Omadacycline for Community-Acquired Bacterial Pneumonia

This supplement contains the following items:

1. Original protocol V1.0
2. Final protocol V2.0
3. Summary of changes protocol V2.0 versus V1.0
4. Original/Final Statistical Analysis Plan V1.0

PROTOCOL PTK0796-CABP-1200

Study Title	A Phase 3 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)
IND Numbers:	75,928 73,431
EudraCT Number:	2013-004071-13
Protocol Number:	PTK0796-CABP-1200
Indication:	Community-Acquired Bacterial Pneumonia
Phase:	3
Investigational Drug:	Omadacycline (PTK 0796)
Dose Form(s):	Intravenous and oral
Sponsor:	Paratek Pharma, LLC A wholly-owned subsidiary of Paratek Pharmaceuticals, Inc. 75 Kneeland Street Boston, MA 02111 USA Tel: +1 617-275-0040
Protocol Version:	Version 1.0
Date:	13-FEB-2015

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1 DISCLOSURE STATEMENT

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: Paul Eckburg, MD, Global Medical Monitor
Phone (during business hours):
Phone (after business hours):
E-mail (not for emergencies):
Address:

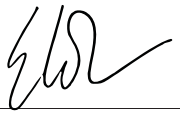
Name/Title: Philippe Vitou, MD, Regional Medical Monitor
Phone (during business hours):
Phone (after business hours):
E-mail (not for emergencies):
Address:

2.2 Additional Contacts

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

3 SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.



Evan Loh, MD Chief Medical Officer Paratek Pharma, LLC	19 February 2015 Date of Signature (DD-MMM-YYYY)	9 AM HST/2 pm EST Time (24-hour clock, time zone)

4 INVESTIGATOR AGREEMENT

I have read the foregoing protocol (PTK0796-CABP-1200) and agree to the following:

The protocol contains all necessary details for carrying out this study;
I will conduct the study as detailed in the protocol and will abide by all its provisions;
I will conduct the study in compliance with the most current versions of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP), all applicable government regulations and the requirements of the IRB that approved the study.
I will train and supervise all individuals delegated to assist me in conducting this study, including providing copies of the protocol and all pertinent information and discussing the material with them to ensure they are fully informed regarding the investigational drug, the protocol and their responsibilities and obligations.
I will use only the informed consent form (ICF) approved by PARATEK (or their designee) and by the IRB responsible for this study.
I will fulfill all requirements for submitting pertinent information to the IRB and to PARATEK, including reportable serious adverse events (SAEs).
I will provide PARATEK (or their designee) with access to any source documents from which case report form information may have been generated.
I understand that the information in this protocol and the referenced Investigator's Brochure (IB) is confidential and that its disclosure to any third parties (other than those involved in approving or conducting the study) is prohibited. I will take the necessary precautions to protect this information from loss, inadvertent disclosure or access by third parties.
I will complete the study within the time designated.
My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the ICH Guideline for GCP, the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature	Date of Signature (DD-MMM-YYYY)	Time (24-hour clock, time zone)

Investigator Name and Title (print)

5 LIST OF ABBREVIATIONS

ABG	Arterial Blood Gas
ABSSSI	Acute Bacterial Skin and Skin Structure Infections
ACM	All-Cause Mortality
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
AUC	Area Under the (Concentration/Time) Curve
BMI	Body Mass Index
BP	Blood Pressure
bpm	beats per minute
CABP	Community-Acquired Bacterial Pneumonia
cc	cubic centimeter
CD4	Cluster of differentiation 4
CE	Clinically Evaluable
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatinine phosphokinase
C_{max}	Maximum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
CrCL	Creatinine Clearance
CSA	Clinical Study Agreement
CSR	Clinical Study Report
cSSSI	Complicated Skin and Skin Structure Infection
CT	Computed Tomography
CXR	Chest X-ray
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

EMA	European Medicines Agency
EMEA	Agency for the Evaluation of Medicinal Products
EOT	End of Treatment
FDA	Food and Drug Administration
FD&C	Food, Drug, and Cosmetic Act
g	Gravity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
HAP	Hospital-Acquired Pneumonia
HCAP	Healthcare-Associated Pneumonia
HDPE	High-Density Polyethylene
hERG	human Ether-à-go-go-Related Gene
β-hCG	beta – human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPFB	Health Products and Food Branch
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
IxRS	Interactive Voice Response System/Interactive Web Response System
LC/MS/MS	Liquid Chromatography/Tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
lpf	Low Power Field

MDR-SP	Multi-drug Resistant *Streptococcus pneumoniae*
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
microITT	Microbiological Intent-To-Treat
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
NI	Non-Inferiority
NS	Normal Saline (0.9% sodium chloride)
PaO_2	Partial pressure of arterial oxygen
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PORT	Pneumonia Severity Index
PT	Preferred Term (MedDRA)
PTE	Post Therapy Evaluation (visit)
PVC	Polyvinyl Chloride
q12h	Every 12 hours
q24h	Every 24 hours
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
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SOC	System Organ Class (MedDRA)
spp.	species (plural)
ss	steady state

TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
TGA	Therapeutic Goods Administration
T_{max}	Time to Maximum Plasma Concentration
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell

6 DEFINITIONS

Term	Definition
Regulation	The term *regulation* refers to all applicable regulations, laws, and guidelines. The regulations may be international, national, or local and may include but are not limited to the Code of Federal Regulations (CFR); the Good Clinical Practice (GCP); Consolidated Guideline (Canada); the International Conference on Harmonisation Guideline for Good Clinical Practice; the Therapeutic Goods Administration Annotated International Conference on Harmonisation Guidelines (Australia); the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.
Regulatory agency	The term *regulatory agency* refers to all health and regulatory agencies with oversight responsibility for the study. These may be international, national, or local and may include but are not limited to the Australian Therapeutic Goods Administration (TGA), the Canadian Health Products and Food Branch (HPFB), the European Agency for the Evaluation of Medicinal Products (EMEA), the United States (US) Food and Drug Administration (FDA).
Sponsor	The term *sponsor* refers to, but is not limited to the sponsor listed in the front of this document and any contract research organization that is being used for the study.
Test article	Any study drug, device, biologic agent, or comparator (including placebo) used in sponsor studies. For test article accountability, this term applies to the above articles when they are required by the protocol and supplied (shipped) by the sponsor (including diluents such as normal saline [NS] for injection).
Adverse Event	An adverse event (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.

7 PROTOCOL SYNOPSIS

Study Title	A Phase 3 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)
Clinical Phase	3
Study Rationale	PTK 0796 (hereafter referred to as omadacycline) is the first member of the aminomethylcycline class of antibiotics, which are semi-synthetic derivatives of the tetracycline class. As a class, the tetracyclines have been in use for over 50 years. They are well-tolerated, and have proven effective in the treatment of a variety of bacterial infections. Omadacycline was evaluated in a Phase 2 study of 219 subjects with complicated skin and skin structure infection (cSSSI) and a sponsor-terminated Phase 3 study that enrolled 143 subjects with cSSSI. Omadacycline was well-tolerated and demonstrated efficacy similar to an established comparator (linezolid). Omadacycline has been shown to have *in vitro* activity against the most common typical and atypical causes of CABP. Further, it has been shown to be effective in animal models of lower respiratory tract infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae.* It is expected that omadacycline will achieve levels in the lower respiratory tract comparable to related tetracyclines (doxycycline and tigecycline) which have been used to successfully treat subjects with CABP. Omadacycline has demonstrated activity against the most common CABP pathogens, including isolates resistant to standards of care. 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 adults with CABP.
Study Objective(s)	**Primary objective:** The primary objective of this study is to demonstrate that omadacycline 100 mg iv every 12 hours (q12h) for 2 doses, followed by 100 mg iv/300 mg po once every 24 hours (q24h) is non-inferior to moxifloxacin 400 mg iv/po q24h in the treatment of adults with 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 (Pneumonia Severity Index [PORT] Risk Class II, III, or IV). Both iv and po phases of the study will be double-blind. Enrollment of subjects with disease characterized as PORT Risk Class II will be limited to no more than 15% of randomized subjects. Enrollment of subjects who have received a single dose of an allowed short-acting antibiotic (see Appendix 1) within the 72 hours prior to the first dose of test article will be limited to no more than 25% of randomized subjects.
Approximate Duration of Subject Participation	Subjects will participate in the study for approximately 30 days. Following Screening, eligible subjects will be randomly assigned to receive 7 to 14 days of treatment with either omadacycline or moxifloxacin. A post therapy evaluation visit will occur approximately 5 to 10 days after the last dose of test article and a follow-up telephone contact will occur approximately 30 to 37 days after the first dose of test article.
Approximate Duration of Study	The study is expected to be clinically complete in approximately 18 months.
Approximate Number of Subjects	750 randomized subjects.
Approximate Number of Study Centers	150
Diagnosis and Main Criteria for Inclusion	1. Written and signed informed consent must be obtained before any assessment is performed. 2. Male or female, age 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 (po or rectal temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F]) • Hypotension with systolic blood pressure (SBP) < 90 mm Hg • Heart rate > 90 beats per minute (bpm) • Respiratory rate (RR) > 20 breaths/minute 5. Has at least 1 clinical sign or laboratory finding associated with

