16.1.1 Protocol and Amendments

Version 5.0 (Dated 19-NOV-2020)

Clinical Trial Protocol: 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
Product Name:	Omadacycline (PTK 0796)
IND Number:	75,928 73,431
Indication:	Community Acquired Bacterial Pneumonia
Investigators:	Multicenter
Sponsor:	Paratek Pharmaceuticals, Inc. 75 Park Plaza, 4th Floor Boston, MA 02116 1000 First Ave Suite 200 King of Prussia, PA 19406
Sponsor Contact:	Tel: +1 617-275-0040
Global Medical Monitor	[redacted] MD

Original Protocol Version 5: 19-November-2020

Confidentiality Statement

The study was in accordance with the International Council on Harmonisation Harmonised Tripartite Guidelines for Good Clinical Practice.

SYNOPSIS

Sponsor:
Paratek Pharmaceuticals, Inc.

Name of Finished Product:
Omadacycline for injection, 100 mg lyophilized vial drug product
Omadacycline oral tablet, 150 mg

Name of Active Ingredient:
Omadacycline

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

Study Rationale:
Omadacycline is an aminomethylcycline in the tetracycline class of antibiotics. NUZYRA™ (omadacycline) is available for both intravenous (iv) and oral (po) administration and has been approved by the United States (US) Food and Drug Administration (FDA) for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms.

Omadacycline is active in vitro against the most common CABP pathogens, including isolates resistant to currently marketed antibiotics. This study is intended to evaluate the safety and efficacy of iv and po omadacycline as compared to iv and po moxifloxacin in the treatment of adults with pneumonia patient outcomes research team (PORT) Risk Class III and IV CABP.

Primary Objective:

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.

Secondary Objectives:

- To evaluate the safety of omadacycline in the treatment of adult subjects with CABP in the Safety population.
- To evaluate the Clinical Response according to the identified causative pathogen.
- To evaluate the pharmacokinetics (PK) of omadacycline in adult subjects with CABP.

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.

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 (PaO2) ≥ 60 mm Hg by arterial blood gas (ABG)
- Normal (“absence of confusion”) or return to baseline mental status
- Ability to maintain po intake.

Subjects may receive iv treatment in certain outpatient centers in circumstances where the principal site investigator has identified that sufficient resources are available to complete all study procedures as defined in the protocol and the sponsor or sponsor’s designee has reviewed and approved the process for outpatient iv test article administration.

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 100mg 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.

Refer to Appendix 1 for the summary of subject visits and assessments through end of treatment (EOT).

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 had an outcome of Clinical Success in the opinion of the investigator at 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.

Rationale for Omadacycline Dose Regimen Selection:

The dosing regimen of omadacycline selected for this study is based on the nonclinical and clinical experience to date, including in-vitro antibacterial activity, PK characteristics, clinical efficacy in prior studies, the overall safety and tolerability profile, and the FDA approved dosing regimen for CABP.

Either a regimen of 200 mg iv omadacycline once or 100 mg iv omadacycline q12h on Day 1 followed by 100 mg iv omadacycline administered once daily OR 300 mg po omadacycline once daily has been approved by US FDA for the treatment of adult patients with CABP caused by susceptible microorganisms. The FDA-approved treatment duration for omadacycline is 7 to 14 days total.

The duration for the iv to po regimen in this study will be 7 to 10 days with up to 14 days allowed for subjects with bacteremia identified at the Screening visit. This dosing regimen is supported by the efficacy observed in the previously completed CABP Phase 3 study, PTK0796-CABP-1200, where by Day 7 of treatment, > 80% of patients in the omadacycline treatment group had symptom improvement (as defined by the Early Clinical Response [ECR] endpoint) and had reached clinical stability.

Approximate Number of Subjects/Sites:

Approximately 670 subjects will be enrolled at approximately 75 sites globally.

Approximate Duration of the Study:

The study is expected to be complete in approximately 24 months.

Main Criteria for Inclusion:

1. Written and signed informed consent must be obtained before any protocol specific assessment is performed.
2. Male or female, aged 18 years or older.
3. Has at least 3 of the following symptoms:
   - Cough
   - Production of purulent sputum
   - Dyspnea (shortness of breath)
   - Pleuritic chest pain
4. Has at least TWO of the following abnormal vital signs:
   - Fever or hypothermia documented by the investigator (temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
   - Hypotension with SBP < 90 mm Hg
   - Heart rate > 90 beats per minute (bpm)
   - RR > 20 breaths/minute
5. Has at least 1 clinical sign or laboratory finding associated with CABP:
   - Hypoxemia (PaO_2 < 60 mm Hg by ABG or oxygen saturation < 90% by pulse oximetry)
   - Physical examination findings of pulmonary consolidation (eg, dullness on percussion, bronchial breath sounds, or egophony)
   - 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)
6. Has disease categorized as being PORT Risk Class III or IV at Screening (see PORT Risk Class calculation in Appendix 5).
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.
8. Is expected to require a minimum of at least 2 days of iv therapy for the initial treatment of CABP.
9. Females must have a negative pregnancy test at Screening and agree to comply with using an acceptable method of birth control as per your local requirements (eg, abstinence, po contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation,

hysterectomy, bilateral oophorectomy, postmenopausal or vasectomized partner) from Screening through PTE. Males must agree to use an acceptable method of birth control with female partner(s) and must not donate sperm from Screening through PTE.

Main Criteria for Exclusion:

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 list in Appendix 4).
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).
3. Suspected or confirmed empyema (a parapneumonic pleural effusion is not an exclusion criteria) or lung abscess.
4. Confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection based on local standard-of-care assessments available during Screening.
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).
6. Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia) within the 3 months prior to Screening or presents with a tachyarrhythmia (excluding sinus tachycardia).
7. Has a QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec (males) or > 470 msec (females), are known to have long QT syndrome, use drugs of potential proarrhythmic or QT prolonging effect.
8. Has other contraindications to receiving a systemic fluoroquinolone antibiotic, including confirmed or suspected peripheral neuropathy, tendon disorder, myasthenia gravis, cirrhosis, aortic aneurysm, or central nervous system (CNS) disorder that may predispose to seizures or lower the seizure threshold.
9. History or evidence of severe renal disease or has a calculated creatinine clearance (CrCl) of < 30 mL/minute, using the Cockcroft-Gault equation (Appendix 2). Requires any form of dialysis (eg, hemodialysis, peritoneal dialysis).
10. Significant immunological disease determined by any of the following:
    - Current or anticipated neutropenia defined as < 500 neutrophils/mm^3

- Known infection with Human Immunodeficiency Virus (HIV) and a cluster of differentiation 4 (CD4) count that is unknown or documented to be < 200 cells/mm^3 within the last year, or an Acquired Immune Deficiency Syndrome (AIDS)-defining illness

11. The receipt of cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs (eg, cyclosporine, azathioprine, tacrolimus, immune- modulating monoclonal antibody therapy, etc) within the past 3 months, or the receipt of corticosteroids equivalent to or greater than 40 mg of prednisone per day or for more than 14 days in the prior 30 days (Appendix 2). Exception: Systemic corticosteroids administered within 24 hours of randomization or any time after randomization as adjunctive therapy for the current episode of CABP (at any dosage) is allowed.
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)
13. PORT Risk Class I, II, and V patients.
14. Requires or expected to require Intensive Care Unit (ICU) admittance or invasive or non-invasive ventilation.
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).
16. Pregnant or nursing (breastfeeding) women.
17. Has a history of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline),to any fluoroquinolone or any of the components of the investigational product or comparator.
18. Has a history of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
19. Has a history of systemic lupus erythematosus or lupus-like syndrome.
20. History of lactose intolerance, lactase deficiency, or glucose-galactose malabsorption.
21. Has current evidence of pancreatitis.
22. Use of other investigational drugs within 5 half-lives or 30 days prior to Screening, whichever is longer.
23. Has previously been treated with omadacycline or previously enrolled in this study.

24. Any planned medical intervention that might interfere with the ability to comply with the study requirements.
25. Has a life expectancy of less than or equal to 3 months or any concomitant condition that, in the opinion of the investigator, is likely to interfere with evaluation of the response of the infection under study, determination of AEs, or completion of the expected course of treatment.

Test Article; Dose; and Mode of Administration:

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.

Duration of Treatment:

The total duration of therapy will be for a minimum of 7 and up to 10 days, with a total duration of up to 14 days for subjects with bacteremia identified at Screening.

Pharmacokinetic Assessments

Blood Collection (plasma):

Blood samples will be collected and analyzed for omadacycline concentration at the following times:

- Day 1, 2 to 3 hours after the start of infusion 1, regardless of once a day (QD) or twice a day (BID) dosing
- ECR visit (Days 4 to 6), date and time of collection must be recorded in the eCRF

Safety Assessments:

- Physical examinations;
- Vital signs (body temperature, BP, pulse rate, respiratory rate, pulse oximetry);
- Laboratory tests (Hematology, serum chemistry, prothrombin time, urinalysis, SARS-CoV-2);
- 12-lead ECGs;
- AEs, serious adverse events (SAEs), and mortality;

- Pregnancy assessments.

Efficacy Assessments:

- In order to satisfy different health authority requirements, the primary variables assessing efficacy will be tested with 2 response endpoints:
  - ECR Success (72 to 120 hours after first dose) will be determined programmatically and defined as survival with improvement in at least 2 of 4 subject symptoms (cough, sputum production, pleuritic chest pain, dyspnea), as assessed by the investigator, without deterioration in any of these 4 symptoms.
  - Investigator's Assessment of Clinical Success at the PTE visit, defined as survival after completion of a test article regimen, with resolution of signs and symptoms of the infection to the extent that further antibacterial therapy is not necessary.
- Assessment of signs and symptoms of CABP by the investigator.
- Microbiological assessment of the infection.
- Patient reported outcome assessment.
- Clinical stability.

Resource Utilization:

- Hospital discharge.
- Hospital re-admission.
- Duration (days) and number of doses on iv therapy (test article)
- Duration (days) and number of outpatient iv doses (test article)
- Duration (days) and number of doses on po therapy (test article)
- ER/ED and Physician visits.

Statistical Methods:

The following subject populations have been defined for the various analyses of efficacy and safety:

- The intent-to-treat (ITT) population will consist of all randomized subjects.
- The microbiological intent-to-treat (micro-ITT) population will consist of subjects in the ITT population who have at least 1 causative pathogen identified at Screening from culture of a respiratory specimen (eg, respiratory fluid obtained by bronchoalveolar lavage or bronchoscopy; pleural fluid obtained by thoracentesis; or expectorated or induced sputum meeting adequacy criteria), culture of blood, or from a culture-independent method (eg, positive urinary antigen test for *Streptococcus pneumoniae* or *Legionella pneumophila*, or positive serology for *L. pneumophila*, *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae*).

- The clinically evaluable (CE) population will consist of all ITT subjects who received test article, have a qualifying CABP, an assessment of outcome, and meet all other evaluability criteria detailed in the Statistical Analysis Plan (SAP).
- The microbiologically evaluable (ME) population will include subjects in the CE population who have at least 1 causative pathogen identified at Screening.
- The Safety population will consist of all randomized subjects who receive test article.

A 2-sided 95% confidence interval (CI) approach for the difference in the rate of ECR success in the ITT population (primary analysis for the US FDA) will be used to test for non-inferiority (NI) of the omadacycline arm compared to the moxifloxacin arm. For the primary analysis for the European Medicines Agency (EMA), 95% CIs for the difference in the rate of clinical success at PTE in the ITT and CE populations will be used to test for the NI of the omadacycline arm compared to the moxifloxacin arm.

Safety will be assessed through the use of summary statistics and clinical review of reported AEs/SAEs, changes in vital signs, ECGs, and laboratory results obtained from blood samples taken during the study.

Data Monitoring Committee (DMC):

A DMC (independent of the sponsor) will provide ongoing monitoring of safety data. Data will be provided to the DMC as treatment A and treatment B.

Rationale for Number of Subjects:

This study is designed to have sufficient power for the primary efficacy analyses in for both the FDA and EMA regulatory authorities. 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 about 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 80% 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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABG	arterial blood gas
AE	adverse event
AIDS	acquired immune deficiency syndrome
ACM	all-cause mortality
β-hCG	serum β-human chorionic gonadotropin
BID	twice a day dosing
BP	blood pressure
bpm	beats per minute
CABP	community-acquired bacterial pneumonia
CD4	cluster of differentiation 4
CE	clinically evaluable
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CT	computed tomography
CXR	chest X-ray
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
ECR	Early Clinical Response
eCRF	electronic case report form
ED	emergency department
EMA	European Medicines Agency
EOT	end of treatment
ER	emergency room
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	good clinical practice
GCS	Glasgow Coma Scale
HIV	human immunodeficiency virus

ICF	informed consent form
ICH	International Council on Harmonisation
ICU	Intensive Care Unit
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
iv	intravenous
IxRS	interactive voice/web response system
LPF	low power field
MAP	mean arterial pressure
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
micro-ITT	microbiological intent-to-treat
NI	non-inferiority
OTC	over-the-counter
PaO2	partial pressure of arterial oxygen
PI	principal investigator
PK	pharmacokinetics
po	per oral
PORT	pneumonia patient outcomes research team
PT	preferred term
PTE	post-therapy evaluation
q24h	every 24 hours
q12h	every 12 hours
QD	once a day dosing
qSOFA	quick Sequential Organ Failure Assessment
QTc	corrected QT interval
QTcB	QTc Bazzett's Correction Formula
QTcF	QTc Fridericia's Correction Formula
REB	research ethics board
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software

SBP	systolic blood pressure
SOC	system organ class
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
US	United States
USP	United States Pharmacopeia
USPI	United States Prescribing Information
WBC	white blood cell (count)

1 DISCLOSURE STATEMENT

1.1 Restricted Distribution of Documents

This document contains information that is confidential and proprietary to the sponsor. This information is being provided to you solely for the purpose of evaluating and/or conducting a clinical study for the sponsor. You may disclose the contents of this document only to study personnel under your supervision, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs)/Research Ethics Boards (REBs), or duly authorized representatives of regulatory agencies for this purpose under the condition that they maintain confidentiality.

