group. Baseline is defined as the value closest to but prior to the initiation of test article administration. If no value is available prior to the initiation of test article administration, a value within 2 hours after initiation of test article administration.

The number and percentage of subjects with any post-baseline increase in QTcF and any post-baseline increase of > 30 msec or > 60 msec in QTcF will be summarized by treatment group. The number and percentage of subjects with a baseline QTcF ≤ 450 msec and with a post-baseline QTcF of > 450 msec and with a baseline QTcF ≤ 500 and with a post-baseline QTcF of > 500 msec will also be summarized by treatment group. The number and percentage of subjects with a post-baseline increase in QTcF of > 30 msec resulting in a post-baseline QTcF of > 450 msec or > 500 msec will also be summarized by treatment group. Any post-baseline ECG includes unscheduled ECGs as well as the ECG completed at EOT. A listing will also be provided of subjects with a QTcF that meets one of the criteria listed above and will list all QTcF values for the subject.

The distribution of QTcF values (≤ 450 msec, > 450 - ≤ 480 msec, > 480 - ≤ 500 msec, and > 500 msec) at EOT and the distribution of change from baseline in QTcF values at EOT (0 or less [no increase], 1-29 msec, 30-60 msec, and > 60 msec) will be summarized by treatment group.

10.4 Laboratory Values

Summaries of laboratory data will include hematology, chemistry, and coagulation (INR only) parameters. Laboratory parameters will be presented in alphabetic order with the following exceptions: differentials of white blood cell (WBC) counts will be presented following the WBC results, and chemistry parameters will first be grouped by organ class (renal, liver, electrolytes, and other) and presented alphabetically within each of these classes, as shown below.

Table 10. Laboratory Parameters and Organ Class

Organ Class	Laboratory Parameter
Renal	Blood urea nitrogen (BUN)
Renal	Creatinine
Liver	Alkaline phosphatase (ALP)
Liver	Alanine aminotransferase (ALT)
Liver	Aspartate aminotransferase (AST)
Liver	Total bilirubin
Liver	Gamma-glutamyl transpeptidase (GGT)
Electrolytes	Calcium (Ca)
Electrolytes	Carbon dioxide (CO_2)
Electrolytes	Chloride (Cl)
Electrolytes	Magnesium (Mg)
Electrolytes	Phosphorus (P)
Electrolytes	Potassium (K)
Electrolytes	Sodium (Na)

Table 10. Laboratory Parameters and Organ Class

Organ Class	Laboratory Parameter
Other	Creatinine phosphokinase (CK)
Other	Lipase

Baseline is defined as the central lab value closest to and prior to the first dose of study drug. If no central lab value is available prior to the first dose of study drug, the local lab value that is closest to and prior to the first dose of study drug will be used as baseline. For by visit analyses, central lab values will be used unless no central lab value was obtained in the visit window. In this case, local lab values will be used for the by visit analyses. All lab values (central and local) are used for determination of the overall worst post-baseline value.

Several analyses of the laboratory data will be presented. Descriptive statistics (based on International System units) for chemistry, hematology and coagulation values, and the change from baseline will be summarized by treatment group at each time point (ECR Visit, EOT Visit and PTE Visit), and for the overall worst value post-baseline (which includes unscheduled visits). Appendix 4 provides the directionality of the worst values for each laboratory parameter.

Clinically notable laboratory values will be determined based on the modified Division of Microbiology and Infectious Diseases (DMID) criteria in Appendix 5. Shift tables will be presented to show the number of subjects with a laboratory value with a grade of 0, 1, 2, 3 or 4 at baseline versus the value at each visit and the worst post-baseline value. Number and percentage of subjects with at least a 2-grade increase from baseline (based on DMID criteria) will be summarized by treatment arm. Percentages for each laboratory test will be based on the number of subjects with a baseline and post-baseline evaluation of the specific laboratory test. A listing will be provided which gives all laboratory results for a given laboratory test for subjects who have at least one 2-grade increase from baseline.