	CABP: • Hypoxemia (partial pressure of arterial oxygen [PaO_2]) < 60 mm Hg by arterial blood gas (ABG) • 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. 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 24 hours prior to the first dose of test article. 7. Has disease categorized as being PORT Risk Class II, III, or IV at Screening (See Appendix 2). 8. Is expected to require a minimum of at least 3 days of iv therapy for the initial treatment of CABP. 9. Females must have a negative urine pregnancy test at Screening and agree to comply with using a highly effective form of birth control (eg, abstinence, po contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, or vasectomized partner) from Screening through post therapy evaluation (PTE). Males must agree to use a highly effective 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 may be eligible despite prior antibacterial therapy if they have been treated with a single dose of a short-acting antibacterial (ie, an antibacterial whose standard dosing regimen is more frequent than once per day, see Appendix 1). 2. Is known or suspected to have CABP caused by a pathogen that may be resistant to either test article (eg, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *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. Subjects with known or suspected hospital-acquired pneumonia (HAP) or healthcare-associated pneumonia (HCAP). HAP is defined as pneumonia with onset of clinical signs and symptoms ≥ 48 hours after hospitalization in an acute in-subject health care facility. HCAP is defined as pneumonia acquired in a long-term care or subacute/intermediate healthcare facility (eg, nursing home) or in a subject admitted with pneumonia following a recent hospitalization (discharged within 90 days of current admission and previously hospitalized for ≥ 48 hours).
5. Has known or is clinically suspected to have 1 or more of the following prior to randomization:
   - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2 × Upper Limit of Normal (ULN),
   - total bilirubin > 1.5 × ULN, or
   - evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy).
6. Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, congestive heart failure, cardiac arrhythmia, etc.) within the 3 months prior to Screening.
7. Are diagnosed with long corrected QT interval (QTc) syndrome, use drugs of potential proarrhythmic or QTc prolonging effect, and/or present with tachyarrhythmia.
8. Requires any form of dialysis (eg, hemodialysis, peritoneal dialysis).
9. History or evidence of severe renal disease or is known to have a calculated creatinine clearance (CrCl) of < 30 mL/minute, using the Cockcroft-Gault equation (see Appendix 4).
10. Evidence of significant immunological disease determined by any of the following:
    - Current or anticipated neutropenia defined as < 500 neutrophils/mm^3
    - Infection with Human Immunodeficiency Virus (HIV) and a cluster of differentiation 4 (CD4) count < 200 cells/mm^3, or another Acquired Immune Deficiency Syndrome (AIDS)-defining illness
    - 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.

11. Requires acute pharmacologic intervention to stabilize blood pressure (BP) and/or adequate tissue perfusion, OR has evidence of septic shock defined by ALL of the following:
    - Fever or hypothermia documented by the investigator (po or rectal temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°C])
    - Heart rate > 90 beats/minute
    - RR > 20 breaths/minute
    - WBC > 12,000 cells/mm^3 or < 4,000 cells/mm^3 or > 10% immature (band) forms regardless of the total peripheral WBC count
    - Hypotension with SBP < 90 mm Hg despite an iv fluid challenge of 20-30 cc/kg over a 30 minute period
    - Perfusion abnormalities that may include, but are not limited to, lactic acidosis (blood lactate concentration ≥ 4 mmol/L), oliguria, or acute alteration in mental status.
12. Known or suspected primary or metastatic neoplastic lung disease, aspiration pneumonia, cystic fibrosis, bronchiectasis, bronchial obstruction (eg, post-obstructive pneumonia), chronic neurological disorder preventing clearance of pulmonary secretions, or severe chronic obstructive pulmonary disease (COPD).
13. Pregnant or nursing (breastfeeding) women.
14. Has a history of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or to any fluoroquinolone antibiotic.
15. Has a history of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
16. Has a history of systemic lupus erythematosus or lupus-like syndrome.
17. Has current evidence of pancreatitis.
18. Has a history of a central nervous system disorder that may predispose to seizures or lower the seizure threshold.
19. Use of other investigational drugs within 5 half-lives or 30 days prior to Screening, whichever is longer.
20. Has previously been treated with omadacycline or previously enrolled in this study.
21. Any planned medical intervention that might interfere with the ability to comply with the study requirements.

	22. 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 adverse events (AEs), or completion of the expected course of treatment.
Prior and Concomitant Treatment	No systemic prior or concomitant antibacterial therapy is allowed, other than a single dose of a short-acting antibacterial (see Exclusion 1 and Appendix 1), within the 72 hours prior to the first dose of test article. All other medications not prohibited by the protocol and considered necessary for the subject's welfare may be administered and/or continued under the supervision of the investigator.
Test Article(s)	Subjects will be randomized (1:1) to 1 of the following 2 treatment arms: • Omadacycline • Moxifloxacin
Dosage and Administration	• Omadacycline 100 mg iv q12h for 2 doses followed by 100 mg iv q24h (starting 24h after first dose), with the option to switch to 300 mg po q24h after a minimum of 3 days (4 doses) of iv treatment. • Moxifloxacin 400 mg iv q24h (with a single placebo infusion to match the omadacycline dosing regimen 12 hours after the first dose on Day 1) with the option to switch to 400 mg po q24h after a minimum of 3 days (4 doses) of iv treatment.
Safety Evaluation	• Physical exams • AEs and SAEs • Vital signs • Laboratory assessments • Electrocardiogram (ECG) • Pregnancy assessments
Efficacy Evaluation	• In order to satisfy different health authority requirements, the primary variables assessing efficacy will be tested with 2 response endpoints: ❖ Successful Early Clinical Response (72-120 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. ❖ Successful Investigator's Assessment of Clinical Response 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 • Assessment of clinical response
Health Outcomes Assessment	• Resource utilization
Pharmacokinetics	• Population PK analysis
Statistical Analysis	A number of subject populations have been defined for the various analyses of efficacy and safety, as follows: • The intent-to-treat (ITT) population will consist of all randomized subjects. • The microbiological intent-to-treat (microITT) 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 *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 received at least 1 dose of test article. A 2-sided 95% confidence interval (CI) approach for the difference in the rate of early clinical 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), 97.5% 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, changes in vital signs, ECGs, and laboratory results obtained from blood samples taken during the study. **Data and Safety Monitoring Committee:** A Data and Safety Monitoring Committee (DSMC) (independent of the sponsor) will provide ongoing monitoring of safety data. Data will be provided to the DSMC as treatment A and treatment B.
Rationale for Number of Subjects	The study is designed to show NI in the primary efficacy outcome of Early Clinical Response 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 the historical data regarding the treatment effect of antibiotics in pneumonia. The sample size determination is based on ensuring sufficient power for the secondary efficacy analyses of Investigator's Assessment of Clinical Response at PTE in the CE and ITT populations (co-primary efficacy outcomes for EMA) as well as the primary efficacy analysis of Early Clinical Response (efficacy outcome for FDA). For the Investigator's Assessment of Clinical Response at PTE endpoint in the ITT population (PORT Risk Class III and IV) assuming an outcome rate of 79% in both treatment groups, NI margin of 10%, 80% power and a 1-sided alpha level of 0.0125 (since 1 CABP study is being conducted), using the sample size determination method of Farrington and Manning (Farrington and Manning, 1990), a total of 638 subjects (PORT Risk Class III and IV) are required. Assuming an 80% evaluability rate, 510 subjects will be available in the CE population. Assuming an 85% response rate in both treatment groups, a 10% NI margin, 1-sided alpha level of 0.0125, there is 81% power to show NI for Investigator's Assessment of Clinical Response at PTE in the CE population. If 15% of enrolled subjects are assumed to have CABP of PORT Risk Class II, a total of 750 subjects are required. For the Early Clinical Response primary efficacy endpoint, with 750 subjects in the ITT population, a response rate of 79% for both treatment groups with a NI margin of 10%, a 1-sided alpha level of 0.025, there is a 92% power to show NI. Assuming the microbiological evaluability rate is 27%, a total of 202 subjects are expected to be in the microITT population. Thus, 750 subjects provides sufficient power for the primary efficacy analyses for both the FDA and EMA regulatory authorities.
Ethical Considerations	This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline of Technical Requirements for Registration of

	Pharmaceuticals for Human use (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. The institutional review board (IRB)/independent ethics committee (IEC)/research ethics board (REB) must review and approve the protocol and informed consent form (ICF) before any subjects are enrolled. The subject must be consented using the approved ICF before any procedures specified in the protocol are performed.