The contents of this document may not be used in any other clinical study, disclosed to any other person or entity, and/or published without the prior written permission of the sponsor. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to the sponsor of any such disclosure. All other nonpublic information provided by the sponsor and any information that may be added to this document also is confidential and proprietary to the sponsor and must be kept in confidence in the same manner as the contents of this document.

2 CONTACTS

2.1 Emergency Contacts

Name/Title:	[redacted] MD Medical Monitor
Phone (during business hours): Phone (after business hours): E-mail (not for emergencies): mailto:Address:	[redacted]
Name/Title:	[redacted] MD Vice President, Medical and Scientific Strategy
Phone (during business hours): Phone (after business hours): E-mail (not for emergencies): Address:	[redacted] 1000 First Avenue, Suite 200 King of Prussia, PA 19406

2.2 Additional Contacts

SAE contact information E-Mail:	[redacted]

3 INTRODUCTION

3.1 Community-acquired Bacterial Pneumonia

Community-Acquired Bacterial Pneumonia (CABP) is a leading cause of morbidity and mortality in the United States (US) and throughout the world.[1] Four to 6 million cases of CABP occur per year in the US, resulting in 10 million physician visits, 600,000 hospitalizations, and tens of thousands of deaths. The total cost of CABP to the annual US health care budget exceeds $10 billion (in 2007-adjusted dollars).[2] Furthermore, there is increasing resistance to antibiotics among common pathogens, with a resulting critical need for new antibiotics.[3] Bacterial resistance to the most frequently prescribed, currently available antibiotics has limited their potential to treat infections, which prevents their use as a first-line empiric monotherapy. Methicillin-resistant *Staphylococcus aureus* and multi-drug resistant *Streptococcus pneumoniae* in the community have posed treatment challenges because of resistance to penicillins (resistance rate 100% for both), cephalosporins (100% and 11%, respectively, for ceftriaxone), macrolides (83% and 86%, respectively, for azithromycin/erythromycin), and quinolones (73% and 2%, respectively, for levofloxacin), in CABP. In addition, the growing concern about, “collateral damage” associated with use of quinolone and beta-lactam class antibiotics further underscores the need for new antibiotic treatment options for CABP.[4] Failure of therapy due to resistance will continue to contribute to the morbidity and mortality of CABP and treatment failures of mild disease will result in increased hospitalizations and contribute to increased healthcare costs.

3.2 Omadacycline

The investigational product, omadacycline (formerly named PTK 0796), is the first member of the aminomethylcycline class of antibiotics, which are semisynthetic derivatives of the tetracycline class. As a class, the tetracyclines have been in use for approximately 70 years. They are well-tolerated and have proven effective in the treatment of a variety of bacterial infections. NUZYRA™ (omadacycline) has been approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with CABP caused by susceptible microorganisms.

Omadacycline has demonstrated activity against the most common CABP pathogens, including isolates resistant to older antibiotics. This study is intended to evaluate the safety and efficacy of intravenous (iv) and oral (po) omadacycline as compared to iv and po moxifloxacin in the treatment of pneumonia patient outcomes research team (PORT) Risk Class III and IV adults with CABP.

Please refer to the current version of the Investigator's Brochure or the NUZYRA™ (omadacycline) United States Prescribing Information (USPI) for additional information on omadacycline.[5]

4 STUDY OBJECTIVES

4.1 Primary Objective

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 of this study are:

- To evaluate the safety of omadacycline in the treatment of adults with CABP in the Safety population.
- To evaluate the Clinical Response according to the identified causative pathogen.
- To evaluate the pharmacokinetics (PK) of omadacycline in adults with CABP.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Description

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.

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. Subject randomization will be stratified by PORT Risk Class (III or IV), and by receipt of an allowed antibacterial therapy (see Appendix 4) in the 72 hours prior to study treatment.

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 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.

Refer to the Schedule of Events (Appendix 1) for a complete summary of subject visits and assessments.

5.2 Rationale for Study Design

The study was designed in accordance with the FDA [6] and European Medicines Agency (EMA)[7] guidance on developing antimicrobial drugs for the treatment of CABP, in addition to the guidelines created jointly by the Infectious Diseases Society of America and the American Thoracic Society.

5.3 Rationale for Control Group

Moxifloxacin (400 mg iv every 24 hours [q24h] with the option to transition to 400 mg po q24h) was chosen as the comparator given the wide acceptance of fluoroquinolone monotherapy as a safe, first-line option for treating subjects with CABP. Moxifloxacin provides a broad spectrum of activity against respiratory pathogens that are causative agents of CABP, including typical (eg, *Streptococcus pneumoniae*) and atypical (eg, *Legionella, Chlamydophila*, and *Mycoplasma* spp.) pathogens, with a similar spectrum of activity to that of omadacycline. Like omadacycline, moxifloxacin has both iv and po formulation options and is administered once daily.

5.4 Approximate Duration of Subject Participation

Subjects will participate in the study for up to 37 days. Eligible subjects will be randomly assigned to receive to 7 to 10 days of iv/po treatment of either omadacycline or moxifloxacin. Subjects with bacteremia confirmed from local blood culture drawn at Screening can receive up to 14 days of treatment. Subjects will return to the site for an EOT visit on the day of or within 2 days following the last dose of test article. Subjects will return to the study site for a PTE 5 to 10 days after the last dose of test article. A Final Follow-up assessment will be conducted within 30 to 37 days following the first dose of test article.

5.5 Approximate Duration of Study

The study is expected to be clinically complete in approximately 24 months.

5.6 Approximate Number of Subjects

Approximately 670 subjects will be enrolled at approximately 75 sites globally.

6 STUDY POPULATION SELECTION

Each subject must participate in the informed consent process and sign and date an IRB/IEC/REB approved informed consent form (ICF) before any procedures specified in this protocol are performed.

6.1 Study Population

Approximately 670 patients will be enrolled at approximately 75 sites globally. Subjects will be randomized in a 1:1 ratio.

6.2 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Written and signed informed consent must be obtained before any protocol specific assessment is performed.
2. Male or female, aged 18 years or older.
3. Has at least 3 of the following symptoms:
   - Cough
   - Production of purulent sputum
   - Dyspnea (shortness of breath)
   - Pleuritic chest pain
4. Has at least TWO of the following abnormal vital signs:
   - Fever or hypothermia documented by the investigator (temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
   - Hypotension with SBP < 90 mm Hg
   - Heart rate > 90 beats per minute (bpm)
   - RR > 20 breaths/minute
5. Has at least 1 clinical sign or laboratory finding associated with CABP:
   - Hypoxemia (PaO_2 < 60 mm Hg by ABG or oxygen saturation < 90% by pulse oximetry)
   - Physical examination findings of pulmonary consolidation (eg, dullness on percussion, bronchial breath sounds, or egophony)
   - 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)
6. Has disease categorized as being PORT Risk Class III or IV at Screening (see PORT Risk Class calculation in Appendix 5).
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.

8. Is expected to require a minimum of at least 2 days of iv therapy for the initial treatment of CABP.
9. Females must have a negative pregnancy test at Screening and agree to comply with using an acceptable method of birth control as per your local requirements (eg, abstinence, po contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal or vasectomized partner) from Screening through PTE. Males must agree to use an acceptable method of birth control with female partner(s) and must not donate sperm from Screening through PTE.

6.3 Exclusion Criteria

Patients who meet any of the following exclusion criteria will be excluded from the study:

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 list in Appendix 4).
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).
3. Suspected or confirmed empyema (a parapneumonic pleural effusion is not an exclusion criteria) or lung abscess.
4. Confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection based on local standard-of-care assessments available during Screening.
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).
6. Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia) within the 3 months prior to Screening or presents with a tachyarrhythmia (excluding sinus tachycardia).
7. Has a QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec (males) or > 470 msec (females), are known to have long QT syndrome, use drugs of potential proarrhythmic or QT prolonging effect.
8. Has other contraindications to receiving a systemic fluoroquinolone antibiotic, including confirmed or suspected peripheral neuropathy, tendon disorder, myasthenia gravis, cirrhosis, aortic aneurysm, or central nervous system (CNS) disorder that may predispose to seizures or lower the seizure threshold.

9. History or evidence of severe renal disease or has a calculated creatinine clearance (CrCl) of < 30 mL/minute, using the Cockcroft-Gault equation (Appendix 2). Requires any form of dialysis (eg, hemodialysis, peritoneal dialysis).
10. Significant immunological disease determined by any of the following:
    - Current or anticipated neutropenia defined as < 500 neutrophils/mm3
    - Known infection with Human Immunodeficiency Virus (HIV) and a cluster of differentiation 4 (CD4) count that is unknown or documented to be < 200 cells/mm^3 within the last year, or an Acquired Immune Deficiency Syndrome (AIDS)-defining illness
11. The receipt of cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs (eg, cyclosporine, azathioprine, tacrolimus, immune- modulating monoclonal antibody therapy, etc) within the past 3 months, or the receipt of corticosteroids equivalent to or greater than 40 mg of prednisone per day or for more than 14 days in the prior 30 days (Appendix 2). Exception: Systemic corticosteroids administered within 24 hours of randomization or any time after randomization as adjunctive therapy for the current episode of CABP (at any dosage) is allowed.
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)
13. PORT Risk Class I, II, and V patients.
14. Requires or expected to require Intensive Care Unit (ICU) admittance or invasive or non-invasive ventilation.
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).
16. Pregnant or nursing (breastfeeding) women.
17. Has a history of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline), to any fluoroquinolone or any of the components of the investigational product or comparator.
18. Has a history of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
19. Has a history of systemic lupus erythematosus or lupus-like syndrome.

20. History of lactose intolerance, lactase deficiency, or glucose-galactose malabsorption.
21. Has current evidence of pancreatitis.
22. Use of other investigational drugs within 5 half-lives or 30 days prior to Screening, whichever is longer.
23. Has previously been treated with omadacycline or previously enrolled in this study.
24. Any planned medical intervention that might interfere with the ability to comply with the study requirements.
25. Has a life expectancy of less than or equal to 3 months or any concomitant condition that, in the opinion of the investigator, is likely to interfere with evaluation of the response of the infection under study, determination of AEs, or completion of the expected course of treatment.

6.4 Screen Failures

Subjects who sign the ICF but withdraw or are withdrawn from the study before random assignment to double-blind treatment are defined as screen failures. All screen failures should be recorded on the subject master list. Limited information including reason for screen failure will be recorded on the eCRF or interactive voice/web response system (IxRS) system for screen failures. Screen failure subjects may be re-screened at the discretion of the investigator and in consultation with the medical monitor as needed. Any subject who discontinues participation or is withdrawn before receiving a treatment assignment, and who is re-screened at a later time will be assigned a new subject number and recorded as re-screened.

7 STUDY TREATMENT(S)

7.1 Treatments Administered

Test articles will be supplied by Paratek Pharmaceuticals, Inc. (the sponsor). Test articles will be labeled according to regulations.

The test articles should be administered only to subjects who have provided informed consent and who meet all of the inclusion criteria and none of the exclusion criteria. Once the test article has been assigned to a subject, it must not be reassigned to another subject.

Following a Screening period of up to 24 hours, eligible subjects will be randomly assigned a dosing regimen of omadacycline or moxifloxacin. Intravenous treatment will be double-blind and oral treatment will be double-blind and double-dummy.

7.2 Identity of the Investigational Product: Omadacycline

Intravenous Formulation (Omadacycline)

Name	**Omadacycline**
[redacted]	
Administration	Please reference Section 7.6

Oral Formulation (Omadacycline)

Name	**Omadacycline , 150 mg**
[redacted]	

Preparation and handling	No special requirements
Administration	Please reference Section 7.6

7.3 Comparator Test Article: Moxifloxacin

Intravenous Formulation (Moxifloxacin)

Name	Moxifloxacin
Excipients	Sodium chloride, USP, glycine, Water for Injection, USP, disodium edetate, and hydrochloric acid for pH adjustment.
How supplied	Single-use ready-to use 250 mL flexibags as a sterile, preservative free, 0.8% sodium chloride solution of moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin).
Storage	Store at 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F). Do not store below 15°C (59°F).
Preparation and handling	No special requirements Please refer to Pharmacy Manual for additional information.
Administration	Please reference Section 7.6

Oral Formulation (Moxifloxacin)

Name	Moxifloxacin Tablet, 400 mg
Excipients	Microcrystalline cellulose, mannitol, silica colloidal anhydrous, sodium starch glycolate, hydroxypropyl cellulose, talc, magnesium stearate, and film coat (polyvinyl alcohol, titanium dioxide, macrogol, iron oxide yellow, iron oxide red, and talc). Tablet is over-encapsulated with a Size 000 Swedish Orange hard gelatin capsule (red iron oxide and titanium dioxide).
How supplied	High-Density Polyethylene (HDPE) bottles with induction seal, child resistant closure and desiccant
Storage	Store at 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F)
Preparation and handling	No special requirements
Administration	Please reference Section 7.6

7.4 Dose Selection Rationale

The dosing regimen of omadacycline selected for this study is based on the nonclinical and clinical experience to date, including in vitro antibacterial activity, PK characteristics, clinical efficacy in prior studies, the overall safety and tolerability profile, and the FDA approved dosing regimen for CABP.