The number and percentage (based on the number of subjects with a normal level at baseline) of subjects in each treatment group with an elevated transaminase level (> 3 × upper limit of normal [ULN], > 5×ULN, and > 10 × ULN), an elevated bilirubin level (> 1.5 × ULN and > 2 × ULN) will be presented by study visit. A listing of subjects who meet the laboratory criteria for Hy's law at the same visit will also be provided. The laboratory criteria for Hy's law is defined as 1) ALT or AST> 3 × ULN, ALP ≤ 2.0 × ULN, and total bilirubin > 1.5 ULN and 2) ALT or AST> 3 × ULN, ALP ≤ 2.0 × ULN, and total bilirubin > 2 × ULN.

Detailed subject listings of all laboratory data collected during the study (local and central laboratory data) will be provided, including calculated creatinine clearance (using the Cockcroft-Gault equation). Laboratory values outside normal limits will be identified in the subject data listings with flags for low (L) and high (H) as will laboratory values that meet the clinically notable thresholds (CN).

10.5 Physical Examinations

Subject listings of all physical examination results by body system will be provided. Physical examination results will be coded using MedDRA (Version to be delineated in the CSR) . Any changes from baseline will be recorded as AEs.

11 RESOURCE UTILIZATION ANALYSES

Descriptive statistics of the following resource utilization parameters will be provided by treatment group:

- Number of days in the hospital from the time of initiation of test article until discharge. Subjects who are not admitted to the hospital will be assigned a value of 0 for number of days in the hospital. Analyses will also be completed by country due to varying clinical practices per country.
- Number of days in the hospital from the time of initiation of rescue antibiotic (ie, a second antibiotic) therapy until discharge. Analyses will be completed only for those subjects admitted to the hospital and who required a second antibiotic therapy (ie, were treatment failures) and separately for all subjects. For the latter, subjects who are not admitted to the hospital or who did not require a second antibiotic therapy will be assigned a value of 0 for number of days in the hospital. Analyses will also be completed by country.
- Number of days in the hospital from the time of admission for CABP until discharge. Subjects who are not admitted to the hospital will be assigned a value of 0 for number of days in the hospital. Analyses will also be completed by country.
- Number of hospital re-admissions after discharge from the hospital for the CABP admission through the Final Follow-up Visit will be summarized.
- Number of emergency room/department and physician visits after discharge from the hospital for the CABP admission through the Final Follow-up Visit will be summarized.

12 OTHER RELEVANT DATA ANALYSES/SUMMARIES

12.1 Protocol Deviations

A listing of all protocol deviations will be provided. Deviations will also be reviewed by the Sponsor and categorized into general categories such as: randomization, at least one inclusion criterion not met, at least one exclusion criteria met, study procedures/visits not done, study visit outside window, noncompliance with dose, and use of prohibited medications or treatments, consent-Institutional Review Board compliance issues, etc. The Sponsor will also categorize the protocol deviations as major and minor. Review of protocol deviations will be conducted and finalized prior to unblinding the database. The number of subjects with at least one protocol deviation, the number of subjects with a minor protocol deviation, the number of subjects with a major protocol deviation, and the number of subjects with at least one major deviation in each category will be presented by treatment group for the ITT population. A major deviation is defined as one that potentially affects the efficacy and/or safety analyses.

12.2 Prior and Concomitant Medications

All medications taken within 7 days prior to the date of informed consent through the Final Follow-up Visit will be recorded on the eCRF. Prior medications will be summarized by WHODRUG (Version to be delineated in the CSR) Anatomical Therapeutic Chemical Classification (ATC) level 3 (third level indicates the therapeutic/pharmacologic subgroup) and generic medication name. Medications are considered prior if taken prior to the first infusion of test article or if their start date is unknown. Subjects will be counted only once for an ATC class and generic medication name. Concomitant medications taken during and after the study treatment period will be similarly summarized. Medications are considered concomitant if taken on or after the first infusion of test article, or if their stop date is unknown or marked as continuing.