8 STUDY FLOWCHART

Study Phase	**Screening**[b]	**Double-Blind Phase**										**Follow-up Phase**	
	-	iv Treatment Phase				iv or po Treatment Phase							
Study Day[a]		Day 1		Day 2	Day 3	Day 4	Day 5	Day 6[c]	Day 7	Day 10[c]	EOT[d]	PTE[e]	Final Follow-up[f]
		iv dose 1	iv dose 2										
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	
Chest X-ray or CT scan[i]	X												
PORT Risk Class, ABG[j]	X												
Blood and urine samples for local lab hematology/chemistry/urinalysis/pregnancy[k]	X												
Review of Inclusion and Exclusion criteria/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		
Physical examination[m]	X			X	X	X	X	X	X	X	X	X	
Vital signs	X	X[n]	X[n]	X[n]	X	X	X	X	X	X	X	X	
12-lead ECG[o]	X	X		X					X		X		
Blood for Central Lab tests: hematology/chemistry/pregnancy	X[p]					X			X	X	X[p]	X[p]	
Adverse Events[q]	X	X---------- X											

Study Phase	**Screening**[b]	**Double-Blind Phase**										**Follow-up Phase**	
	-	iv Treatment Phase				iv or po Treatment Phase							
Study Day[a]		Day 1		Day 2	Day 3	Day 4	Day 5	Day 6[c]	Day 7	Day 10[c]	EOT[d]	PTE[e]	Final Follow-up[f]
		iv dose 1	iv dose 2										
Prior & Concomitant Medications[r]	X	X----------X											
Plasma samples (in heparin) for PK analyses[s]				X	X	X	X						
Assessment for po Switch or need for continued therapy[t]						X	X	X	X	X			
Investigator's Assessment of Clinical Response											X	X	
Microbiological Procedures													
Blood culture[u]	X	As Clinically Indicated											
Respiratory culture & Gram stain[v]	X										X		
Urine for Local lab *Legionella pneumophila* and *Streptococcus pneumoniae* antigen test	X											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; eCRF = electronic case report form; EOT = end of treatment; ICF = informed consent form; IxRS = Interactive Voice Response System/Interactive Web Response System; PK = pharmacokinetics; PTE = post-therapy evaluation; 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 should be completed within the 24 hours prior to the first dose of test article.

[c] The Day 6 visit is optional for subjects that have been switched to po test article and have been discharged from a hospital setting. A Day 10 visit should be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the EOT visit.

[d] 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.

[e] To be conducted 5 to 10 days after the subject's last day of therapy.

[f] To be conducted 30 to 37 days after the start of the first infusion 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 Successes and had no AEs noted at or after the PTE visit. Otherwise, the visit must be conducted in person.

[g] Written and signed ICF must be obtained before any 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 in Appendix 3.

[i] Subjects must have a confirming CXR or CT scan consistent with acute bacterial pneumonia within the 24 hours prior to the first dose of test article.

[j] Only subjects with a PORT Risk Class of II, III or IV are eligible for enrollment, see Appendix 2.

[k] Local laboratory hematology and chemistry evaluations required for assessing subject eligibility, urinalysis for WBC, a urine pregnancy test (for women only), serum transaminase or bilirubin levels.

[l] The total duration of test article therapy (iv plus po) for all subjects will be at least 7 days and no more than 14 days. The pharmacist or designee will be unblinded to prepare appropriate doses of the IxRS identified test article. An unblinded monitor will perform drug accountability and review the pharmacist's records. Subjects discharged with po test article will be asked to return all unused test article and packaging at each visit (see Section 24). At the EOT visit subjects discharged with po test article will return any remaining unused po test article and site staff will peform accountability.

[m] A full physical examination will be completed at Screening (see Section 14.2.2), thereafter only changes from Screening measurements should be recorded as AEs in the eCRFs.

[n] For the first 3 doses of test article heart rate and BP should be recorded at the following times: just prior to the first infusion, within 30-90 minutes after the start of the first infusion, and at 3.5-5.5 hours after the start of the first infusion (see Table 1 and Section 16.1.2).

[o] A 12-lead ECG should be performed just prior (within 30 minutes) and 30-90 minutes after the start of the first infusion of the first and third doses of test article, at the Day 7 visit, at the EOT visit, and as otherwise clinically indicated (see Section 16.1.4.1).

[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] A subject's AEs and SAEs will be recorded and reported from signing of the ICF to the Final Follow-up assessment.

[r] Treatments that have been administered within the 7 days prior to the date of signing the ICF or during the Screening phase will be recorded in the eCRF. All medications and significant non-drug therapies administered after the first dose of test article must be recorded in the eCRF (see Section 13).

[s] Up to 4 samples will be collected per subject. The PK sample collection schedule for the individual subject will be provided by the sponsor (see Section 19).

[t] At any time after the first 3 days of iv treatment (after 4 iv doses) the subject may be switched to po medication based upon determination of clinical stability. Refer to protocol Section 14.3.1.2 for required criteria to switch to po treatment. At the investigator's discretion, all therapy may be discontinued after the seventh day of

treatment (after 8 iv or po total doses), when the infection is considered clinically cured (based on normalization of the clinical signs and symptoms of infection and the investigator's clinical assessment that continued systemic antibacterial therapy is no longer needed).

[u] If Screening blood cultures are positive for a potential pathogen, blood cultures must be repeated at each visit or more frequently if clinically indicated until negative cultures are obtained. (see Section 16.1.4.3)

[v] Culture and Gram stain from an adequate quality sputum specimen or other respiratory specimen. At the EOT visit respiratory specimen cultures and Gram stains should be obtained only for subjects who are Clinical Failures and require alternative antibacterial treatment for CABP (see Section 17.2.2.1).

9 INTRODUCTION

9.1 Background

Community Acquired Bacterial Pneumonia (CABP) is a leading cause of morbidity and mortality in the United States (US) and throughout the world (Mandell, et al., 2007). 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) (Niederman, et al., 1998). Furthermore, there is increasing resistance to antibiotics among common pathogens, with a resulting critical need for new antibiotics (Spellberg, et al., 2008). 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* (MRSA) and multi-drug resistant *Streptococcus pneumoniae* (MDR-SP) 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 (Paterson DL, 2004). 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.

The investigational product – PTK 0796 (hereafter referred to as omadacycline) – is the first member of the aminomethylcycline class of antibiotics, which are semi-synthetic derivatives of the tetracycline class (Noel, et al., 2012). As a class, the tetracyclines have been in use for over 50 years. They are well-tolerated, and have proven effective in the treatment of a variety of bacterial infections.

Omadacycline is very active *in vitro* against most Gram-positive pathogens. It also exhibits activity against atypical pathogens (eg, *Legionella* species (spp.), *Chlamydophila* spp.), and some anaerobic and Gram-negative pathogens. The drug is active against strains expressing both mechanisms of tetracycline resistance, as well as strains that are resistant to currently available antibiotics, including methicillin, vancomycin, erythromycin, and ciprofloxacin (Omadacycline Investigator's Brochure [IB], Paratek, 2014).

Omadacycline has been shown to have *in vitro* activity against the most common typical and atypical causes of CABP including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and *Legionella pneumophila*. Omadacycline has potent activity against each of these pathogens and is not affected by tetracycline, penicillin, macrolide (inducible or constitutive ribosome methylation or efflux), or quinolone resistance in *Streptococcus pneumoniae*, nor penicillin or macrolide resistance in *Haemophilus influenzae*. Omadacycline has potent activity against methicillin-susceptible *Staphylococcus aureus* (MSSA) and is equally

potent against multi-drug resistant MRSA. In addition, omadacycline has demonstrated activity against *Chlamydophila pneumoniae* using a macrophage culture system and is expected to be active against *Mycoplasma pneumoniae* based on mechanism of action, intracellular penetration, and the activity of the tetracycline family. The *in vitro* activity of omadacycline was not affected by serum or lung surfactant, an important characteristic that is consistent with potential utility in infections involving the lower respiratory tract. Further, it has been shown to be effective in animal models of lower respiratory tract infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. It is expected that omadacycline will achieve levels in the lower respiratory tract comparable to related tetracyclines (doxycycline and tigecycline) which have been used to successfully treat subjects with CABP.

Omadacycline has been developed for both intravenous (iv) and oral (po) administration and has been well characterized in 16 Phase 1 studies. In addition, omadacycline has been evaluated in a randomized Phase 2 safety and efficacy study of 219 subjects with complicated skin and skin structure infections (cSSSI) and in a sponsor-terminated (for administrative reasons) randomized Phase 3 study that enrolled 143 subjects with cSSSI. Within the limits of the study sizes, omadacycline demonstrated numerical efficacy similar to an established comparator (linezolid) (Noel, et al., 2012; Paratek, 2014).