Either a regimen of 200 mg iv omadacycline once daily or 100 mg iv omadacycline every 12 hours (q12h) on Day 1 followed by 100 mg iv omadacycline administered once daily OR 300 mg po omadacycline once daily has been approved by US FDA for the treatment of adult patients with CABP caused by susceptible microorganism. The FDA-approved treatment duration for omadacycline is 7 to 14 days total.

The duration for the iv to po regimen in this study will be 7 to 10 days, with up to 14 days allowed for subjects with bacteremia at the Screening visit. The shorter regimen is supported by the efficacy observed in the previously completed CABP Phase 3 study, PTK0796-CABP-1200 where by Day 7 of treatment, > 80% of patients in the omadacycline treatment group had symptom improvement (as defined by the Early Clinical Response [ECR] endpoint) and had reached clinical stability.

7.5 Description of Treatments

Subjects will be randomized to 1 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 identified at Screening.

7.6 Test Article Administration

7.6.1 Intravenous Treatment Phase

The iv-treatment phase (minimum 2 days) will follow a double-blind, double-dummy design for omadacycline and moxifloxacin. Infusions of 100 mg omadacycline or matched placebo will be administered continuously, without interruptions, over 30 minutes (± 5 minutes). On Day 1, if QD dosing is selected, the 200 mg infusion of omadacycline or matched placebo will be administered continuously, without interruptions, over 60 minutes (± 5 minutes). On Day 1 of iv treatment, if twice a day dosing (BID) was selected, subjects on the moxifloxacin treatment arm will receive an additional placebo infusion to match the t = 12 h infusion. Infusions of moxifloxacin or matched placebo will be administered continuously, without interruptions, over 60 minutes (± 5 minutes).

The first dose of test article should be administered within 4 hours of randomization. All infusion start and stop times are to be recorded in the source documents and on the eCRF. Because the color of the test article and placebo infusions are different, all infusion bags and iv tubing will be covered with materials provided by the sponsor (as described in the Pharmacy Manual) so that

subjects and blinded study personnel will not know the identity of the test article being administered. Subjects in each study arm will receive the same infusion volumes with the same blinded administration instructions. All iv infusions will be administered by qualified blinded personnel. However, unblinded personnel may administer the iv infusions provided they will not be performing any efficacy assessments. If gravity administration is not the standard of care, then an infusion pump may be used. If an infusion pump is used, then an unblinded administrator will be required. Subjects may receive iv treatment in certain outpatient centers in circumstances where the principal site investigator has identified that sufficient resources are available to complete all study procedures as defined in the protocol and the sponsor or sponsor's designee has reviewed and approved the process for outpatient iv test article administration.

Please refer to Table 1 for more detail on the Treatment regimens for iv dosing.

Table 1. Treatment Regimens for IV Test Article

Infusion Timepoint[a]	Infusion Number	Omadacycline Arm[b,c]	Moxifloxacin Arm[b,c]
t = 0 h	1	omadacycline 100 mg in 100 mL NS	100 mL NS placebo
	2	250 mL NS placebo	moxifloxacin 400 mg in 250 mL 0.8% saline
		OR	
	1	omadacycline 200 mg in 100 mL NS	
	2	250 mL NS placebo	
t = 12 h (Only for BID dosing Day 1)	1	omadacycline 100 mg in 100 mL NS	100 mL NS placebo
t = 24 h	1	omadacycline 100 mg in 100 mL NS	100 mL NS placebo
	2	250 mL NS placebo	moxifloxacin 400 mg in 250 mL 0.8% saline
t = 48 h, then q24h	1	omadacycline 100 mg in 100 mL NS	100 mL NS placebo
	2	250 mL NS placebo	moxifloxacin 400 mg in 250 mL 0.8% saline

BID = twice a day dosing, NS = Normal saline (0.9% sodium chloride) for injection, t = time.

[a] See Section 7.6.2 for allowed adjustments in iv dosing schedules.

[b] All 100 mg in 100 mL infusions of omadacycline or 100 mL NS placebo are administered continuously over 30 minutes (± 5 minutes). On Day 1, if QD dosing is selected, the 200 mg in 100 mL infusion of omadacycline or matched placebo will be administered continuously, without interruptions, over 60 minutes (± 5 minutes).

[c] All 250 mL infusions of moxifloxacin or 250 mL NS placebo are administered continuously over 60 minutes (± 5 minutes).

7.6.2 Selection and Timing of iv Dose for Each Subject

To facilitate study enrollment at all times of the day and permit subjects to be "shifted" to a more practical dosing schedule consistent with hospital schedules, a provision is made for limited

adjustment of the dosing interval. Specifically, infusion times may be adjusted up to ± 2 hours per infusion interval until the desired administration schedule is achieved.

Once the desired start of infusion time is determined, subsequent infusions should be "anchored" to that time. That is, thereafter, the start of infusion should be within ± 1 hour of the specified target infusion time.

7.6.3 Management While on iv Test Article

While the subject is receiving iv therapy, the investigator will assess the subject daily and choose one of the following outcomes based on the overall clinical response of the subject:

- Continue iv test article
- Assess for po test article using the protocol defined criteria (after a minimum of 2 days of iv therapy), see Section 7.6.5.
- Discontinue test article – this decision will prompt the EOT evaluation (even if the subject does not complete the minimum of 7 days of dosing)

At all times during the study the decision to continue iv, switch to po, or discontinue test article is made based on the patient's response including the attainment of clinical stability and the clinical judgment of the investigator. Each daily decision is to be recorded on source documents and the information to be transferred to eCRFs by blinded study site personnel.

7.6.4 Investigator's Decision to Continue or Discontinue Treatment

At all times during the study the decision to continue iv, switch to po, or discontinue test article is made based on the patient response including the attainment of clinical stability and the clinical judgment of the investigator.

The investigator may use microbiological results (e.g., culture and susceptibility results) from the local microbiology laboratory to help guide therapy; however, investigator decisions to continue or discontinue test article should be based on *clinical response* rather than susceptibility results. For example, if a respiratory pathogen is detected after randomization that is not susceptible to omadacycline and/or moxifloxacin and the subject is stable or clinically improving, blinded study treatment may continue unless the investigator perceives an undue risk to the subject.

Similarly, if a viral respiratory pathogen is detected after randomization (including but not limited to SARS-CoV-2), study drug may be continued if the investigator continues to suspect co-infecting bacterial pathogen(s) and the subject is stable or clinically improving , and concomitant treatment for the viral pathogen may be administered as appropriate. Questions about individual cases should be discussed with the Medical Monitor prior to discontinuing study drug or administering additional antimicrobial agents, and decisions should be recorded in source documents.

7.6.5 Investigator's Decision to Switch from iv to po Treatment

Initially, all randomized subjects will receive at least 2 days of iv antibacterial therapy. Beginning on the Day 3 visit, the subject may be eligible to switch from iv to po therapy. 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 eCRF:

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

The first po dose should be administered in the morning, 12 to 24 hours after the last dose of iv test article. Switch to po will not be permitted until after the subject has completed at least the 2 days of iv treatment. The date and time the investigator confirmed the criteria for the subject's eligibility for po treatment were met and made the decision to switch to po treatment will be recorded on source documents and the information transferred to eCRFs by study site personnel.

7.6.6 Oral Treatment Phase

Treatment regimens for po dosing are shown in Table 2 below. When switching from iv to po test article, the recommended interval between doses will be maintained. The first po dose, for both omadacycline and moxifloxacin treatment arms, should be given in the morning 12 to 24 hours after the last dose of iv test article.

The po treatment phase will employ a double-blind, double-dummy design. To maintain investigator and subject blinding, subjects in both arms will receive 2 tablets and 1 over-encapsulated tablet in the morning, as shown in Table 2 below. All doses of oral test article should be taken with water.

All oral doses should be taken in a fasted state. Fasting is defined as 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.

Table 2. Treatment Regimens for Oral Test Article

Time of Dosing	Omadacycline Arm	Moxifloxacin Arm	Dosing Condition[a,b]
Morning (upon awakening) [a]	Two 150 mg omadacycline tablets and 1 over-encapsulated placebo tablet	One 400 mg over-encapsulated moxifloxacin tablet and 2 placebo tablets	Fasting overnight (no food or drink except water) before dosing; after dosing, no food for 2 hours, no dairy products for 4 hours

po = per oral.
[a] All doses of po test article should be taken with water.
[b] All subjects will be instructed to avoid taking antacids and multivitamins while taking po test article.

7.6.6.1 Management While on Oral Test Article

When subjects are switched to po therapy, subjects will be given instructions on how to administer the po therapy, a subject diary to record dates and times of po treatment, and a day supply of po test article. Study personnel will review the dosing diary and tablet count with the subject when the po therapy is first dispensed to the subject and at subsequent visits until the subject has completed therapy. Study personnel will review and record which medication is taken in the eCRF.

While the subject is receiving po therapy, the investigator will assess the subject and choose one of the following outcomes based on the overall clinical response of the subject:

- Continue po test article
- Discontinue test article – this decision will prompt the EOT evaluation (even if the subject does not complete the minimum days of dosing)

At all times during the study the decision to continue or discontinue test article is made based on the clinical judgment of the investigator. Each daily decision is to be recorded on source documents and the information transferred to eCRFs by blinded study site personnel.

7.7 Dose Adjustments and Interruptions of Test Article

No dose adjustments or planned interruptions of test article will be permitted during this study.

7.8 Method of Assigning Patients to Treatment Groups

All eligible subjects will be randomized via an IxRS that assigns them to 1 of the treatment arms (in a 1:1 ratio). The site delegate will contact the IxRS 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 or IV) and receipt of an allowed antibacterial (see Appendix 4) in the 72 hours prior to study treatment as defined in the

IxRS specifications and Statistical Analysis Plan (SAP). Subjects randomized into the study will be assigned the treatment corresponding to the next available number from the computer-generated randomization schedule. The subject is considered randomized when the IxRS provides the test article assignment, 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 subjects randomized.

7.8.1 Subject Numbering

Upon signing the informed consent, the subject will be assigned a unique subject number. Subjects who have been pre-screened, but who do not sign an ICF will not be assigned a subject number. A subject who discontinues participation or is withdrawn before receiving a treatment assignment, and who is re-screened at a later time will be assigned a new subject number and recorded as re-screened. Re-screening is at the discretion of the investigator and in consultation with the medical monitor. The investigator will maintain a subject master list to document every subject who has signed an ICF. A copy of this list should be retained in the investigator's study files.

7.9 Dispensing Test Article

Each study site will be supplied by the sponsor with the investigational product and comparator. The IxRS will instruct the pharmacist or designee as to the appropriate therapy, omadacycline or comparator, to be administered. The unblinded site pharmacist or designee will prepare the test article as instructed. The unblinded pharmacist or designee will provide the blinded nurse administering the infusion with the appropriate solutions for each subject covered to conceal the identity of the test article using materials provided by the sponsor and labeled with blinded administration instructions. The po test article will be supplied to the sites in kits that contain bottles of active omadacycline tablets or matched placebo tablets, and bottles of active over-encapsulated moxifloxacin tablets or matched over-encapsulated placebo tablets. Oral test article supplies are completely blinded. Therefore, oral test article supplies can be transferred from the unblinded study personnel to blinded study personnel for storage, dispensation, and reconciliation. The study coordinator/staff will instruct the subject on the use of po test article. The procedures are detailed in the Pharmacy Manual.

7.10 Blinding

The investigator and sponsor will be blinded to treatment arm assignments in both the iv and po phases of the study.

The sponsor designee (eg, study statistical team, IxRS vendor, etc) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind is properly maintained, and that only sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in maintaining the randomization codes).

Because the color of the iv test article infusions and placebo infusions differ, all infusion bags and iv tubing will be covered with materials provided by the sponsor so that subjects and blinded

study personnel will not know the identity of the test article being administered. The infusion regimen will follow a blinded design with subjects in each study arm receiving the same infusion volumes with the same administration instructions. Blinded study personnel will administer the infusions and collect, review and enter data regarding the iv infusions (eg, start and stop times) into an eCRF. If gravity administration is not the standard of care, then an infusion pump may be used. If an infusion pump is used, then an unblinded administrator will be required. Personnel identified as unblinded administrators will not participate in any study procedures other than iv administration of test article and the collection, review and entry of iv related data (eg, start and stop times) into an eCRF.