The number and percentage of subjects who receive the following prior and concomitant medications will be summarized by treatment group:

- Systemic antibacterial medications taken within 72 hours prior to first infusion of test article and the reasons for receipt (ITT and CE-PTE populations)
- Systemic antibacterial medications (excluding test article) taken between first infusion of test article and the EOT Visit (CE-EOT population) and the reasons for receipt
- Systemic antibacterial medications (excluding test article) taken between first infusion of test article and the PTE Visit (CE-PTE population) and the reasons for receipt
- Non-antibacterial medications taken prior to informed consent through the first infusion of test article (ITT and Safety populations)
- Non-antibacterial medications taken from the first infusion of test article through the Final Follow-up Visit (ITT and Safety populations)

13 REFERENCES

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14 APPENDICES

Appendix 1 Schedule of Assessments and Procedures

Study Phase	**Screening[b]**	**iv Treatment**		**iv or po Treatment**											**EOT and Follow-up**		
Study Day[a]	-1	1	2	3	4 inpatient only	5	6 inpatient only	7 [d]	8	9	10	11	12	13	EOT[e]	PTE	FFU[f]
									inpatient only			inpatient only					
					← ECR visit must occur 72 to 120 hours after first dose [c] →				Perform only if study treatment is continuing and this is not the EOT visit. Treatment past 10 days is allowed for subjects with bacteremia at Screening.							5 to 10 days after last day of therapy	30 to 37 days after Day 1
Screening and eligibility procedures																	
Signed informed consent[g]	X																
Medical history, current medical conditions, demography	X																
Assessment of CABP symptom severity[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chest X-ray or CT scan[i]	X																
PORT risk class, ABG (or pulse oximetry)[j]	X																
Blood and urine samples for local lab hematology/chemistry/pregnancy[k]	X																
SF-36v2® Health Survey	X																X
Review of Inclusion/Exclusion criteria	X																
Randomization (if Eligible)		X															
Clinical Procedures and Test Article Administration																	
Test article administration and accountability[l]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Physical examination[m]	X		X	X	X	X	X	X			X				X		
Vital signs[n]	X	X[o]	X[o]	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[w]	X														X		
Blood for central lab tests: hematology/chemistry/pregnancy	X[p]					X									X[p]	X[p]	
AEs, SAEs, and mortality[q]	X	X X															
Prior & concomitant medications[r]	X	X X															
Plasma samples (in heparin) for PK analyses[s]		X				X											

Study Phase	**Screening[b]**	**iv Treatment**		**iv or po Treatment**											**EOT and Follow-up**		
Study Day[a]	-1	1	2	3	4 inpatient only	5	6 inpatient only	7 [d]	8	9	10	11	12	13	EOT[e]	PTE	FFU[f]
									npatient only			inpatient only					
Assessment for po switch or need for continued therapy[t]				X ---------- X													
Investigator's Assessment of Clinical Response															X	X	X
Assessment of Resource Utilization		X ---------- X															
Microbiological Procedures																	
Blood culture[u]	X	As Clinically Indicated															
Respiratory culture & Gram stain[v]	X														X	X	
Urine for Local lab *Legionella pneumophila* and *Streptococcus pneumoniae* antigen test	X																
Blood for Central lab *Legionella pneumophila*, *Mycoplasma pneumoniae* & *Chlamydophila pneumoniae* serology	X															X	

ABG = arterial blood gas, AE = adverse event, BP = blood pressure, β-hCG = beta-human Chorionic Gonadotropin, CABP = community-acquired bacterial pneumonia, CT = computed tomography, CXR = chest X-ray, ECG = electrocardiogram, ECR = Early Clinical Response, eCRF = electronic case report form, EOT = end of treatment, FFU = final follow-up, ICF = informed consent form, iv = intravenous, IxRS = interactive voice/web response system, PK = pharmacokinetics, po = per oral, PORT = Pneumonia Patient Outcomes Research Team, PTE = post-therapy evaluation, RR = respiratory rate, SAE = serious adverse event.