In the Phase 1 studies, 536 subjects were exposed to omadacycline iv or po formulations and 83 were exposed to placebo. Single iv doses up to 600 mg and single po doses up to 600 mg have been investigated. Multiple iv doses of 100 mg once daily and 200 mg once daily for up to 14 and 7 consecutive days, respectively, have been investigated. Multiple po doses of 200 mg once daily and 300 mg once daily for up to 10 consecutive days have also been investigated. In a Phase 2 study, 219 subjects with cSSSI were treated with omadacycline (n = 111) or linezolid (n = 108) for a mean of 10 and maximum of 20 days. In the sponsor-terminated Phase 3 study, 140 subjects with cSSSI were treated with omadacycline (n = 68) or linezolid (n = 72) for a mean of 10 and maximum of 20 days for omadacycline and 22 days for linezolid.

In Phase 1 studies, there were no discontinuations due to drug-related adverse events (AEs) in any subject who received multiple doses of omadacycline. An increased incidence of gastrointestinal (GI) AEs, particularly nausea, was noted in early po studies.

In iv studies in healthy subjects, modest and reversible alanine aminotransferase (ALT) increases were seen most notably with iv doses of 300 mg or greater (3 × higher than the therapeutic dose of 100 mg iv). There were no differences in ALT changes in the Phase 2 study compared to linezolid. Transient increases in heart rate were observed following administration of single and multiple doses of omadacycline, with a dose dependent mean increase of up to 15-20 beats per minute (bpm) compared to placebo for the first 4 hours after dosing. The increases in heart rate were not reported as AEs and not associated with any other cardiac findings. These increases were observed most consistently during the 2 hours immediately post-infusion. Beyond 6 hours after the start of the infusion, heart rate in all subjects, including controls, were comparable. A listing of all Phase 1 AEs is provided in Appendix I of the IB (Paratek, 2014).

In the Phase 2 study, omadacycline was well-tolerated. The most frequently reported AEs were GI-related occurring in 21 (18.9%) of 111 omadacycline-treated, and 18 (16.7%) of 108 linezolid-treated subjects. Nausea and vomiting were reported in 11 (9.9%) and 5 (4.5%), respectively, of omadacycline-treated subjects primarily during po treatment, compared to 8 (7.4%) and 4 (3.7%), respectively, of linezolid-treated subjects. Premature discontinuation of treatment due to an AE was very infrequent, occurring in 0.9% and 1.9% of omadacycline and linezolid-treated subjects, respectively.

There was no pattern of adverse changes in laboratory safety parameters among subjects treated with omadacycline or linezolid; changes in omadacycline-treated subjects were comparable to those observed with linezolid. In particular, there was no clinical or statistical difference between the treatment groups in ALT values or in other liver function tests (LFTs).

An increase in mean heart rate was observed, but to a much lesser extent than what was observed in Phase 1 studies. During the first 4 hours following the start of the first infusion of omadacycline there was a mean increase in heart rate from Baseline of 2.5 bpm for omadacycline (range from -20 to 40 bpm), peaking at 4 hours, as compared to a slight decrease of -0.1 bpm effect on heart rate for the linezolid treatment arm (range from -21 to 22 bpm), $p = 0.005$. This effect was transient and no QT prolongation was observed, consistent with the omadacycline thorough corrected QT interval (QTc) and human Ether-à-go-go-Related Gene (hERG) studies. Three subjects treated with omadacycline had AEs of tachycardia; 1 other subject reported palpitations. All 4 of these AEs were mild in intensity, all were assessed as either unrelated or unlikely related to test article, and none resulted in discontinuation of study treatment. Three of these AEs occurred during the first week of treatment; 1 AE occurred 8 days after completing therapy and was associated with a new infection (at a different site).

A Phase 3 cSSSI study enrolled 143 subjects prior to being discontinued due to a change in the Food and Drug Administration (FDA) Guidance for the development of antimicrobials for acute bacterial skin and skin structure infections (ABSSSI). The overall incidence of reported AEs in this study was comparable between the 2 treatment groups. The most commonly reported AEs (≥ 10% frequency in either treatment group) were nausea (26.5% omadacycline, 26.4% linezolid), headache (23.5% omadacycline, 6.9% linezolid), vomiting (8.8% omadacycline, 15.3% linezolid), diarrhea (4.4% omadacycline, 18.1% linezolid), and dizziness (10.3% omadacycline, 8.3% linezolid). Creatinine phosphokinase (CK) elevation was reported in 8.8% of omadacycline-treated subjects compared to 2.8% for linezolid. AEs associated with ALT increases were reported in 4 linezolid-treated subjects (5.6%) compared to 1 omadacycline subject (1.5%). Six linezolid subjects (8.3%) reported rash compared to 1 subject (1.5%) on omadacycline. Four subjects experienced serious adverse events (SAEs) (3 omadacycline and 1 linezolid). The 3 omadacycline SAEs consisted of small bowel obstruction, large left pleural effusion, and worsening depression. The 1 linezolid SAE consisted of worsening right hand cellulitis.

For full details of safety findings in nonclinical and clinical studies, see the IB (Paratek, 2014).

Omadacycline has demonstrated activity against the most common CABP pathogens, including isolates resistant to standards of care. 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 CABP.

10 STUDY OBJECTIVES

10.1 Primary Objective

The primary objective of this study is to demonstrate that omadacycline 100 mg iv once every 12 hours (q12h) for 2 doses, followed by 100 mg iv/300 mg po once every 24 hours (q24h) is non-inferior to moxifloxacin 400 mg iv/po q24h in the treatment of adults with CABP.

10.2 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.

11 STUDY DESIGN

11.1 Description

This is a randomized (1:1), double-blind, active comparator-controlled, Phase 3 study comparing omadacycline and moxifloxacin for the treatment of adults with CABP. The number of subjects in Pneumonia Severity Index (PORT) Risk Class II will be limited to no more than 15% of randomized subjects. Subject randomization will be stratified by PORT Risk Class (II or III/IV), receipt of an allowed antibacterial therapy (see Appendix 1) in the 72 hours prior to study treatment, and geographic region as defined in the Interactive Voice Response System/Interactive Web Response System (IxRS) specifications and statistical analysis plan (SAP) (see Section 25.1). All subjects are expected to present with CABP severe enough to require a minimum of at least 3 days of iv treatment.

The study will consist of 3 phases: Screening, Double-Blind Treatment and Follow-up. All Screening procedures should be performed within 24 hours prior to the first dose of double-blind treatment if eligible.

11.2 Rationale of Study Design

The study was designed in accordance with the FDA (FDA, 2014) and European Medicines Agency (EMA) (EMA 2011; EMA 2013) guidance on developing antimicrobial drugs for the treatment of CABP, in addition to the guidelines created jointly by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (Mandell, et al., 2007).

11.3 Rationale for Choice of Comparator

Given the wide acceptance of fluoroquinolone monotherapy as a safe, first-line option for treating subjects with CABP, the comparator drug for this study was selected to be moxifloxacin (400 mg iv q24h with the option to transition to 400 mg po q24h). 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.

11.4 Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 30 days. Following Screening, eligible subjects will be randomly assigned to receive 7 to 14 days of treatment with omadacycline or moxifloxacin. A follow-up office visit will occur 5 to 10 days after the last dose of test article, and another follow-up telephone contact will occur approximately 30 to 37 days after the first dose of test article.

11.5 Approximate Duration of Study

This study will be clinically complete in approximately 18 months.

11.6 Approximate Number of Subjects

Approximately 750 subjects will participate in this study at up to approximately 150 sites.

12 SELECTION OF SUBJECTS

Each subject must participate in the informed consent process and sign and date an institutional review board (IRB) or independent ethics committee (IEC) or research ethics board (REB) approved informed consent form (ICF) before any procedures specified in this protocol are performed.

12.1 Inclusion Criteria

To be eligible for randomization in this study, a subject must fulfill ALL of the following criteria:

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 (po or rectal temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
   - Hypotension with systolic blood pressure (SBP) < 90 mm Hg
   - Heart rate > 90 bpm
   - Respiratory rate (RR) > 20 breaths/minute.
5. Has at least 1 clinical sign or laboratory finding associated with CABP:
   - Hypoxemia Partial pressure of arterial oxygen (PaO_2) < 60 mm Hg by arterial blood gas (ABG)
   - 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. 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 24 hours prior to the first dose of test article.
7. Have disease categorized as being PORT Risk Class II, III, or IV at Screening (See Appendix 2).
8. Are expected to require a minimum of at least 3 days of iv therapy for the initial treatment of CABP.
9. Females must have a negative urine pregnancy test at Screening and agree to comply with using a highly effective form of birth control (eg, abstinence, po contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, or vasectomized partner) from Screening through post therapy evaluation (PTE). Males must agree to use a highly effective method of birth control with female partner(s) and must not donate sperm from Screening through PTE.

12.2 Exclusion Criteria

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 may be eligible despite prior antibacterial therapy if they have been treated with a single dose of a short-acting antibacterial (ie, an antibacterial whose standard dosing regimen is more frequent than once per day, see Appendix 1).