During the po phase, a double-blind, double-dummy design will be used to ensure the blind is maintained. Subjects in the omadacycline arm will receive active omadacycline tablets and matched comparator over-encapsulated placebo tablets. Subjects on the moxifloxacin arm will receive omadacycline placebo tablets and active over-encapsulated moxifloxacin tablets.

The unblinded source documentation binder containing all descriptions of pharmacy preparations and infusions or distributions of test article and any unblinded subject randomization data should be stored separately, and under lock and key, separate from the documents containing blinded information.

Data that could potentially lead to unblinding will not be accessible to anyone other than the following site personnel:

- unblinded study pharmacist or designee
- unblinded study monitor
- unblinded administrator(s)

Unblinding by site personnel is only to occur in the case of subject emergencies (see Section 7.11, below) and at the conclusion of the study.

7.11 Emergency Unblinding of Treatment Assignment

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, test article discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. It is encouraged for the investigator, when contemplating unblinding, to contact the sponsor or sponsor's designated Medical Monitor or designee to confirm the need to unblind, prior to unblinding (see Section 2 for contact information). However, if required, the investigator can unblind without consulting the Medical Monitor.

Emergency code breaks are performed using the IxRS. When the investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. The investigator will then receive details of the drug treatment for the specified subject and a fax or e-mail confirming that the treatment assignment of the subject was unblinded. The system will automatically inform the sponsor's monitor for the site and the sponsor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place at their site to allow access to the IxRS code break information in case of emergency. The investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, test article name if available, subject number, and instructions for contacting the sponsor (or any entity to which it has delegated responsibility for emergency code breaks) to the subject in case emergency unblinding is required at a time when the investigator and backup are unavailable.

All steps outlined above will be followed, including contacting the Medical Monitor as soon as possible and not more than 24 hours afterwards. It will be the responsibility of all study personnel to ensure that, except for the above procedure, investigator blinding is maintained until after study completion.

7.12 Prior & Concomitant Therapy

Treatments that have been administered within the 7 days prior to the date of informed consent, or during the Screening phase, will be recorded in the eCRF. The investigator is to instruct the subject to notify the study site about any new medications he/she takes after the start of the test article. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with test article must be listed in the eCRF (see Section 10). In addition, for antibacterial agents administered, the dose, unit, frequency and route must be entered in the eCRF.

7.13 Prohibited Therapy

All investigational medications or devices used during the 30 days prior to Screening are prohibited.

All of the following therapies are excluded starting from the time of consent through EOT visit:

- More than 1 dose of a potentially therapeutic antibacterial agents (with potential activity against pathogens responsible for CABP) are prohibited for 72 hours prior to randomization through EOT, with the exception of cases where a subject is deemed a clinical failure during the course of the study and requires treatment with an additional antibacterial agent
- Subjects will be instructed to avoid taking antacids and multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours before and within 4 hours after oral doses

7.13.1 Concomitant Medications That May Interact With Moxifloxacin

Use of proarrhythmic or QT prolonging medications is prohibited through the EOT. After EOT through Final Follow-up, the investigator should use clinical judgement regarding the use of such medications, given the half-life of moxifloxacin. For other warnings, precautions, and drug interactions for moxifloxacin please see the most current version of the moxifloxacin full prescribing information provided under separate cover.

7.14 Permitted Treatments

All other treatments not specified as prohibited are permitted during the study. Subjects requiring additional or alternative antibacterial therapy for their CABP will be judged as Clinical Failures and test article will be discontinued. Further treatment for their infection is at the discretion of the investigator or the subject's health care provider and will be considered as a concomitant medication.

Subjects should be encouraged to contact site personnel before starting any new treatment.

For all treatments received by the subject during the study, relevant information must be recorded on the subject's eCRF.

7.15 Treatment Compliance

Intravenous and oral administration will be managed by study personnel. Compliance and any unresolved discrepancies will be documented in the source document and on the drug inventory record. The test article eCRF should reflect the reconciled dosing information provided by the subject charts.

7.16 Packaging and Labeling

The investigational test article, omadacycline and moxifloxacin will be packaged by the sponsor and supplied to the investigator. Please refer to the Pharmacy Manual for additional information.

7.17 Storage and Accountability

Test article must be received at the study site by a designated person, acknowledged in the IxRS, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access. Upon receipt, the test article should be stored according to the instructions specified on the drug labels. Storage conditions must be adequately monitored, and appropriate temperature logs maintained as source data.

The designated study personnel must maintain an accurate record of the shipment and dispensing of test articles in the study specific medication accountability ledger. Intravenous drug accountability will be performed by unblinded personnel. Oral drug accountability can be performed by blinded or unblinded personnel.

7.18 Investigational Product Retention at Study Site

At the conclusion of the study, and as appropriate during the course of the study, with instruction from the sponsor, the designated study personnel will destroy on site as permitted by local site operating procedures, or return all unused test articles, packaging, and drug labels. Destruction/return of all test article will be documented and maintained in the site files.

8 STUDY PROCEDURES

Written, signed, and dated informed consent will be obtained before any study-related procedures have been performed. Upon signing the informed consent, the subject will then be assigned a study subject number. Adverse events must be recorded from the time the ICF is signed. Subjects who have been pre-screened on the telephone but who do not sign an ICF will not be assigned a subject number. The investigator will maintain a subject master list to document every subject who has signed an ICF. A copy of this list should be retained in the investigator's study files.

8.1 Informed Consent

The investigator will provide for the protection of the subjects by following all applicable regulations. These regulations are available upon request from the sponsor. The ICF must be reviewed by the sponsor and approved by the IRB/IEC/REB.

Before any procedures specified in the protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent
- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB/IEC/REB approved ICF

8.2 Subject Demographics/Other Baseline Characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include: date of birth (per local regulations), gender, and race/ethnicity.

8.3 Medical History

The investigator will perform a comprehensive history at the Screening visit. Significant medical history (at any time) and any medical history within the past 6 months including ongoing medical conditions at the time of signing of the ICF will be recorded. In addition, subject's history of prior CABP will be captured and the following:

- Predisposing factors that may affect lung function (eg, prior lung infection, mild to moderate COPD, symptomatic asthma with wheezing, history of smoking, chronic cough with and without sputum production, etc).
- Cardiovascular disease and risk factors
- History of pneumococcal vaccination (eg, Pneumovax, Prevnar 13).
- All systemic antimicrobials from onset of the infection will be recorded under concomitant medications.

Where possible, diagnoses are to be recorded. Any event or change in the subject's condition or health status occurring after signing the ICF will be reported as an AE.

8.4 Physical Examination

At Screening, a full physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological systems. Beyond the Screening visit, abbreviated physical examinations may be performed (see Appendix 1).

Information for all physical examinations must be included in the source documentation at the study site. Significant and relevant findings that are present prior to the signing of the ICF must be included in the subject's eCRF. Relevant findings that are present prior to the signing of the ICF must be included in the relevant medical history/current medical conditions screen on the subject's eCRF. New clinically significant findings made after the signing of the ICF which meet the definition of an AE must be recorded as an AE in the subject's eCRF.

8.5 Vital Signs

Vital signs including BP, heart rate, respiratory rate, pulse oximetry and body temperature will be measured at the timepoints as specified in Appendix 1. Additionally, BP 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.

The subject's BP and heart rate should be captured after at least 5 minutes (+ 5 minutes) of rest while in a non-standing position (supine or semi-recumbent, head of bed from 0° to 90°). Subsequent vital sign measurements should be captured in the same non-standing position.

Systolic and diastolic BP will be measured using an automated calibrated device, with an appropriately sized cuff.

Heart rate will be measured using an automated calibrated device, when available. If not available, heart rate will be measured manually.

Temperature will be obtained using an electronic (rapid reading) device whenever possible and the same device should be used for all study assessements.

8.6 Electrocardiogram

A standard 12-lead ECG should be obtained using site equipment. The ECG will be obtained after the subject has been in a semi-recumbent position for approximately 10 minutes at the following times:

- Screening-any time during the visit
- EOT-any time during the visit
- In any case in which a subject develops an AE of non-pleuritic cardiac chest pain, palpitations, tachyarrhythmia, or as otherwise clinically indicated
- Additional ECGs can be performed as needed at the discretion of the investigator.

Reading and interpretation of the ECG will be performed locally and reviewed by the investigator for interpretation, and hard copies of the reports retained in the files.

8.7 Height and Weight

Height and body weight will be collected and recorded in the eCRF.

8.8 Assessment of CABP Symptom Severity

The investigator will specifically assess the presence and severity level of the subject's symptoms of cough, sputum production, pleuritic chest pain and dyspnea 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 (see Appendix 3) and enter the symptom severity level into the eCRF. Subjects must have at least 3 of these 4 symptoms of CABP to be eligible for randomization in the study.

8.9 Radiologic Evaluation of Pneumonia

A CXR or CT scan will be obtained for all subjects at Screening (within 48 hours prior to the first dose of test article, see Inclusion Criteria 7). These studies may be obtained as part of routine, non-study evaluation of a subject presenting with signs and symptoms of CABP and therefore may be performed in some circumstances before informed consent is obtained for participation in this study. If a CXR or CT scan is obtained during the course of therapy or during the period up to the Final Follow-up assessment, the results of the study will be collected. Radiologic evaluation(s) will be performed locally and interpreted by appropriately qualified personnel who are certified or licensed to interpret chest radiographs according to applicable regional requirements, reviewed by the investigator or qualified personnel and the conclusions of this review will be the basis for subject inclusion. The review report should be included in the source documents.

8.10 PORT Risk Class

All subjects who are being screened for the study will have their PORT Risk Class assessed at the Screening evaluation only (see Appendix 5). As part of the Inclusion Criteria to this study, all subjects must have disease characterized as PORT Risk Class of III or IV at randomization and randomization will be stratified by PORT Risk Class to ensure balance between treatment arms.

8.11 SF-36v2® Health Survey

At the Screening and Final Follow-up visits, the subject will complete a SF-36v2® Health Survey (Medical Outcomes Trust, Optum™). The SF-36v2® Health Survey asks 36 questions to measure functional health and well-being from the subject's point of view. It is a practical, reliable and valid measure of physical and mental health that can be completed in five to ten minutes. It is referred to as a generic health survey because it can be used across age (18 and older), disease, and treatment group, as opposed to a disease-specific health survey, which focuses on a particular condition or disease.

8.12 Clinical Laboratory Tests

Clinical safety laboratory tests to be performed include hematology, prothrombin time (international normalized ratio), serum chemistry, and pregnancy tests (urine or serum). The Central Laboratory will be used for safety analysis of all specimens collected. Details on the collection tubes and containers, shipment of samples and reporting of results by the Central Laboratory are provided to investigators in the Central Laboratory Manual.

Because subject enrollment will not permit using Central Laboratory results to assess a subject's eligibility, it is expected that local laboratory testing will be used in circumstances where this testing is needed..

8.12.1 Central Laboratory Parameters

Clinical laboratory tests will include the following:

Clinical Laboratory Tests (Central)

Hematology: • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count with differential Coagulation: • Prothrombin time international normalized ration (INR) Pregnancy (all female subjects): • Serum β-human chorionic gonadotropin (β-HCG)	Serum Chemistry: • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO_2) • Chloride (Cl) • Creatinine • Creatine phosphokinase (CK) • Gamma-glutamyl transpeptidase (GGT) • Lipase • Magnesium • Phosphorus (P) • Potassium (K) • Sodium (Na) • Total bilirubin

In addition, blood samples will be collected and sent to the Central Laboratory for serologic microbiology testing (Section 8.12.2.2).

8.12.2 Local Laboratory Parameters

8.12.2.1 Pregnancy Assessments

All subjects will have a local urine or serum pregnancy test at the site at the Screening. Urine pregnancy test kits will be provided by the sponsor through the Central Laboratory. If a positive urine or serum pregnancy test result is obtained at the site during Screening, the subject is not to be randomized. A serum sample for serum β-human chorionic gonadotropin (β-hCG) testing will

be collected at the Screening visit and sent to the Central Laboratory for confirmation of the local urine or serum pregnancy test results as well as at EOT and PTE. If a positive β-hCG result is reported by the Central Laboratory after a subject is enrolled, test article administration should be discontinued (see Section 8.22).

8.12.2.2 Blood Cultures

Two sets of blood cultures (1 set = 1 aerobic bottle + 1 anaerobic bottle) should be collected within the 24 hours prior to the first dose of test article. Each set of blood cultures should be collected by direct venipuncture from independent body sites at least 15 minutes apart. 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. Blood culture isolates should be sent to the Central Laboratory.

8.12.2.3 Sputum and Urine Samples

Samples of sputum and urine will be collected and sent to the local laboratory for microbiology testing (Section 8.14.1).

8.12.2.4 SARS-CoV-2 Sample

In addition to any local SOC assessment of SARS-CoV-2, molecular testing for SARS-CoV-2 will be performed at the local laboratory (or a regional reference laboratory) using an upper respiratory sample (e.g. nasopharyngeal swab or saliva) collected at Screening. Test results from this sample are not required before a subject is randomized. However, test results will be documented in the database. If a positive test result is obtained after randomization, the investigator will determine whether a subject should continue study treatment (see Section 7.6.4). Repeat testing may be completed as clinically indicated and should be recorded. Please see laboratory manual for additional testing information.