[a] Study Day 1 is the first day of test article administration. Subsequent study days may be consecutive calendar days.

[b] Following the signing of an ICF, all Screening evaluations (except radiographic confirmation of pneumonia), should be completed within the 24 hours prior to randomization. The radiographic confirmation of pneumonia should be completed within the 48 hours prior to the first dose of test article.

[c] The ECR visit must be conducted within 72 to 120 hours after the first dose of test article; the study day for this visit could be on Days 4, 5, or 6, depending on the time of the first dose of test article. Subjects who remain hospitalized (inpatients) during study treatment will have daily assessments. For subjects who are not hospitalized, only 1 visit is required between Study Days 4 to 6.

[d] If the investigator determines that no additional treatment is required beyond Day 7, the Day 7 visit can be considered the EOT visit and a separate EOT visit is not required.

[e] To be conducted on the day of, or within 2 days following the last dose of test article. Should also be conducted for any prematurely withdrawn subject on the day of, or within 2 days following the last dose of test article.

[f] The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be Clinical Successes and had no ongoing AEs, clinically significant laboratory findings or ECG abnormalities noted at or after the PTE visit. Otherwise, the visit must be conducted in person.

[g] Written and signed ICF must be obtained before any study assessment is performed.
[h] The investigator should assess the severity of the subject's CABP symptoms of cough, sputum production, pleuritic chest pain, and dyspnea based upon the Community-Acquired Bacterial Pneumonia Subject Symptom Severity Guidance Framework for Investigator Assessment (Appendix 3 of the protocol).
[i] Subjects must have a confirming CXR or CT scan consistent with acute bacterial pneumonia within the 48 hours prior to the first dose of test article.
[j] Only subjects with a PORT Risk Class of III or IV are eligible for enrollment.
[k] Local laboratory hematology and chemistry evaluations required for assessing subject eligibility, including (at minimum): white blood cell count, serum transaminases and bilirubin levels, and serum or urine pregnancy test (for women only).
[l] Subjects should receive their first dose of test article within 4 hours after randomization. The total duration of test article therapy (iv plus po) for all subjects will be 7-10 days (up to 14 days for subjects with bacteremia identified at Screening). The pharmacist or designee will be unblinded to prepare appropriate iv doses of the IxRS identified test article. An unblinded field monitor will perform drug accountability and review the pharmacist's records. Oral test article may be dispensed and reconciled by blinded or unblinded personnel. All oral doses should be taken in a fasted state (no food, antacids or multivitamins containing multivalent cations [eg, aluminum, magnesium, calcium, bismuth, iron, or zinc] or drink except water for at least 4 hours before dosing). After dosing, no food is permitted for 2 hours as well as no dairy products, antacids, or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours. Subjects discharged with po test article will be asked to return all unused test article and packaging at each visit.At the EOT visit subjects discharged with po test article will return any remaining unused po test article and site staff will perform accountability.
[m] A full physical examination will be completed at Screening. Thereafter, abbreviated physical examinations may be performed at the indicated timepoints. Additional physical examinations may be performed as clinically indicated.
[n] Vital signs include body temperature, BP, pulse oximetry, heart rate, and RR.
[o] Blood pressure and heart rate should be measured within 30 minutes before, and approximately 1 hour (± 15 minutes) after the completion of the infusions on Day 1 and Day 2.
[p] Blood will be collected from all female subjects for a serum β-hCG pregnancy test at the Central Laboratory at the Screening, EOT and PTE visits.
[q] AEs and SAEs will be recorded from the time of signing of the ICF to the Final Follow-up assessment.
[r] Medications administered within the 7 days prior to the date of signing the ICF or during the Screening phase will be recorded in the eCRF, as will all medications and significant non-drug therapies administered after the first dose of test article.
[s] PK sample collection to occur on Day 1 (2 to 3 hours after the start of Dose 1) and at the ECR visit (Days 4 to 6; at any time during the visit).
[t] At any time after the second day of iv treatment (Day 2), the subject may be switched to po medication based upon determination of clinical stability. Refer to Section 7.6.5 of the protocol for required criteria to switch to po treatment. The first po dose should be administered in the morning, 12-24 hours after the last iv dose. Test article administration and total duration of study treatment are outlined in footnote l.
[u] If bacteria are isolated from baseline blood cultures, repeat blood cultures must be collected on the day that the positive blood culture is detected. If subsequent blood cultures are also positive, repeat the blood cultures as necessary until negative blood cultures are obtained.
[v] Culture and Gram stain from an adequate quality sputum specimen or other respiratory specimen. At the EOT and/or PTE visit, respiratory specimen cultures and Gram stains should be obtained only for subjects who are Clinical Failures and require alternative antibacterial treatment for CABP.
[w] Additional ECGs can be performed as clinically indicated, at the discretion of the investigator.