2. Is known or suspected to have CABP caused by a pathogen that may be resistant to either test article (eg, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *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. Subjects with known or suspected hospital-acquired pneumonia (HAP) or healthcare-associated pneumonia (HCAP). HAP is defined as pneumonia with onset of clinical signs and symptoms ≥ 48 hours after hospitalization in an acute in-subject health care facility. HCAP is defined as pneumonia acquired in a long-term care or subacute/intermediate healthcare facility (eg, nursing home) or in a subject admitted with pneumonia following a recent hospitalization (discharged within 90 days of current admission and previously hospitalized for ≥ 48 hours.
5. Has known or is clinically suspected to have 1 or more of the following prior to randomization:
    - ALT or aspartate aminotransferase (AST) ≥ 2 × Upper Limit of Normal (ULN),
    - total bilirubin > 1.5 × ULN, or
    - evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy).
6. Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, congestive heart failure, cardiac arrhythmia, etc.) within the 3 months prior to Screening.
7. Are diagnosed with long QTc syndrome, use drugs of potential proarrhythmic or QTc prolonging effect and/or present with tachyarrhythmia.
8. Requires any form of dialysis (eg, hemodialysis, peritoneal dialysis).
9. History or evidence of severe renal disease or is known to have a calculated creatinine clearance (CrCL) < 30 mL/minute, using the Cockcroft-Gault equation (see Appendix 4).
10. Evidence of significant immunologic disease determined by any of the following:
    - Current or anticipated neutropenia defined as < 500 neutrophils/mm^3
    - Infection with human immunodeficiency virus (HIV) and a cluster of differentiation 4 (CD4) count < 200 cells/mm^3, or another Acquired Immune Deficiency Syndrome (AIDS)-defining illness
    - 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
11. Requires acute pharmacologic intervention to stabilize blood pressure (BP) and/or adequate tissue perfusion, OR has evidence of septic shock, defined by ALL of the following:
    - Fever or hypothermia documented by the investigator (po or rectal temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
    - Heart rate > 90 beats/minute
    - RR > 20 breaths/minute
    - WBC > 12,000 cells/mm^3 or < 4000 cells/mm^3 or > 10% immature [band] forms regardless of the total peripheral WBC count

- Hypotension with SBP < 90 mm Hg despite an iv fluid challenge of 20-30 cc/kg over a 30 minute period
- Perfusion abnormalities that may include but are not limited to lactic acidosis (blood lactate concentration ≥ 4 mmol/L), oliguria, or acute alteration in mental status.

12. Known or suspected primary or metastatic neoplastic lung disease, aspiration pneumonia, cystic fibrosis, bronchiectasis, bronchial obstruction (eg, post-obstructive pneumonia), chronic neurological disorder preventing clearance of pulmonary secretions, or severe chronic obstructive pulmonary disease (COPD).
13. Pregnant or nursing (breastfeeding) women.
14. Has a history of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or to any fluoroquinolone antibiotic.
15. Has a history of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
16. Has a history of systemic lupus erythematosus or lupus-like syndrome.
17. Has current evidence of pancreatitis.
18. Has a history of a central nervous system disorder that may predispose to seizures or lower the seizure threshold.
19. Use of other investigational drugs within 5 half-lives or 30 days prior to Screening, whichever is longer.
20. Has previously been treated with omadacycline or previously enrolled in this study.
21. Any planned medical intervention that might interfere with the ability to comply with the study requirements.
22. 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.

12.3 Screen Failures

Subjects who sign the ICF but withdraw or are withdrawn from the study before random assignment to a 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 electronic case report form (eCRF) or IxRS system for screen failures.

13 PRIOR AND CONCOMITANT TREATMENT

Treatments that have been administered within the 7 days prior to the date of informed consent, or during the Screening period, 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 recorded as concomitant medications/significant non-drug therapies in the eCRF.

13.1 Permitted Treatment

Any concomitant treatment that is not prohibited explicitly in the protocol is permitted. A single dose of a short-acting potentially effective systemic antibacterial agent (see list in Appendix 1) administered within the 72 hours prior to the first dose of test article will be allowed for 25% or less of randomized subjects. Subjects requiring additional or alternative antibacterial therapy for 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.

13.2 Prohibited Treatment

The following treatments are prohibited:

All investigational medications or devices used during the 30 days prior to Screening are prohibited. Long-acting systemic antibacterial agents potentially effective for CABP are prohibited for 72 hours prior to randomization and concomitantly (see list in Appendix 1).

During po treatment, subjects will be instructed to avoid taking antacids and multivitamins.

13.3 Prohibited Concomitant Medications that may Interact with Moxifloxacin

Use of proarrhythmic or QTc prolonging medications is prohibited. 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.

14 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 should then be assigned a study subject number. AEs must be recorded from the time the ICF is signed. Subjects who have been pre-screened and 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.

14.1 Visit Schedule and Assessments

Refer to STUDY FLOWCHART for the study procedures and their time points. There are 3 protocol defined phases of the study: Screening, Double-Blind Treatment and Follow-up. The study will have the following protocol-defined evaluations:

- Visits will be conducted daily on study Days 1 through 7. The Day 6 visit is optional for subjects that have been switched to po test article and have been discharged from a hospital setting. A Day 10 visit should be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the End of Treatment (EOT) visit.

- End of Treatment: to 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 before completion, the EOT visit should be conducted.
- PTE: to be performed 5 to 10 days after the subject's last day of therapy.
- Final Follow-up assessment: Study Day 30 to 37 (after start of first infusion of test article).

Subjects who discontinue study treatment prematurely should have the EOT visit and the procedures listed for that visit in the STUDY FLOWCHART, a PTE visit and a Final Follow-up assessment, if possible. The site should also collect subject safety information through the Final Follow-up assessment.

14.2 Screening Phase

Due to the nature of the disease under study, the Screening period should be completed within 1 day (24 hour period). The Screening will be used to establish subject eligibility and Baseline characteristics for each subject. Subjects are eligible for Screening if they present with CABP. Following the signing of an ICF, site personnel will collect the following information:

- Demographics
- Medical/surgical history and current medical conditions
- Physical examination
- Vital signs
- Review of inclusion/exclusion criteria
- Local and Central Laboratory tests: hematology, chemistry, urinalysis, pregnancy test (for women only)
- 12-lead electrocardiogram (ECG)
- Concomitant medications (past 7 days)
- AEs since the signing of the ICF
- Assessment of CABP symptom severity (cough, sputum production, pleuritic chest pain, dyspnea) (See Appendix 3 for symptom severity scale)
- Radiologic (CXR or CT scan) evaluation of pneumonia
- ABG and PORT Risk Class Assessment
- Microbiological assessments (blood culture, respiratory culture & Gram stain, local lab urine antigen tests, and blood for Central Lab testing)

14.2.1 Subject Demographics/Other Baseline Characteristics

Subject demographic and Baseline characteristic data to be collected on all subjects include: date of birth, gender, race, ethnicity and childbearing potential. Medical history/current medical

condition data includes data until the signing of informed consent. Whenever possible, diagnoses are to be recorded.

The investigator will perform a comprehensive history and physical examination at the Screening evaluation with particular attention to items indicated below.

14.2.1.1 Medical History Relating to the Infection Under Study

- 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.).
- History of pneumococcal vaccination (eg, Pneumovax, Prevnar 13).
- All systemic antimicrobials from onset of the infection will be recorded under concomitant medications.

14.2.2 Physical Examination

At Screening, the physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams may be performed. Height and body weight will be measured.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of test article must be included in the subject's eCRF.

14.2.3 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 (see Section 12.1).

14.2.4 Radiologic Evaluation of Pneumonia

A CXR or CT scan will be obtained for all subjects at Screening (within 24 hours prior to the first dose of test article). 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.

14.2.5 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 2). As part of the Inclusion Criteria to this study, all subjects must have disease characterized as PORT Risk Class of II, III, or IV at randomization.

14.2.6 Urinalysis

A urine dipstick will be performed during Screening. Urine WBC results will be recorded on the eCRF. A urine pregnancy test will be performed during Screening for all women. Urine will also be tested at Screening for the presence of *Legionella pneumophila* and *Streptococcus pneumoniae* antigens.

14.3 Double-blind Treatment Phase

14.3.1 Assessments While on Test Article

The double-blind treatment period is up to 14 days in duration. Subjects who met inclusion criteria and did not meet exclusion criteria will be randomly assigned to a treatment group, and should receive their first dose of test article.