8.12.3 Blood Volume

The total volume of blood collected from each subject will be approximately 4 to 15 mL per visit, or approximately 51 mL (approximately 3.5 tablespoons) over the course of the study. In addition, a blood culture will be collected at Screening and repeated if positive. The preferred volume for each blood culture bottle is 10 mL. However, since these are analyzed locally, site staff should refer to their individual laboratory or manufacturers' recommendation.

8.13 Efficacy Assessments

8.13.1 Investigator's Assessment of Clinical Response

In order to satisfy different health authority requirements, the primary variables assessing efficacy will be tested with 2 response endpoints.

8.13.1.1 Evaluation of the Infection Under Study at the Early Clinical Response Assessment

The formal determination of the response to therapy at the ECR assessment (72 to 120 hours after administration of the first dose of test article) will be done programmatically using the investigator's assessment of the subject's symptoms associated with CABP entered into the eCRF. The investigator is not responsible for categorizing subjects as Clinical Success, Failure, or Indeterminate at the ECR assessment. The severity of the subject 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 (see Appendix 3). A CABP subject symptom severity assessment should be completed at every scheduled evaluation with the exception of the Final Follow-up assessment (see Section 8.8 and Appendix 1). For subjects that have been switched to po test article and discharged from the hospital prior to Study Day 4, only 1 visit is required between Study Days 4 to 6 (see Appendix 1 for ECR study procedures). Subjects who remain hospitalized during the ECR phase should have the study procedures performed each day (see Appendix 1).

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 Screening in 2 of the 4 CABP symptoms (cough, sputum production, pleuritic chest pain, and dyspnea) with no worsening by at least 1 level in the other inclusion 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: defined as 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 Screening in 2 CABP symptoms.
- Any of the 4 CABP symptoms is worse (by at least 1 level) compared to 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 or (b) development of infectious complications of CABP (eg, empyema, lung abscess).
- The subject is receiving antibacterial therapy that may be effective for the infection under study for a different infection from the one under study.
- Discontinued study therapy due to an AE and received alternative antibacterial treatment for CABP prior to the ECR assessment.
- 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 they withdrew consent or were lost to follow-up.

- Other specified reason.

8.13.1.2 Investigator's Assessment of Clinical Response at EOT

End of treatment assessments should be performed on the calendar day of, or within 2 days following the last dose of any test article. If a subject withdraws prematurely or terminates participation in the study prior to completion of the planned antibiotic therapy, the EOT visit should be conducted.

The investigator will determine which of the following clinical outcomes the subject meets based on the criteria below (must select 1 outcome):

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:
  a. progression or development of new symptoms of CABP or,
  b. development of infectious complications of CABP (eg, empyema, lung abscess) or,
  c. subject developed an AE that required discontinuation of study therapy.

- Other reasons for Clinical Failure are:
  d. Subject is receiving antibacterial therapy that may be effective for the infection under study for a different infection from the one under study.

  e. Death prior to EOT visit.

Indeterminate:

- The Clinical Response to test article could not be adequately inferred due to:
  a. Subjects were not seen for EOT evaluation because they withdrew consent or were lost to follow-up.
  b. Other specified reason.

8.13.1.3 Investigator's Assessment of Clinical Response at PTE

The PTE assessment is to be performed 5 to 10 days after the subject's last day of therapy. The investigator will determine which of the following clinical outcomes the subject meets based on the criteria below (must select 1 outcome):

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:
  a. Progression or development of new symptoms of CABP or
  b. Development of infectious complications of CABP (eg, empyema, lung abscess).

- Other reasons for Clinical Failure are:
  c. The subject is receiving antibiotics that may be effective for the infection under study for a different infection from the one under study.
  d. Death prior to PTE.

Indeterminate:

- The clinical response to test article could not be adequately inferred due to:
  a. Subjects were not seen for PTE evaluation because they withdrew consent or were lost to follow-up.
  b. Other specified reason.

8.13.2 Clinical Stability

The formal determination of the subject's Clinical Stability will be done programmatically using the investigator's assessment of the subject's vital signs entered into the eCRF. The investigator is not responsible for categorizing the subject's Clinical Stability. Clinical Stability will be assessed daily and analyzed by day, ECR window, EOT, and PTE.

Patients will be considered clinically stable if they achieved all of the following criteria:

- Temperature ≤ 37.8°C (100°F);
- Heart Rate ≤ 100 beats/minute;
- RR ≤ 24 breaths/minute;
- SBP ≥ 90 mmHg; and
- Arterial Oxygen Saturation ≥ 90% or PaO_2 ≥ 60 mmHg on room air.

8.14 Microbiologic Response

8.14.1 Respiratory Culture and Gram Stain

At the Screening visit collection of an adequate quality expectorated or induced sputum or other respiratory specimen reflecting fluid from the lower respiratory tract (eg, respiratory fluid obtained by bronchoalveolar lavage or bronchoscopy; pleural fluid obtained by thoracentesis; or expectorated or induced sputum meeting adequacy criteria) should be attempted from all subjects and submitted to the local microbiology laboratory for Gram stain and culture (see Appendix 1). The date, time and type of specimen submitted will be recorded on source documents at the local laboratory. These specimens may be obtained as part of routine, non-study evaluation of a subject being evaluated for CABP and therefore could be obtained prior to obtaining informed consent.

An adequate quality sputum specimen will be defined as having the following 2 findings as reported by the local laboratory:

1. < 10 Squamous epithelial cells/low power field (LPF) (ie, 100×)
2. > 25 Polymorphonuclear cells/LPF (ie, 100×)

Adequate quality sputum specimens and other Screening respiratory specimens for culture should be obtained prior to first dose of test article. In the event that a sputum specimen is determined to be inadequate or cannot be obtained prior to the first dose of test article, collection of a specimen should be attempted within 24 hours after the first dose of test article. As the infection responds to therapy, obtaining repeated specimens for culture or examination may not be clinically appropriate and/or there may be no material for culture. 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.

All respiratory and blood specimens submitted to the local laboratory are to be processed for a Gram stain of the specimen and for aerobic culture. Laboratory reports on Gram stains should include a semi-quantitative description of the number of polymorphonuclear leukocytes per LPF (ie, 100×) and a description of bacteria seen. For Gram stains of respiratory specimens, a semi-quantitative description of the number of squamous epithelial cells per LPF (ie, 100×) should also be included. Culture results are to include identification of all pathogens to the level of genus and species. Susceptibility testing for moxifloxacin (or other fluoroquinolones) can be performed locally using a standard method chosen by the laboratory. Results of this testing can be used by investigators along with clinical findings to help guide therapy.

All isolates identified by the local laboratory from expectorated or induced sputum specimens meeting the 2 criteria that define the specimen as being of adequate quality and/or that are isolated from respiratory specimens or blood and are potential pathogens as defined in the Local/Regional Clinical Microbiology Laboratory Manual, will be submitted to the Central Laboratory for verification of genus and species and for standardized minimum inhibitory concentration (MIC) testing performed for omadacycline, moxifloxacin and a panel of currently approved antibiotics. In the event that local laboratory genus and species identification are not consistent with Central Laboratory results, a back-up isolate should be sent to the Central Laboratory.

Details concerning Gram stains and cultures will be provided in the Local/Regional Clinical Microbiology Laboratory Manual.

8.14.2 Urine for Legionella pneumophila and Streptococcus pneumoniae Antigen Screening

At the Screening visit, urine will be collected to test for the presence of *Legionella pneumophila,* and *Streptococcus pneumoniae* antigens. Testing will be performed at the local laboratory using kits supplied by the sponsor and the results will be recorded on the eCRF.

8.14.3 Serology for Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydophila pneumoniae Titers

At the Screening visit, and at the PTE visit, blood samples will be collected to conduct serology for *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* by the Central Laboratory.

8.15 Pharmacokinetic Assessments

Instructions will be provided to sites with detailed information on sample collection, handling, and shipment requirements. All samples will be given a unique identifier. The exact clock time of dosing, date and time of last food intake, as well as actual sample collection date and time will be entered on the eCRF.

[redacted]

[redacted]

8.16 Adverse Events

An AE is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or in a clinical study. The event does not need to be causally related to the test article or clinical study. An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a preexisting condition.
- An AE occurring from overdose of a test article, whether accidental or intentional. Overdose is a dose greater than that specified in the protocol.
- An AE occurring from abuse (eg, use for nonclinical reasons) of a test article.
- An AE that has been associated with the discontinuation of the use of a test article.

8.17 Serious Adverse Events

A serious adverse event (SAE) is an AE that:

- Results in death.
- Is life-threatening (see below)
- Requires hospitalization or prolongation of an existing hospitalization (see below).
- Results in a persistent or significant disability or incapacity (see below).
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent any one of the outcomes listed above in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of

death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the participating investigator. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This should be recorded in the study file.
- A hospitalization for a preexisting condition that has not worsened

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

8.18 Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- Pregnancy exposure to a test article: If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.
- Lactation exposure to a test article with or without an AE.
- Overdose of a test article as specified in this protocol with or without an AE.
- Inadvertent or accidental exposure to a test article with or without an AE.

8.19 Overdose

Any administration of omadacycline of greater than 600 mg within a 24-hour period will be an overdose, regardless of whether the overdose is intentional or accidental, it is a reportable event and the sponsor must be notified within 1 business day. Any administration of greater than 2.8 g of moxifloxacin in a single administration will be an overdose. In the event that a study subject takes an overdose of test article, the investigator may obtain the subject's treatment assignment

by contacting the IxRS. Interactive Response System will also provide a confirmation report of the drug assignment to site personnel. The site personnel will retain this confirmation report. In the case of a potential overdose, the subject should maintain a high level of fluid intake to promote urinary excretion (as recommended in the moxifloxacin USPI).

The physician managing the overdose may order any test he/she thinks is necessary to manage the subject properly.

8.20 Medication Errors

Medication errors are the result of administration or consumption of the wrong product, by the wrong subject, at the wrong time, and/or by the wrong administration route, due to human error.

Medication errors include, but are not limited to, the following:

- The administration and/or consumption of test article that has not been assigned to the subject
- Administration of expired test article

All AEs and SAEs must be handled as specified in this protocol whether or not they are associated with a medication error. A medication error associated with an SAE (including overdose, inadvertent exposure, and/or accidental exposure) will be reported with the SAE on the SAE Report Form. All other medication errors will be reported by e-mailing the Clinical Test Article Error Incident Report Form as indicated in the Emergency Contacts (see Section 2.1).

8.21 Recording and Reporting

A subject's AEs and SAEs will be recorded and reported from the signing of the ICF to the time of the Final Follow-up assessment. The investigator must instruct the subject to report AEs and SAEs during this time period. Reports of death after the last contact with the subject will be reported to the sponsor and additional information relative to the cause of death will be sought and documented.

All AEs and SAEs must be recorded on source documents. All AEs and SAEs for subjects who receive a treatment assignment will be recorded in the eCRFs.

The investigator must follow-up as medically necessary on all AEs and SAEs until the events have subsided, the condition has returned to Baseline, or in case of permanent impairment, until the condition stabilizes.

AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Whenever possible, AEs should be reported as a diagnosis rather than individual signs and symptoms. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded using standard medical terminology.

If an AE requires a surgical or diagnostic procedure, the illness leading to the procedure should be recorded as the AE, not the procedure itself.

Death should be recorded in the eCRF as an outcome of an AE. Any unanticipated risks to the subjects must be reported promptly to the IRB/IEC/REB.

8.21.1 Serious Adverse Event Reporting

All SAEs and follow-up information must be reported within 1 business day or 24 hours as required by local regulations by emailing a completed SAE Report to the email address below.

Serious Adverse Event (SAE) contact information
E-Mail: [redacted]

8.21.2 Assessment of Relatedness

The investigator will assess causality (ie, whether there is a reasonable possibility that test article caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Not Related: This relationship suggests that there is no association between test article and the reported event. The event can be explained by other factors such as an underlying medical condition, concomitant therapy, or accident, and no plausible temporal or biologic relationship exists between test article and the event.
- Related: This relationship suggests that a definite causal relationship exists between test article administration and the AE, or there is a reasonable possibility that the event was caused by the study medication, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

Adverse events and SAEs also will be assessed for their potential relationship to the protocol. A protocol-related AE is one that is not related to the test article, but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, ie, related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event related to a medical procedure required by the protocol.

8.21.3 Assessment of Severity

The severity (or intensity) of an AE will be classified using the following criteria:

- Mild: These events are usually transient, require minimal or no treatment, and do not interfere with the subject's daily activities.
- Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning but pose no significant or permanent risk of harm.

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

Changes in the severity of an AE should be documented as a new event to allow an assessment of the duration of the event at each level of intensity to be performed.

8.21.4 Laboratory Findings

Protocol-defined safety laboratory test results will be analyzed as part of specific laboratory safety analyses. Additional laboratory test results at other time points may be available to the investigator as part of standard clinical practice. Throughout the study, laboratory-related abnormalities should be recorded as AEs only if considered clinically significant, outside the range of expected values given the subject's Baseline assessments and clinical course, and not known to be part of another AE diagnosis.