Appendix 2 Summary of Efficacy Analyses

	72 to 120 hours post first dose	End of Therapy Visit (EOT)	Post Treatment Evaluation Visit (PTE)
ITT	ECR	IA	IA
MicroITT	ECR ECR (by pathogen) ECR (by pathogen and MIC)	Micro (by subject) Micro (by pathogen)	IA IA (by pathogen) IA (by pathogen and MIC) Micro (by subject) Micro (by pathogen)
CE-EOT		IA	
CE-PTE			IA
ME-EOT		Micro (by subject) Micro (by pathogen)	
ME-PTE			IA IA (by pathogen) IA (by pathogen and MIC) Micro (by subject) Micro (by pathogen)

Appendix 3 Adverse Event and Prior/Concomitant Medication Date Imputations

Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.
In all cases, if it cannot be determined if the adverse event occurred prior to or after the first dose of test article, the adverse event should be defined as treatment emergent.

Prior and Concomitant Medication Start Date Imputation

Parameter	Type of Medication	Imputation
Start date for con meds	Non-Antibacterial	If it cannot be determined whether or not the start date of a medication (non-antibacterial) is prior to the first dose of study drug, it will be assumed that the medication was received prior to the first dose of study drug.
	Antibacterial	Missing start dates for antibacterials will be queried for a value. If it cannot be determined whether or not the start date of an antibacterial is prior to the first dose of study drug, it will be assumed that the medication was received prior to the first dose of study drug unless the indication notes that the medication was received after the first dose of study drug.
Stop date for con meds	Non-Antibacterial	If it cannot be determined whether or not the stop date of a medication (^{nonantibacterial}) is after the first dose of study drug, it will be assumed that the medication was received after the first dose of study drug
	Antibacterial	Missing stop dates for antibacterials will be queried for a value. If it cannot be determined whether or not the stop date of an antibacterial is after the first dose of study drug, it will be assumed that the medication was received after the first dose of study drug unless the indication notes that the medication was received prior to the first dose of study drug. If it cannot be determined whether the antibacterial was received prior to the assessment of Early Clinical Response, the EOT and/or the PTE Visit, the antibacterial will be assumed to have been received through the PTE Visit.

Appendix 4 Directionality of Worst Laboratory Parameters

Laboratory Test	Parameter	Worst Value
Hematology	Hematocrit	Lowest value
	Red blood cell count	Lowest value
	Mean corpuscular hemoglobin	Lowest value
	Mean corpuscular hemoglobin concentration	Lowest value
	Hemoglobin	Lowest value
	Mean corpuscular volume	Lowest value
	White blood cell count	Lowest value
	Platelets	Lowest value
	Eosinophils/Differential	Highest Value
	Neutrophils	Lowest Value
Chemistry		
	Alkaline phosphatase (ALP)	Highest value
	Alanine aminotransferase (ALT)	Highest value
	Aspartate aminotransferase (AST)	Highest value
	Bicarbonate	Lowest value
	Blood glucose	Both highest value and lowest value
	Blood urea nitrogen	Highest value
	Calcium	Both highest value and lowest value
	Chloride	Both highest value and lowest value
	Creatinine	Highest value
	Creatine phosphokinase (CK)	Highest value
	Gamma-glutamyl transpeptidase (GGT)	Highest value
	Lipase	Highest value
	Magnesium	Both highest value and lowest value
	Phosphorus	Both highest value and lowest value
	Potassium	Both highest value and lowest value
	Sodium	Both highest value and lowest value
	Total bilirubin	Highest value
Coagulation	Prothrombin time international normalized ratio (INR)	Highest value