The following assessments (see STUDY FLOWCHART) will be done:

- Vital signs
- Physical examinations (worsening of observations since the Screening examination will be recorded as AEs)
- AEs
- Concomitant treatments
- CABP symptom severity scale (performed by the investigator)
- Microbiological assessments
- ECG (should be performed just prior [within 30 minutes] and 30-90 minutes after the start of the first infusion of the first and third doses of test article, at the EOT visit, and as otherwise clinically indicated)
- Blood for Central Laboratory assessments: hematology, chemistry, pregnancy (for women only)
- Test article administration and accountability
- Assessment for po switch or need to continue therapy

Investigator's assessment of clinical response

14.3.1.1 Intravenous Treatment Phase (Test Article)

The iv treatment phase (minimum of 3 days, 4 doses) will follow a double-dummy design with placebo infusions matched to active omadacycline and moxifloxacin infusions as shown in Table 1. Infusions of omadacycline and matched placebo will be administered continuously over approximately 30 minutes. During the first 24 hours of iv treatment, subjects on the moxifloxacin treatment arm will receive a placebo infusion to match the t = 12h infusion in the omadacycline arm as shown in Table 1.

Infusions of moxifloxacin and matched placebo will be administered continuously over approximately 60 minutes. All infusion start and stop times are to be recorded in 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. If gravity administration is not the standard of care then an infusion pump may be used. If an infusion pump is used then a potentially unblinded administrator will be required (see Section 25.3). All subjects should remain in a hospital setting while on iv test article (for a minimum of 3 days, 4 doses). Thereafter, subjects should not be discharged from the hospital prior to completion of protocol specified assessments, except in circumstances where the Principal Site Investigator has clearly identified that sufficient resources and processes are available to complete all study procedures as defined in the protocol and the sponsor has reviewed and approved the process for outpatient iv test article administration.

Table 1 Treatment Regimens for IV Test Article

Infusion Regimen[a]	Omadacycline Arm[b,c]	Moxifloxacin Arm[b,c]
t = 0h[d]	omadacycline 100 mg in 100 mL NS 250 mL NS placebo	100 mL NS placebo moxifloxacin 400 mg in 250 mL 0.8% saline
t = 12h	omadacycline 100 mg in 100 mL NS	100 mL NS placebo
t = 24h[d]	omadacycline 100 mg in 100 mL NS 250 mL NS placebo	100 mL NS placebo moxifloxacin 400 mg in 250 mL 0.8% saline
t = 48h[d]	omadacycline 100 mg in 100 mL NS 250 mL NS placebo	100 mL NS placebo moxifloxacin 400 mg in 250 mL 0.8% saline
t = 72h[e], then q24h[d]	omadacycline 100 mg in 100 mL NS 250 mL NS placebo	100 mL NS placebo moxifloxacin 400 mg in 250 mL 0.8% saline

Table 1 Treatment Regimens for IV Test Article

Infusion Regimen[a]	Omadacycline Arm[b,c]	Moxifloxacin Arm[b,c]

t = time; NS = Normal saline (0.9% sodium chloride) for injection; q12h = every 12 hours; q24h = every 24 hours.

[a] The start time of the first infusion is designated time 0 (t = 0h), followed by 2 q12h doses (t = 12h, t = 24h), and then all subsequent doses are q24h for a minimum of 3 days, 4 doses of iv treatment (through t = 48h). See Section 14.3.1.1.2 for allowed adjustments in iv dosing schedules.

[b] All 100 mL infusions of omadacycline or 100 mL NS placebo are administered continuously over 30 minutes (at least 30 minutes and not more than 45 minutes).

[c] All 250 mL infusions of moxifloxacin or 250 mL NS placebo are administered continuously over approximately 60 minutes.

[d] At these time points a 100 mL infusion will be administered first, followed by a 250 mL infusion. It is important to follow this sequence of administration.

[e] Beginning with the fifth dose (t = 72h), based on the investigator decision the therapy could be iv or switch to po therapy.

14.3.1.1.1 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 based on the overall clinical assessment of the subject:

- continue iv test article;
- switch to po test article (after a minimum of 3 days [4 doses] of iv therapy);
- discontinue test article – this decision will prompt the EOT evaluation.

Each daily decision is to be recorded on source documents and the information transferred to eCRFs by blinded study site personnel.

Note the following:

- At all times during the study the decision to continue iv, switch to po, or discontinue test article is made based on the clinical judgment of the investigator.
- The investigator may use the culture and susceptibility results from the local microbiology laboratory to help guide therapy; however, decisions to continue or discontinue test article should be based on clinical response rather than susceptibility results (as omadacycline susceptibility testing is not available at the local site). If the CABP is caused by a microorganism that is not susceptible to moxifloxacin *in vitro,* the decision to continue or discontinue study treatment should be based on the subject's clinical course and the investigator's clinical judgment. These cases should be discussed with the Medical Monitor. The rationale for this decision should be recorded in source documents.

14.3.1.1.2 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, 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.

14.3.1.2 Switch to Oral Treatment

The decision to switch to po treatment should be made by the investigator. For a subject to be considered clinically stable and meet criteria for transition to a po regimen, they must have the following findings noted in source documents and recorded on the eCRF:

- Temperature ≤ 37.8°C (100°F), measured orally or rectally
- Heart rate ≤ 100 beats/minute
- RR ≤ 24 breaths/minute
- SBP ≥ 95 mm Hg
- Oxygen saturation ≥ 90% as measured by pulse oximetry or PaO_2 ≥ 60 mm Hg by ABG
- No worsening of CABP symptoms (cough, sputum production, pleuritic chest pain, dyspnea) compared to Screening
- Normal mental status ("absence of confusion" or pre-illness Baseline for subjects who did not have normal mental status before onset of pneumonia)
- Ability to maintain po intake.

Switch to po will NOT be permitted until after the subject has completed at least the first 3 days of iv treatment (4 doses).

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. For subjects that have been switched to po test article and discharged from the hospital prior to study Day 6, visits must be conducted on study Days 4 and 5, while a study Day 6 visit is optional.

14.3.1.3 Oral Treatment Phase (Test Article)

Treatment regimens for po dosing are shown in Table 2. 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 12 to 24 hours after the last iv dose.

The po treatment phase will employ a double-blind, double-dummy design using omadacycline placebo comparator tablets of matching size and shape to active omadacycline tablets and matching over-encapsulated placebo and active moxifloxacin tablets.

To maintain investigator and subject blinding, subjects on both arms will receive 2 tablets and 1 over-encapsulated tablet in the morning as shown in Table 2 below.

Table 2 Treatment Regimens for Oral Test Article

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

[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.

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 7-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.

14.3.1.3.1 Management while on Oral Test Article

While the subject is receiving po therapy, the investigator should assess the subject on study Day 7, 10 and 14 and choose 1 of the following actions:

- continue po test article;
- discontinue test article – this decision will prompt the EOT evaluation.

The date, time and the decision of the investigator will be recorded on source documents and the information transferred to eCRFs by study site personnel.

The investigator may use the culture and susceptibility results from the local microbiology laboratory to help guide therapy; however, decisions to continue or discontinue test article should be based on clinical response rather than susceptibility results (as omadacycline susceptibility testing is not available at the local site). If the CABP is caused by a microorganism that is not susceptible to moxifloxacin *in vitro,* the decision to continue or discontinue study treatment should be based on the subject's clinical course and the investigator's clinical judgment. These

cases should be discussed with the Medical Monitor. The rationale for this decision should be recorded in the source documents.

14.3.2 Permitted Dose Adjustments and Interruptions of Test Article

None.

14.4 Follow-up Phase

Subjects will be evaluated at 2 visits after the completion of treatment: at the PTE 5 to 10 days after the last treatment day and at a Final Follow-up assessment 30 to 37 days after the first dose of treatment (see STUDY FLOWCHART). 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 AEs noted at or after the PTE visit. Otherwise, this assessment is to be performed with an in person study visit.

14.5 Total Volume of Blood Collected

The total volume of blood collected from each subject for this protocol will be up to approximately 170 mL depending on the subject's duration of study participation.

15 TEST ARTICLE AND ADMINISTRATION

Test article will be supplied by Paratek Pharma, LLC (the sponsor). Test article will be labeled according to regulations.

The test article 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.

15.1 Test Article Administration

Subjects will be randomized (1:1) to 1 of the following 2 treatment arms:

- Investigational therapy: omadacycline, 100 mg iv q12h (first 2 doses), followed by 100 mg iv q24h (starting 24 hours after first dose), with the option to switch to 300 mg (two 150 mg omadacycline tablets and 1 over-encapsulated placebo tablet matching moxifloxacin) po q24h after at least 3 days (4 doses) of iv treatment.
- Reference therapy: moxifloxacin, 400 mg iv q24h (with a single placebo infusion to match the omadacycline dosing regimen 12 hours after the first dose on Day 1) with the option to switch to 400 mg (one 400 mg moxifloxacin over-encapsulated tablet and 2 placebo tablets matching omadacycline tablets) po q24h after at least 3 days (4 doses) of iv treatment.

All subjects should receive at least 7 days and at most 14 days (iv and po combined) of test article therapy.