8.21.5 Worsening or Progression of Disease Under Study

Worsening or progression of the qualifying CABP should be recorded as a clinical failure (as part of the efficacy assessment), rather than an AE, unless the worsening/progression also meets the criteria for a serious AE (in which case the event also should be reported as an SAE). In contrast, any new or secondary infections that the investigator considers to be distinct from the qualifying CABP should be reported as AEs in all cases, whether non-serious or serious.

8.22 Pregnancies

To ensure subject safety, each pregnancy in a subject on test article must be reported to the sponsor within 1 business day of learning of its occurrence. Test article should be discontinued immediately, and the pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the test article of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.23 Concomitant Medication Assessments

The investigator should instruct the subject to notify the study site about any new medications they take after the start of the test article.

All prescription medications, over-the-counter (OTC) drugs, and recreational drugs taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant Medications/Non-Drug Therapies page of the eCRF.

8.24 Subject Discontinuation or Withdrawal

Reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to, AE, lost to follow up, withdrawal by subject, physician decision, death, and other (specify reason eg, subject non-compliance or study termination by the sponsor). Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn from the study if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason. If premature withdrawal from the study occurs for any reason, the investigator should determine the primary reason for a subject's premature withdrawal from the study and record this information on the eCRF.

Subjects who discontinue study treatment should not be considered withdrawn from the study (unless the subject withdraws informed consent). The date and primary reason for discontinuation of study treatment should be recorded. Subjects who discontinue study treatment prematurely should complete the EOT visit, PTE visit and Final Follow-up Assessment, if possible (see Schedule of Events - Appendix 1). The site should also collect subject safety information through the Final Follow-up assessment.

Site personnel must also contact the IxRS to register the subject's discontinuation from test article.

For subjects who are lost to follow up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, (eg, dates of telephone calls, registered letters, etc).

9 STUDY ACTIVITIES

9.1 Screening Phase

The Screening visit should be completed within a 24-hour period prior to randomization. The Screening procedures will be used to establish subject eligibility and baseline characteristics for each subject. Following the signing of an ICF, the site staff will collect/perform the assessments detailed in Appendix 1.

9.2 Double-blind Treatment Phase

The double-blind treatment period is 7 to 10 days in duration. Additionally, subjects with bacteremia confirmed from local blood culture drawn at Screening can receive up to 14 days of treatment. Subjects who meet all of the inclusion criteria and none of the exclusion criteria may be randomized.

Visits will occur on Day 1, 2, 3, 4 to 6 (ECR), and Day 7/EOT. Visits will occur on Days 8 to 10 only if the EOT visit does not coincide with day of last dose OR 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 the Day 4 visit, only 1 visit is required between Study Days 4 to 6. Subjects who remain hospitalized during the ECR phase should have the study procedures performed each day (see Appendix 1). Beginning on Day 7, subjects are eligible to have their test article discontinued at the discretion of the investigator (see Section 7.6.4). If the investigator determines that the subject does not need further antibacterial therapy on Day 7, the EOT evaluation may be performed the day of or within 2 days of the last dose of test article. If the subject is hospitalized in the period between the last day of study drug treatment and the EOT evaluation, the study procedures should be performed as outlined in Appendix 1. If the subject is outpatient during this period, the study procedures do not need to be performed until the EOT visit. have their test article discontinued at the discretion of the investigator (see Section 7.6.4). If the investigator determines that the subject does not need further antibacterial therapy on Day 7, the EOT evaluation may be performed the day of or within 2 days of the last dose of test article. If the subject is hospitalized in the period between the last day of study drug treatment and the EOT evaluation, the study procedures should be performed as outlined in Appendix 1. If the subject is outpatient during this period, the study procedures do not need to be performed until the EOT visit.

9.3 EOT Visit Procedures

The EOT evaluation should be conducted on the day of or within the 2 days following the last dose of test article. If the subject voluntarily withdraws or is discontinued from their dosing regimen, the visit procedures should be performed on that day.

9.4 Follow-up Phase

9.4.1 Post-therapy Evaluation Visit Procedures

The PTE visit should be conducted 5 to 10 days after the last dose. This evaluation should also be conducted for any prematurely withdrawn subject.

9.4.2 Final Follow-up

The Final Follow-up assessment should be conducted within 30 to 37 days following the subject's first dose of test article. This evaluation should also be conducted for any prematurely withdrawn subject, with the exception of subjects who withdraw consent. The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who are a Clinical Success and had no AEs or clinically significant laboratory, or ECG abnormalities noted at or after the PTE visit. Otherwise, the visit must be conducted in-person.

10 STUDY SUSPENSION, TERMINATION, AND COMPLETION

10.1 Study Completion and Post-study Test Article

A subject will have successfully completed the study after the planned test article regimen has been administered, and all assessments and visits have been performed up through the final follow-up assessment (Final Follow-up). The study will be completed when the last subject has either discontinued or completed the Final Follow-up assessment.

No long-term follow-up of subjects is planned, with the exception of pregnancies, as described in Section 8.22 , and SAEs described in Section 8.21.

Sites will be notified by either the Sponsor or IxRS to stop enrollment when the desired number of treated subjects have been enrolled. Subjects already consented, but not yet randomized will be allowed to continue Screening procedures.

Upon study completion, the investigator will provide the sponsor, IRB/IEC/REB, and regulatory agency with final reports and summaries as required by regulations. The investigator must submit a written report to the sponsor and the IRB/IEC/REB within 3 months after the completion or termination of the study.

10.2 Study Suspension or Termination

The sponsor may suspend or terminate the study or part of the study at any time for any reason. Should this be necessary, subjects should be seen as soon as possible and treated as described in Section 8.24 for prematurely withdrawn subjects. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs and/or Ethics Committees (ECs) of the early termination of the study.

If the investigator suspends or prematurely terminates their participation in the study, the investigator will promptly inform the sponsor and the IRB/IEC/REB and provide them with a detailed written explanation. Subjects should be seen as soon as possible and treated as described in Section 8.24 for prematurely withdrawn subjects. The investigator will also return all test articles, containers, and other study materials to the sponsor.

11 QUALITY CONTROL AND ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the Investigator's Brochure, the case report forms (CRFs) and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor monitors the conduct of the study by visiting the site and by contacting the site by telephone and e-mail. During these site visits, information recorded in the CRFs is verified against source documents.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

All analyses of data for this study will comply with International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E9) and the sponsor's guidance documents and standards. Statistical analyses will be performed using Statistical Analysis Software (SAS®).

The SAP incorporating the sections below, along with mock tables, figures, and listings (TFL) shells, will be prepared, approved, and finalized by the sponsor prior to database lock. This plan will define populations for analysis, outline all data handling conventions, and specify statistical methods to be used for analysis of safety and efficacy. Analyses of PK endpoints will be described in a separate analysis plan.

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviation, medians, minimums, and maximums for continuous variables will be provided. Exploratory analyses may also be performed. Listings of individual subject's data will be produced.

All eCRFs must be completed, entered, and source data verified; all safety and microbiology laboratory results must have been reported; all AEs must have been fully characterized (eg, relationship to test article determined) and coded; and all queries must have been resolved prior to database lock and unblinding. Determination of inclusion in the analysis populations, characterization of protocol deviations as major/minor and final approval of the SAP will also be completed prior to database lock.

12.2 Determination of Sample Size

Table 3 provides a summary of clinical success rates in the CABP-1200 study at ECR and PTE in the PORT III and IV subjects.

Table 3. 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)	228/332 (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 about 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 80% 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 4.

Table 4. 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.

12.3 Analysis Populations

The following subject analysis populations have been defined for the various analyses of efficacy and safety:

- The ITT population will consist of all randomized subjects.
- The micro-ITT population will consist of subjects in the ITT population who have at least 1 causative pathogen identified at Screening from culture of a respiratory specimen (eg, respiratory fluid obtained by bronchoalveolar lavage or bronchoscopy; pleural fluid obtained by thoracentesis; or expectorated or induced sputum meeting adequacy criteria), 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 *Chlamidophila pneumoniae*).
- The CE population will consist of all ITT subjects who received test article, have a qualifying CABP, an assessment of outcome, and meet all other evaluability criteria detailed in the SAP.
- The microbiologically evaluable (ME) population will include subjects in the CE population who have at least 1 causative pathogen identified at Screening.
- The Safety population will consist of all randomized subjects who receive test article.

12.4 Demographics and Other Baseline Characteristics

Descriptive statistics, by treatment arm, will be provided for the following:

- Subject disposition:
  - completed test article
  - discontinued test article by reason for discontinuation

  - completed study
  - discontinued study by reason for discontinuation
- Protocol deviations
- CABP background information
  - subject demographics: age (years), gender, race, height (cm), weight (kg), Body Mass Index (BMI) (kg/m2)
- PORT Risk Class
- Medical histories and continuing medical conditions

Baseline demographic and medical variables will be analyzed using a 2-sided Fisher's exact test (for categorical variables) or a 2-sided Wilcoxon Rank Sum test (for ordinal and continuous variables).

12.5 Treatments (Test Article, Rescue Medication, Other Concomitant Therapies, Compliance)

The number of iv infusions will be summarized. Number of days on iv before switch to po will be summarized. For the po medication, actual tablet count taken will be presented.

The total number of days on study therapy will also be provided by treatment group.

Prior medications, concomitant medications, separately for antibiotics and non-antibiotics will be summarized. For prior and concomitant antibiotics, the reason for receipt will be provided.

12.6 Primary Efficacy Analysis

For all efficacy analyses, subject data will be analyzed in the group to which the subject was randomized. For the primary analyses for both the FDA and EMA, subjects will be analyzed in the stratum to which they were randomized.

12.6.1 Early Clinical Response Efficacy Variable

The Early Clinical Response can be Clinical Success, Clinical Failure or Indeterminate (defined in Section 8.13.1.1).

An Indeterminate Response is included in the denominator for the calculation of the percentage of subjects with a Clinical Success in the ITT population and thus, is essentially considered as a Clinical Failure for the purpose of the primary analysis for the FDA.

12.6.2 Investigator's Assessment of Clinical Response at PTE Efficacy Variable

The investigator will make an assessment of Clinical Response at the EOT and PTE Visits. The primary outcome for the EMA, Investigator's Assessment of Clinical Response at the PTE visit, is derived from the assessments at EOT and PTE visits in that a subject with a clinical response of failure at EOT is considered to have a clinical response of failure at PTE (ie, the clinical failure is carried forward) and a subject with an indeterminate response at EOT is considered to

have an indeterminate response at PTE, unless the outcome is a clinical failure at PTE. Investigator's Assessment of Clinical Response has outcomes of Clinical Success, Clinical Failure or Indeterminate (defined in Section 8.13.1.3) in the ITT population and Clinical Success and Clinical Failure in the CE population. An Indeterminate Response is included in the denominator for the calculation of the percentage of subjects with a Clinical Success in the ITT population and thus, is essentially considered a Clinical Failure for the purpose of the primary analysis for the EMA.

12.6.3 Statistical Model, Hypothesis, and Method of Analysis

To demonstrate that the efficacy of omadacycline is non-inferior to moxifloxacin in the treatment of adults with CABP, the following hypothesis will be evaluated by analysis of the Clinical Success rates.

The null hypothesis and alternate hypothesis for the ECR endpoint will be assessed in the ITT population as follows:

Ho: $\theta_T - \theta_C \leq -\Delta$

Hai: $\theta_T - \theta_C > -\Delta$

Where the Clinical Success rate for the omadacycline regimen is θ_T and for moxifloxacin is θ_C,

Δ is the non-inferiority (NI) margin and is 0.10.

Similar null and alternative hypotheses can be set up with Δ of 0.10 for the PTE endpoint. For the ECR (FDA) endpoint, a 2-sided 95% confidence interval (CI) approach for the difference of clinical success rates (using the point estimate of the difference: omadacycline response proportion minus moxifloxacin response proportion) will be used to test for the NI of the omadacycline arm compared to the moxifloxacin arm in the ITT population. The 95% CI will be calculated using the unstratified method proposed by Miettinen and Nurminen.[8] Omadacycline will be considered non-inferior to moxifloxacin if the lower bound of the CI is greater than -0.10.

For Investigator's Assessment of Clinical Response at PTE (EMA) primary efficacy analyses in both the ITT and CE populations, a 2-sided 95% CI approach for the difference of clinical success rates (using the point estimate of the difference: omadacycline response proportion minus moxifloxacin response proportion) will be used to test for the NI of the omadacycline arm compared to the moxifloxacin arm. The 95% CI will be calculated using the stratified (for the randomization stratification factors) method proposed by Miettinen and Nurminen.[8] Omadacycline will be considered non-inferior to moxifloxacin if the lower bound of the CI is greater than -0.10.

Early Clinical Response and Investigator's Assessment of Clinical Response at PTE will be tested separately and are not co-primary endpoints. The probability of showing NI for an ineffective drug based on PTE efficacy is 2.5%, regardless of the result for the ECRendpoint and vice versa. In addition, no alpha adjustment is needed for the co-primary efficacy endpoints for

the EMA (ITT and CE populations) since NI must be shown in both populations to conclude NI. Hence there will be no adjustment for multiple endpoints.

12.6.4 Additional Analyses of Primary Efficacy Outcomes

Additional and sensitivity analyses of the primary efficacy outcomes (ECR and Investigator's Assessment of Clinical Response at PTE) will be performed. Analyses for the FDA primary outcome will be described here and in more detail in the SAP. Analyses for the EMA primary outcome will be described in the SAP.