Appendix 5 Modified Division of Microbiology and Infectious Diseases Adult Toxicity Table

The DMID Adult Toxicity Table (21-NOV-2007) was modified to exclude the clinical component of the toxicity grading because clinical signs and symptoms related to abnormal laboratory values are not collected in this study. In addition, Grade 0 was added to the table so that shifts from normal could be analyzed. Grades for enzymes were modified as indicated in the table below.

For toxicity grades based on a multiple of the ULN, the normal range from the central laboratory will be applied.

For toxicity grades based on fixed values, the grades will be assigned regardless of the normal actual range values from the central laboratory. For example, a hemoglobin value of 10.0 gm/dL will be assigned a grade of 1 toxicity, even if the lower limit of normal from the laboratory was 9.8 gm/dL.

HEMATOLOGY					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin (gm/dL)	> 10.5	9.5-10.5	8.0-9.4	6.5-7.9	< 6.5
Absolute Neutrophil Count (count/mm^3)	> 1500	1000-1500	750-999	500-749	< 500
Platelets (count/mm^3)	≥ 100,000	75,000-99,999	50,000-74,999	20,000-49,999	< 20,000
WBCs (count/mm^3)	1000-10,999	11,000-12,999	13,000-14,999	15,000-30,000	> 30,000 or < 1,000

CHEMISTRY

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia (mEq/L)	> 135	130-135	123-129	116-122	< 116
Hypernatremia (mEq/L)	< 146	146-150	151-157	158-165	> 165
Hypokalemia (mEq/L)	> 3.4	3.0-3.4	2.5-2.9	2.0-2.4	< 2.0
Hyperkalemia (mEq/L)	< 5.6	5.6-6.0	6.1-6.5	6.6-7.0	> 7.0
Hypoglycemia (mg/dL)	≥ 65	55-64	40-54	30-39	< 30
Hyperglycemia (mg/dL) (nonfasting and regardless of prior history of diabetes)*	< 116	116-160	161-250	251-500	> 500
Hypocalcemia (mg/dL) (corrected for albumin)	> 8.4	8.4-7.8	7.7-7.0	6.9-6.1	< 6.1
Hypercalcemia (mg/dL) (correct for albumin)	≤ 10.5	10.6-11.5	11.6-12.5	12.6-13.5	> 13.5
Hypomagnesemia (mEq/L)	> 1.4	1.4- 1.2	1.1-0.9	0.8-0.6	< 0.6
Hypophosphatemia (mg/dL)	≥ 2.5	2.0-2.4	1.5-1.9	1.0-1.4	< 1.0
Hyperbilirubinemia (total bilirubin)	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.5×ULN	> 2.5-5×ULN	> 5×ULN
Urea	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Hyperuricemia (uric acid) (mg/dL)	< 7.5	7.5–10.0	10.1–12.0	12.1–15.0	> 15.0
Creatinine	< 1.1×ULN	1.1-1.5×ULN	> 1.5-3.0×ULN	> 3.0-6×ULN	> 6×ULN

*The DMID toxicity table reports hyperglycemia detected in nonfasting specimens obtained from subjects with no prior diabetes.

ENZYMES

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
ALT (SGPT)	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
GGT	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Alkaline Phosphatase	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Amylase	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.0×ULN	> 2.0-5.0×ULN	> 5.0×ULN
Lipase	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.0×ULN	> 2.0-5.0×ULN	> 5.0×ULN

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