15.1.1 Identity of the Investigational Product

Table 3 Intravenous Formulation

Active ingredient	Omadacycline
[redacted]	[redacted]

Table 4 Oral Formulation

Active ingredient	Omadacycline
[redacted]	[redacted]

15.2 Investigational and Comparator Test Article

15.2.1 Investigational Test Article: Omadacycline

- 100 mg iv q12h for first 2 doses followed by 100 mg iv q24h (starting 24 h after first dose)
- 300 mg po q24h after completion of at least 3 days (4 doses) of iv treatment at the discretion of the investigator and meeting minimum criteria for po switch as outlined in Section 14.3.1.2
- Total treatment duration of 7 to 14 days

15.2.2 Comparator Test Article: Moxifloxacin

- 400 mg iv q24h (with a single placebo infusion to match the omadacycline dosing regimen 12 hours after the first dose on Day 1)
- 400 mg po q24h after completion of at least 3 days (4 doses) of iv treatment at the discretion of the investigator and meeting minimum criteria for po switch as outlined in Section 14.3.1.2
- Total treatment duration of 7 to 14 days

15.3 Subject Compliance while on Oral Test Article

Intravenous administration and compliance will be managed by study personnel prior to switching to po test article. Study personnel at the site, should monitor po test article compliance at each study visit, by comparing the returned test article with the dosing information reported in the subject charts. 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.

16 SAFETY

Any subject who receives at least 1 dose of test article will be included in the evaluation for safety.

Safety is assessed by the following measures:

- Physical exams
- AEs and SAEs
- Vital signs
- Laboratory assessments
- ECG
- Pregnancy assessments

16.1.1 Physical Examinations

After Screening, a physical examination should be conducted on the study days indicated in the STUDY FLOWCHART and at the EOT and PTE visits. Any abnormalities or changes in intensity noted during the review of the body systems should be documented in the source documents. If a new clinically significant finding occurs (ie, not noted at Screening) after the Screening exam, it must be captured as an AE. In addition, resolution of any clinically significant abnormal findings that have been reported as an AE will be noted in the medical record and the AE eCRF.

16.1.2 Vital Signs

Vital signs including temperature, BP, pulse/heart rate, and RR should be recorded prior to each infusion while the subject is on iv treatment. Thereafter vital signs should be recorded at all visits, with the exception of the Final Follow-up visit.

- In addition, for the first 3 doses of test article (t = 0 hours, t = 12 hours, t = 24 hours; see Table 1) heart rate and BP should be recorded at the following times: just prior to the first infusion, within 30-90 minutes after the start of the first infusion, and again 3.5-5.5 hours after the start of the first infusion.

All vital signs should be captured after 10 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 validated device, with an appropriately sized cuff.

Pulse will be measured using an automated validated device, when available. If not available, pulse will be measured manually.

In addition to the above, BP and heart rate may be measured whenever clinically indicated at the discretion of the treating physician. Any subject who experiences an AE of non-pleuritic cardiac chest pain, palpitations, or tachyarrhythmia while on study should have an ECG and an evaluation by the investigator (see Section 16.1.4.1).

Temperature will be obtained using an electronic (rapid reading) device whenever possible.

RR will be determined by observation.

Once the subject is discharged from the hospital, vital signs will be recorded at each return clinical visit by blinded study personnel.

16.1.3 Laboratory Evaluations

Blood samples for hematology, chemistry and coagulation (prothrombin time only) should be drawn at Screening, Day 4, Day 7, Day 10, EOT, and PTE (see STUDY FLOWCHART). At Screening only, 1 sample will be analyzed at a local laboratory for confirmation of eligibility criteria and a second sample will be shipped to the Central Laboratory for analysis. At all other visits samples should be shipped to the Central Laboratory for analysis.

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 meeting inclusion/exclusion criteria, it is expected that local laboratory testing will be used in circumstances where this testing is needed to assess a subject's WBC count or differential, serum transaminase or bilirubin levels, serum creatinine or pregnancy testing (for women only).

16.1.3.1 Hematology

The analytes listed in the table below (Table 5) will be measured at the Central Laboratory.

Table 5 Hematology Panel

Hematocrit	White blood cell differential (as % cell counts)
Total red blood cell count	-Neutrophils
Mean cell hemoglobin	-Lymphocytes
Mean cell hemoglobin concentration	-Monocytes
Mean cell volume	-Eosinophils
WBC count	-Basophils
Platelet count	

16.1.3.2 Clinical Chemistry

The analytes indicated in the table below (Table 6) below will be measured at the Central Laboratory.

Table 6 Clinical Chemistry Panel

Blood glucose	ALT	LDH
Urea	AST	CK
Creatinine	AP	(CK isoenzyme testing as required)
Sodium	Total bilirubin	Calcium
Potassium	Total protein	Phosphate
Chloride	Magnesium	Cholesterol
Bicarbonate	Albumin	Uric Acid
		GGT
		Amylase
		Lipase

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AP = alkaline phosphatase; LDH = lactate dehydrogenase; CK = creatine phosphokinase; GGT = gamma-glutamyl transpeptidase.

16.1.3.3 Other laboratory tests

Table 7 Additional Laboratory Tests

Category	Test	Note
Coagulation	INR	Prothrombin time only
Female endocrinology	β-hCG (for women only)	See Section 16.1.4.2 below. Done both locally (urine) and centrally (serum)

INR = international normalized ratio; β-hCG = beta – human chorionic gonadotropin.

16.1.4 Safety Studies to be Performed Locally

16.1.4.1 Electrocardiogram

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

- Just prior (within 30 minutes) to the start of the first infusion of the first dose of test article (t = 0h on Table 1)
- 30-90 minutes after the start of the first infusion of the first dose of test article
- Just prior (within 30 minutes) to the start of the first infusion of the third dose of test article (t = 24h on Table 1)
- 30-90 minutes after the start of the first infusion of the third dose of test article
- At the Day 7 visit
- At the EOT visit
- In any case in which a subject develops an AE of non-pleuritic cardiac chest pain, palpitations, tachyarrhythmia or as otherwise clinically indicated (see Section 16.1.2)

Reading and interpretation of the ECG will be performed centrally and provided to the investigator. The investigator is responsible for reviewing interpretations and for retaining hard copies of the reports.

16.1.4.2 Pregnancy and Assessments of Fertility

All women will have a urine pregnancy test at the site at the Screening visit. Urine pregnancy test kits will be provided by the sponsor through the Central Laboratory. If a positive urine pregnancy test result is obtained at the site, the woman is not to be randomized. A serum sample for β-hCG testing will be collected at the Screening visit and sent to the Central Laboratory for confirmation of the urine pregnancy results. Serum samples for β-hCG testing at the Central Laboratory also will be collected at EOT and PTE. If a positive β-hCG result is reported by the Central Laboratory after a woman is enrolled, test article administration should be discontinued (see Section 21.6).

16.1.4.3 Blood Cultures

Two sets of blood cultures (first set = 1 aerobic bottle + 1 anaerobic bottle, second set = 2 aerobic bottles) 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 15-30 minutes apart. In the circumstance where bacteria are isolated from blood, repeat blood cultures should be collected at each subsequent visit, or more frequently if clinically indicated, until negative cultures are obtained. Blood culture isolates should be sent to the Central Laboratory (see Section 17.2.2.1).

16.1.4.4 Additional Local Laboratory Tests

The investigator may order additional local laboratory tests consistent with his/her routine standard of care.

16.2 Appropriateness of Safety Measurements

The safety assessments selected are standard for this indication and subject population.

17 EFFICACY

17.1 Primary and Secondary Efficacy Variables

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

- Successful Early Clinical Response (72-120 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.

- Successful Investigator's Assessment of Clinical Response 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.

The Early Clinical Response endpoint will be the primary efficacy outcome supporting registration with the FDA in the US and this will be tested in the intent-to-treat (ITT) analysis population. The Investigator's Assessment of Clinical Response at PTE endpoint will be the primary efficacy outcome supporting registration with the EMA in the European Union (EU) and will be tested in the ITT and clinically evaluable (CE) populations (co-primary endpoints). The analysis of the Investigator's Assessment of Clinical Response at PTE as the primary efficacy outcome will be detailed in a separate SAP for the EMA.

Secondary efficacy variables will include:

- Response category for Early Clinical Response
- Clinical Response category for Investigator's Assessment of Clinical Response at EOT and PTE
- Clinical Response category according to the identified causative pathogen

17.2 Key Assessments

The following is a list of key assessments that will be performed:

- Assessment of signs and symptoms of CABP by the investigator
- Microbiological assessment of the infection
- Assessment of clinical response

Each of the key assessments is described in further detail below.

17.2.1 Assessment of CABP Symptom Severity

The assessment of CABP symptoms observed by the investigator should be conducted at every scheduled evaluation with the exception of the Final Follow-up assessment (see STUDY FLOWCHART) The investigator will specifically assess the 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 scores into the eCRF. For subjects that have been switched to po test article and discharged from the hospital prior to study Day 6, visits must be conducted on study Days 4 and 5, while a study Day 6 visit is optional.