If the null hypothesis of inferiority is rejected for the ECR in the ITT population and the observed success response 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 2-sided CI for the treatment difference is greater than 0%, omadacycline will be considered superior to moxifloxacin.

The primary efficacy outcome will be assessed separately across the stratification factors of PORT Risk Class and receipt of allowed antibacterial therapy in the 72 hours prior to study treatment. For each PORT Risk Class stratum and each prior antibacterial therapy stratum, a 2-sided 95% CI for the observed difference in ECRsuccess rates will be calculated for the ITT population. Additional subgroup analyses of the primary efficacy outcome may be conducted as descriptive analyses.

Sensitivity analyses include conducting an adjusted analysis of the primary efficacy outcome based on the randomized stratum and separately, based on the stratum the subject actually belongs, and conducting an analysis where all subjects with an Indeterminate response are considered Clinical Successes.

12.7 Analysis of Secondary Variables

Analyses for the FDA secondary outcomes will be described here and in more detail in the SAP. Analyses for the EMA secondary outcomes will be described in the SAP.

The number and percentage of subjects classified as a Clinical Success, Clinical Failure and Indeterminate by the Investigator's Assessment at PTE in the ITT and CE populations (by definition subjects with an Indeterminate response are excluded from the CE population) will be calculated for each treatment group. A 2-sided unadjusted 95% CI will be constructed for the observed difference in the clinical success rate using the method of Miettinen and Nurminen.[8] For Investigator's Assessment of Clinical Response at PTE in the ITT and CE populations (FDA secondary outcome) the 95% CI is for descriptive purposes only and no conclusion of NI will be made.

The number and percentage of subjects in each treatment group in each response category for ECRwill be presented for the microITT population. The number and percentage of subjects who are classified as a Clinical Success and Clinical Failure by the investigator at the PTE visit in ME population will be calculated. Two-sided unadjusted 95% CI will be constructed for the observed difference in the clinical success rates using the method of Miettinen and Nurminen.[8]

The number and percentage of subjects with an ECR of success and an Investigator's Assessment of Clinical Response at PTE of Clinical Success by pathogen will be provided in the microITT and ME populations.

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. A 2-sided unadjusted 95% CI for the observed difference in mortality rates will be calculated for ACM.

12.8 Analysis of Additional Efficacy Variables

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.

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 populations (by definition, subjects with an Indeterminate response are excluded from the CE population) will be calculated. A 2-sided unadjusted 95% CI will be constructed for the observed difference in the Clinical Success rate using the method of Miettinen and Nurminen.[8]

The number and percentage of subjects with stabilization of vital signs and clinical signs/laboratory findings associated with CABP at 72-120 hours post first dose of test article will be presented by treatment group in the ITT population. These include body temperature (no fever or hypothermia), SBP (> 90 mm Hg), heart rate (< 90 bpm), RR (< 20 breaths/minute), PaO2 (≥ 60 mm Hg by ABG or oxygen saturation ≥ 90% by pulse oximetry), physical exam findings (no findings of pulmonary consolidation), WBC count (< 12,000 cells/mm3 or ≥ 4,000 cells/mm3) or immature neutrophils (< 15%).

A summary (number and percentage of subjects) of the assessment of clinical signs and symptoms of CABP at each time point throughout the study will be presented by treatment group in the ITT population. The number and percentage of subjects with resolution of signs and symptoms present at Screening (back to pre-CABP status) will also be provided by study visit. 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 in the ITT population.

The per-subject and per-pathogen microbiologic outcomes will be provided for the microITT and ME populations at the EOT and PTE visits. Two-sided unadjusted 95% CIs will be provided for the difference in per-subject microbiological favorable outcome rates.

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 total score, PCS and MCS will be provided at Screening, the Final Follow-up Visit and the change from baseline by treatment group in the Safety Analysis Set.

12.9 Safety Outcome Measures

Safety variables include the incidence rate of AEs, change in vital signs, ECG parameters and laboratory test results obtained during the course of the study. For safety analyses for both the FDA and EMA, subjects will be analyzed according to the treatment actually received.

12.9.1 Adverse Events

Summary tables will be provided for all treatment-emergent adverse events (TEAEs). A TEAE is defined as an AE with a start date and time on or after the first dose of test article. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and percentage of subjects having each TEAE for each treatment group by system organ class (SOC) and preferred term (PT). Additional tabulations will provide summaries by SOC and PT of subjects experiencing SAEs, severe TEAEs, TEAEs judged to be related to test article, TEAEs leading to discontinuation of test article, TEAEs leading to dose interruption of test article, and TEAEs of special interest.

12.9.2 Vital Signs

The following variables will be analyzed descriptively:

- Vital signs (systolic and diastolic BP, pulse rate, body temperature, RR) including change from Screening by visit
- Clinically notable vital signs (meeting predefined criteria as specified in the SAP) by visit

Subjects with notable vital signs data will be listed.

12.9.3 Electrocardiograms

Electrocardiogram data (RR interval, PR interval, QRS interval, Corrected QT interval [QTc], QTc Bazzett's Correction Formula [QTcB], and QTc Fridericia's Correction Formula [QTcF]) will be summarized descriptively at each scheduled evaluation and for the overall worst post-Screening value. Changes from Screening at each visit will also be provided. An outlier analysis will be conducted based on the worst post-Screening value.

12.9.4 Laboratory Tests

The following variables will be analyzed descriptively:

- Laboratory variables by visit
- Change from Screening of laboratory variable by visit

- Clinically notable laboratory values (meeting predefined criteria specified in the SAP) by visit

Listings of individual subject laboratory data will be generated. Values meeting predefined criteria for being clinically notable will be flagged within the listings.

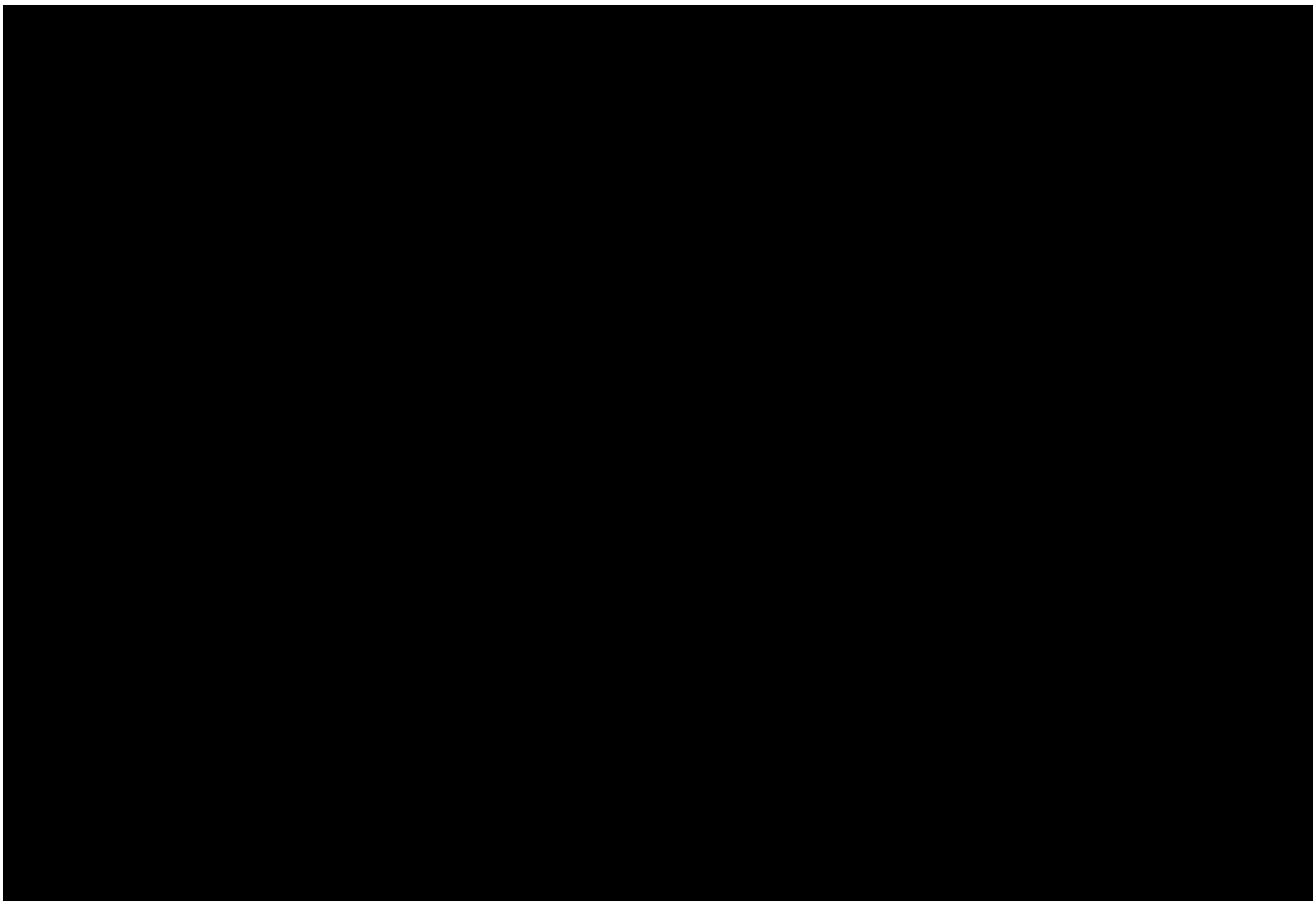
12.10 Resource Utilization

Data for resource utilization will be collected through the Final Follow up assessment and will include:

- number of days in hospital from the time of initiation of therapy, initiation of second therapy, as well as from the first day in hospital to date of discharge for all subjects and by country (due to the varying clinical practices per country)
- number of hospital re-admissions
- duration (days) and number of doses on iv therapy (test article)
- duration (days) and number of outpatient iv doses (test article)
- duration (days) and number of doses on po therapy (test article)
- number of ER/ED and physician visits

Descriptive statistics for the resource utilization parameters will be provided by treatment group for the purpose of health economic evaluation.

[redacted]



12.12 Pharmacogenetics/Pharmacogenomics

Pharmacogenetics/pharmacogenomics studies are not planned as part of this protocol.

12.13 Biomarkers

Not applicable.

12.14 Pharmacokinetics/Pharmacodynamics

The relationship between omadacycline exposure and response (efficacy and safety) will be examined as appropriate for the data. A population PK model will be used to calculate individual subject AUCs and, subsequently, possible AUC/MIC breakpoints.

12.15 Interim Analysis

No interim analyses of efficacy are planned. However, a DMC will review safety data (eg, AEs and SAEs, laboratory data, ECG, and vital signs assessments) while the study is ongoing (see Section 12.17).

12.16 Handling of Missing Values/Censoring/Discontinuations

Missing values will not be imputed for primary and secondary efficacy and safety analyses (except as detailed in the SAP for missing dates) and only observed values will be used in data analyses and presentations. For the primary outcome measure of ECR, if any data field needed to determine the response is missing the subject will be assigned an Indeterminate response. Subjects with an Indeterminate response are included in the denominator, and thus, are considered Clinical Failures. A sensitivity analysis of the primary outcome of ECR will be conducted in which subjects with an Indeterminate response are considered Clinical Successes.

For the EMA primary outcome measure of Investigator's Assessment of Clinical Response at PTE in the ITT population (secondary outcomes for FDA), subjects with missing data are assigned an Indeterminate response. Subjects with an Indeterminate response are included in the denominator, and thus, are considered failures. Table 6 provides a summary of the handling of missing/indeterminate outcomes for the Investigator's Assessment of Clinical Response at PTE.

Table 6 Investigator's Assessment of Clinical Response at PTE Determination Given Missing Data

EOT Visit	PTE Visit	Clinical Response at PTE (Investigator's Assessment)
Missing/indeterminate	Success	Indeterminate
Missing/indeterminate	Failure	Failure
Missing/indeterminate	Missing/indeterminate	Indeterminate
Success	Missing/indeterminate	Indeterminate
Failure	Missing/indeterminate	Failure

For the analysis in the ITT analysis set of Investigator's Assessment of Clinical Response at PTE, Indeterminate outcomes are included in the denominator and are thus considered Clinical Failures.
Missing data are handled in a similar manner for the outcome of microbiological response at PTE.
EOT = end of treatment; ITT = intent-to-treat; PTE = post-therapy evaluation.

12.17 Data Monitoring Committee

A data monitoring committee (DMC) will provide ongoing monitoring of safety data. The charter for the DMC will clearly outline membership, all roles, responsibilities, and decision-making criteria. This will include a detailed description of the manner in which security and blinding of the data for the study management team will be maintained, in addition to the procedures that ensure the independence and objectivity of the DMC's activities. As the DMC will be reviewing data for this study, it may require reports indicating treatment assignment to assist in clinical interpretation of its findings. Therefore, the DMC charter will provide a detailed explanation of the processes by which the DMC will obtain the information necessary for its operation that will not prejudice or create any potential source of bias in the conduct of the study.

12.18 Clinical Events Committee

A clinical events committee (CEC) will adjudicate all deaths to ensure that they have been reported and assessed for relatedness uniformly using the same definition by experts who are blinded to the treatment status. The charter for the CEC will outline membership, roles, responsibilities, and standardized definitions. This will include a detailed description of the way security and blinding of the data will be maintained.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

The investigator will permit study-related monitoring, audits, IRB/IEC/REB review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. All required data will be recorded in the eCRFs.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable solution including but not limited to storage for all study-related documents. Regulatory agencies will be notified with the appropriate documentation.

An updated Form FDA 1572 will be filed with the sponsor for any changes in the study personnel reported in the current Form FDA 1572.

13.2 Institutional Review Board or Independent Ethics Committee Approval

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC/REB must be given to the sponsor before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor, monitors, auditors, designated agents of the sponsor, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

13.3 Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US 21 Code of Federal Regulations [CFR], and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

13.4 Patient Information and Consent

The investigator will provide for the protection of the subjects by following all applicable regulations. These regulations are available upon request from the sponsor. The ICF must be reviewed by the sponsor and approved by the IRB/IEC/REB.

Before any procedures specified in the protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent;
- Be given time to ask questions and time to consider the decision to participate;
- Voluntarily agree to participate in the study;
- Sign and date an IRB/IEC/REB approved- ICF.

13.5 Direct Access, Data Handling, and Record Keeping

13.5.1 Investigator

The investigator will permit study-related monitoring, audits, IRB/IEC/REB review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. All required data will be recorded in the eCRFs.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution.

Regulatory agencies will be notified with the appropriate documentation.

An updated Form FDA 1572 will be filed with the sponsor for any changes in the study personnel reported in the current Form FDA 1572.

13.5.2 Sponsor

The data is entered into an electronic database via eCRFs. The Sponsor Medical Monitor reviews the data for safety information. The data is reviewed for completeness and logical consistency. Automated validation checks identify missing data, out-of-range data, and other data inconsistencies. The central safety and microbiology data will be processed electronically. Requests for data clarification are forwarded to the investigative site for resolution.

13.6 Protocol Adherence

13.6.1 Violations/Deviations

Investigators will agree to apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its agents to request approval of a

prospective protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC/REB, it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

13.6.2 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for subject safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

13.7 Subject Injury

In general, subject to specific provisions in the clinical study agreement (CSA), if a subject is injured as a direct result of a test article, the sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent that such expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the sponsor shall comply with such laws or regulations. Where applicable, the sponsor has taken specific national insurance.

13.8 Pre-study Documentation

The investigator must provide the sponsor with the following documents before enrolling any subjects:

- Completed and signed Form FDA 1572 or equivalent.
- All applicable country-specific regulatory forms.
- Current signed and dated curricula vitae for the investigator, sub-investigators, and other individuals having significant investigator responsibility who are listed on the Form FDA 1572 or equivalent, or the clinical study information form.
- Copy of the IRB/IEC/REB approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the subject must be approved by the IRB/IEC/REB. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC/REB must also be provided to the sponsor.
- Copy of the IRB/IEC/REB-approved informed consent document to be used.
- Where applicable, a list of the IRB/IEC/REB members and their qualifications, and a description of the committee's working procedure.

- Copy of the protocol sign-off page signed by the investigator.
- Fully executed CSA.
- Where applicable, a financial disclosure form.
- A written document containing the name, location, certification number, and date of certification of the laboratories to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the statement of investigator form. The sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.
- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The sponsor must be notified if normal values or units of measurement change.

13.9 Retention of Data

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (a) 2 years after the last marketing authorization for the investigational test article has been approved or the sponsor has discontinued its research with respect to such investigational test article or (b) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the sponsor in writing of its intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

13.10 Publication and Disclosure Policy

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Upon completion of the study, the investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the CSA. Unless otherwise specified in the CSA, the following process shall occur:

The institution and principal investigator (PI) shall not publish or present data from an individual study center until the complete multi-center study has been presented in full or for 2 years after the termination of the multi-center study, whichever occurs first. Subsequent publications must refer to the multi-center findings. Thereafter, if the PI expects to participate in the publication of data generated from this site, the institution and PI shall submit reports, abstracts, manuscripts, and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 days to respond with any requested revisions, including, without limitation, the deletion of confidential information. The PI shall act in good faith upon requested revisions, except that the PI shall delete any confidential information from such

proposed publication. The PI shall delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

14 REFERENCE LIST

1 Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis. 2007; 44:S27-S72.

2 Niederman MS, McCombs JS, Unger AN, Kumar A, Popovian R. The cost of treating community-acquired pneumonia. Clin Ther. 1998; 20(4):820-37.

3 Spellberg et al. The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America. CID. 2008; 46:155-64.

4 Paterson DL. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. Clin Infect Dis. 2004; 38 Suppl 4:S341-5.

5 NUZYRA® (omadacycline) USPI.

6 FDA. Guidance for Industry, Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment. 2014 CDER.

7 EMA. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 2), European Medicines Agency. 2013. EMA/CHMP/351889/2013.

8 Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine. 1985; 4:213-26.

9 FDA. Guidance for Industry, Population Pharmacokinetics. 1999 CDER.

10 Fine MJ, et al. A Prediction Rule to Identify Low-Risk Patients with Community-Acquired Pneumonia. New England Journal of Medicine. 1997; 336(4): 243-250

Appendix 1 Schedule of Events

Study Phase	**Screening**[b]	**iv Treatment**		**iv or po Treatment**											**EOT and Follow-up**[f]		
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]
					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																
Sample collection for local SARS-CoV-2 molecular testing	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[f]**		
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					
Assessment for po switch or need for continued therapy[t]				X ---------- X													
Investigator's Assessment of Clinical Response															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 and blood cultures in some cases), 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. The blood cultures should be collected within 24 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. Home nursing can be considered for EOT, PTE, and in person FFU visits, if deemed necessary and approved by Sponsor.

[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).
[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..
[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 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 Equations and Conversion Factors

1. Cockcroft-Gault equation to calculate creatinine clearance (CrCl) (relevant to Exclusion Criterion number 9):

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

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

2. Corticosteroid conversions (relevant to Exclusion Criterion number 11):

The following have equivalent glucocorticoid activity[a]

Hydrocortisone	160 mg
Prednisone	40 mg
Prednisolone	40 mg
Methylprednisolone	32 mg
Triamcinolone	32 mg
Dexamethasone	6 mg

[a] Axelrod L. Glucocorticoid therapy. In: Jameson JL & De Groot LJ, eds. Endocrinology. 6th ed. Philadelphia, PA: Saunders; 2010:1840.

Appendix 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
CABP = community-acquired bacterial pneumonia				

Appendix 4 Allowed and Disallowed Prior Antibiotics

Allowed Antibiotics (1 dose within 72 hours prior to randomization*)		Disallowed Antibiotics
Penicillins		
Amoxicillin	Nafcillin	Benzathine/Penicillin-G Procaine
Amoxicillin-Clavulanate	Oxacillin	
Amoxicillin-Sulbactam	Penicillin-G or -V	
Ampicillin	Piperacillin	
Ampicillin-Sulbactam	Piperacillin-Tazobactam	
Dicloxacillin	Ticarcillin-Clavulanate	
Cephalosporins		
Cefaclor	Cefpodoxime	Cefixime (400 mg)
Cefadroxil	Cefprozil	Ceftriaxone
Cefazolin	Ceftaroline	
Cefdinir	Ceftazidime	
Cefepime	Ceftibuten	
Cefixime (200 mg)	Cefuroxime	
Cefditoren	Cephalexin	
Cefotaxime	Loracarbef	
Carbapenems		
Doripenem		
Imipenem		Ertapenem
Meropenem		
Glycopeptides		
Televancin		Dalbavancin
Vancomycin		Oritavancin
Fluoroquinolones		
Ciprofloxacin		Levofloxacin
		Moxifloxacin
Macrolides		
Clarithromycin		Azithromycin
Erythromycin		Clarithromycin XL
Tetracyclines		
Doxycycline (100 mg)		Doxycycline (200 mg)
Minocycline		Minocycline Extended Release
		Tigecycline
Oxazolidinones		
Linezolid		Tedizolid
Miscellaneous		
Clindamycin		
Metronidazole		
Trimethoprim-sulfamethoxazole/Co-trimoxazole		

*Prior (within 72 hours prior to randomization) administration of more than 1 dose potentially effective systemic antibacterial therapy is an exclusion criterion; however, subjects may be eligible for the study despite prior antimicrobial therapy if they received a single dose of a short-acting systemic antibiotic within 72 hours prior to randomization (capped at 25% of randomized subjects). For the purposes of this protocol, short-acting is

defined as having a dosage frequency of more than once a day. If a subject received a prior short-acting systemic antibiotic that is not listed here, the investigator must contact the Medical Monitor to ensure subject eligibility.

Appendix 5 PORT Risk Class Calculation

Adapted from Fine et al 1997*.

PORT Risk Class Calculation Worksheet

Subject Characteristic	Point Assignment	Number of Points Added (+0, +10, +20, etc.)
DEMOGRAPHICS		
Male	Age (years)	**Number of Years:**
Female	Age (years) -10	**Number of Years – 10:**
Nursing home resident[1]	+10	***Exclusionary*** *per this protocol*
Sum of numbers in DEMOGRAPHICS:		

COEXISTING ILLNESSES		
Neoplastic disease[2] ***Potentially*** *exclusionary per this protocol*	+30	
Liver disease[3] ***Potentially*** *exclusionary per this protocol*	+20	
Congestive heart failure[4] ***Potentially*** *exclusionary per this protocol*	+10	
Cerebrovascular disease[5]	+10	
Renal disease[6] ***Potentially*** *exclusionary per this protocol*	+10	
Sum of numbers in COEXISTING ILLNESSES:		

PHYSICAL EXAMINATION FINDINGS		
Altered mental status[7]	+20	
Respiratory rate ≥30/minute	+20	
Systolic blood pressure <90 mm Hg	+20	
Temperature <35°C (95°F) or ≥40°C (104°F)	+15	
Pulse ≥125/minute	+10	
Sum of numbers in PHYSICAL EXAMINATION FINDINGS:		

LABORATORY AND RADIOGRAPHIC FINDINGS		
Arterial pH <7.35[8]	+30	
Blood urea nitrogen ≥30 mg/dL (11 mmol/L)[6]	+20	
Sodium <130 mmol/L	+20	
Glucose ≥250 mg/dL (14 mmol/L)	+10	
Hematocrit <30%	+10	
Partial pressure of arterial oxygen <60 mm Hg or oxygen saturation <90% (by pulse oximetry)	+10	
Pleural effusion	+10	
Sum of numbers in LABORATORY AND RADIOGRAPHIC FINDINGS:		

PORT Score	**Sum of numbers in shaded boxes above:**	

PORT Risk Class	**PORT Score**
I (ineligible for study)	0-50
II (ineligible for study)	51-70
III	**71-90**
IV	**91-130**
V (ineligible for study)	≥131

Before you proceed with signing this form, please use medical records and check yourself with online PORT risk class calculator:
https://qxmd.com/calculate/calculator_248/pneumonia-severity-index-port-score

Name:	**Signature:**	**Date:** **Time:**

1. A nursing home is defined as any residence that provides 24-hour medical supervision. Subjects who reside in a long-term care or subacute/intermediate healthcare facility (eg, nursing home) are excluded from the study and should not be enrolled per Exclusion Criterion number 5.
2. Neoplastic disease is defined as any cancer, except basal or squamous cell cancer of the skin that was active at the time of presentation or diagnosed within one year of presentation. Subjects with neoplastic lung disease are excluded from the study and should not be enrolled per Exclusion Criterion number 15; and subjects who received cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs within the past 3 months should not be enrolled per Exclusion Criterion number 11.
3. Liver disease is defined as a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis. Subjects with cirrhosis that would preclude use of systemic fluoroquinolone antibiotic should not be enrolled per Exclusion Criterion number 8.
4. Congestive heart failure is defined as systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest radiograph, echocardiogram, multiple gated acquisition scan, or left ventriculogram. Subjects with unstable cardiac disease (including acute congestive heart failure) within the 3 months prior to Screening should not be enrolled per Exclusion Criterion number 6.
5. Cerebrovascular disease is defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or CT.
6. Renal disease is defined as a history of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in the medical record. Subjects with history or evidence of severe renal disease or who have a calculated creatinine clearance (CrCl) of < 30 mL/minute, or who require any form of dialysis should not be enrolled per Exclusion Criterion number 9.
7. Altered mental status is defined as disorientation with respect to person, place, or time that is not known to be chronic, stupor, or coma.
8. In cases where the arterial blood gas (ABG) test is not collected as part of hospital routine, no points should be added during PORT score calculation. If ABG test results are available, please ensure that arterial pH value is taken into account for PORT risk class calculation.

Appendix 6 Sponsor Signature

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

Study Number: PTK0796-CABP-19302

Final Date: 19- November-2020

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed:_____ Date:_____

[redacted] MD
VP, Medical and Scientific Strategy

Appendix 7 Investigator's Signature

Study Title:	A Phase 3b Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of IV/PO Omadacycline to IV/PO Moxifloxacin for Treating Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP)
Study Number:	PTK0796-CABP-19302
Final Date:	19-November-2020

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Investigator Name:_____

Investigator Title:_____

Investigator Affiliation:_____

Investigator Address:_____

Investigator Phone Number:_____