17.2.2 Microbiological Assessments

17.2.2.1 Respiratory Culture and Gram Stain

At the Screening visit 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 collected and submitted to the local microbiology laboratory for Gram stain and culture (see STUDY FLOWCHART). 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. > 10 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, a specimen should be obtained up to 24 hours after 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.

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 low power field (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 low power field (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 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.

In addition, Gram stained slides of specimens, particularly those of sputum samples, will be submitted to the Central Laboratory. If it is necessary, based on local laboratory requirements, a duplicate slide of the primary specimen can be prepared for the purposes of retaining 1 at the local laboratory.

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

17.2.2.2 Urine for *Legionella pneumophila* and *Streptococcus pneumoniae* Antigen Screening

At the Screening visit, and at the PTE 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.

17.2.2.3 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.

17.2.3 Assessment of Clinical Outcome

Assessment of clinical outcome will occur at Early Clinical Response assessment (programmatically), EOT, and PTE as described below.

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

The formal determination of the response to therapy at the Early Clinical Response 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 Early Clinical Response 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 17.2.1 and STUDY FLOWCHART). For subjects that have been switched to po test article and discharged from the hospital prior to study Day 6, visits must be conducted on study Days 4 and 5, while a study Day 6 visit is optional.

Clinical Success: at the Early Clinical Response 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 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 Early Clinical Response.

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 Early Clinical Response 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 1 under study.
- Discontinued study therapy due to an AE prior to Early Clinical Response assessment.
- Death prior to the Early Clinical Response assessment.

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

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

17.2.3.2 Clinical Evaluation of the Infection Under Study at EOT

EOT 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 whether or not the subject meets the criteria of 1 of the following clinical outcomes:

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 to 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 prior to the EOT.

- Subject is receiving antibacterial therapy that may be effective for the infection under study for a different infection from the 1 under study.
- Death prior to EOT.

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

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

17.2.3.3 Clinical Evaluation of the Infection Under Study at PTE

The PTE assessment is to be performed 5 to 10 days after the subject's last day of therapy. Only subjects determined to be a Clinical Success at EOT or Indeterminate due to missing the EOT visit will be considered for evaluation as Clinical Success at PTE. Subjects assessed as Clinical Failures at EOT or Indeterminate for reasons other than missing the EOT visit, will have this outcome carried forward. The investigator will determine whether or not the subject meets the criteria of 1 of the following clinical outcomes:

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 to CABP or (b) development of infectious complications of CABP (eg, empyema, lung abscess).

- The subject is receiving antibiotics that may be effective for the infection under study for a different infection from the 1 under study.
- Death prior to PTE.

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

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

18 OTHER ASSESSMENTS

18.1 Resource Utilization

The number of hospital days for all hospital admissions during the study period will be calculated. Hospital days will be specified from date of admission to date of discharge.

19 PHARMACOKINETIC PLASMA SAMPLES FOR OMADACYCLINE CONCENTRATION

19.1 Selection of Sites for PK Studies

Pharmacokinetic data will be analyzed using a population PK model. In order to maximize the number of subjects who participate so that this analysis is optimal, 1 criterion for selection of sites in this study will be the site's ability to participate in the PK portion of the study. To assure the quality and accuracy of the PK samples, samples will be obtained only from subjects participating at a center that has the appropriate facilities and capabilities and has been specifically trained by the sponsor.

19.2 Collection of PK Samples

PK samples will be collected using a sparse sampling method for the population PK model. The number of samples and collection schedule will vary for individual subjects. The sponsor will notify the site of the PK sample collection schedule for the individual subject. Up to 4 samples will be collected per subject between study Days 2 to 5 (see STUDY FLOWCHART).

The sponsor will provide heparin tubes for the collection of PK blood samples and will provide freezer tubes for storing the plasma. Blood will be collected either by fresh venipuncture or via a cannula used SOLEY for that purpose; blood for PK samples must NOT be drawn through the same iv access used for administration of test article.

The dates and times for all doses of test article and PK sample collections will be recorded. For intravenously administered doses of test article, the start and stop times for each infusion shall be recorded. The identification of the subject and the time of the sample collection to the nearest minute should be immediately recorded on the tube. The tube will be centrifuged at 1500 × *g* for 10 minutes and the separated plasma transferred in 2 equal aliquots into pre-labeled tubes; and the tubes frozen at -70ºC within 60 minutes of collection. The time the sample is frozen should be recorded to the nearest minute.

19.3 Storing and Shipping of PK Samples

After all of the PK samples from a single subject have been collected and frozen at -70ºC, 1 sample from each time point can be batched together with corresponding complete sample sets from other subjects and be carefully packaged and shipped frozen at -70ºC to the Central

Laboratory. Samples are to be shipped with sufficient dry ice to remain frozen during transit (up to a possible 4-day period). The Central Laboratory will process these samples and forward them at -70ºC to the Analytical Laboratory designated by the sponsor. For each subject and time point, the remaining stored aliquots will be retained on-site at –70ºC until released or requested by the sponsor.

19.4 Analysis of PK Samples

The Analytical Laboratory will assay the samples for omadacycline using a specific, sensitive and validated Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS) method approved by the sponsor.

20 OTHER BIOMARKERS

None.

21 SAFETY MONITORING

21.1 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.

A 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 cancer.
- 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 1 of the outcomes listed 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, 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.

In addition, a hospitalization for a preexisting condition that has not worsened does not constitute an SAE.

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.

A protocol-related AE is an AE occurring during a clinical study 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 an event related to a medical procedure required by the protocol.

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.

21.2 Serious Adverse Event Reporting

All SAEs and follow-up information must be reported within 1 business day by faxing a completed SAE Report Form to the fax number below or emailing a completed SAE Report Form to the e-mail address below.

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

21.3 Overdose

Any administration of omadacycline of greater than 600 mg (iv or po) 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 moxifloxacin of greater than 2.8 grams in 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 24-hours. 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. The IxRS will also provide a confirmation report of the drug assignment to site personnel. The site personnel will retain this confirmation report.

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

21.4 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 faxingor emailing the Clinical Test Article Error Incident Report Form as indicated in the Emergency Contacts (See Section 2).

21.5 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 within 30 days 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?" Signs and symptoms should be recorded using standard medical terminology.

Any unanticipated risks to the subjects must be reported promptly to the IRB/IEC/REB.

21.6 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.

21.7 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee (DSMC), independent of the sponsor, will provide ongoing monitoring of safety data on an approximately quarterly basis. The DSMC will review the data as treatment A and treatment B. The charter for the DSMC will clearly outline 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 sponsor will be maintained, in addition to the procedures that ensure the independence and objectivity of the DSMC's activities. As the DSMC will be reviewing safety data for this study, it may require reports indicating treatment assignment to assist in clinical interpretation of its findings. Therefore, the DSMC charter will provide a detailed explanation of the processes by which the DSMC 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.

22 DATA ANALYSIS

All analyses of data for this study will comply with International Conference on Harmonisation 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).

A SAP incorporating the sections below and with mock table, figure and listing (TFL) shells will be prepared prior to the start of the study and approved and finalized by the sponsor prior 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. As a consequence of differing regulatory requirements for the choice of the primary efficacy outcome and statistical analyses, 2 separate SAPs will be prepared (FDA and EMA). The sections below indicate the overall structure and approach of the analyses.

Inferential statistical analyses of the primary and secondary outcomes will be conducted as outlined below. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations (SD), medians, minimums, and maximums for continuous variables will be provided. All comparisons will be for omadacycline versus moxifloxacin. Exploratory analyses may also be performed. Listings of individual subject's data will be produced.

22.1 Analysis Populations

A number of subject populations have been defined for the various analyses of efficacy and safety, as follows:

- The ITT population will consist of all randomized subjects.

- The microbiological intent-to-treat (microITT) 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 *Chlamydophila 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 at Screening.
- The Safety population will consist of all randomized subjects who received at least 1 dose of test article.

22.2 Subject 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/m^2)
- 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).

22.3 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.

22.4 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 (see Section 25.1).

22.4.1 Early Clinical Response Efficacy Variable

The Early Clinical Response can be Clinical Success, Clinical Failure or Indeterminate (defined in Section 17.2.3.1).

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.

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

This is defined as the Investigator's Assessment of Clinical Response at the PTE visit with outcomes of Clinical Success, Clinical Failure or Indeterminate (defined in Section 17.2.3.3) 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.

22.4.3 Statistical Model, Hypothesis, and Method of Analysis

To demonstrate 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 Early Clinical Response endpoint will be assessed in the ITT population as follows:

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

H_{ai}: $\theta_T - \theta_C > -\Delta$

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 Early Clinical Response (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 (Miettinen and Nurminen, 1985). 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 97.5% 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 those subjects with a PORT Risk Class of III or higher. The 97.5% CI will be calculated using the stratified (for the randomization stratification factors) method proposed by Miettinen and Nurminen (Miettinen and Nurminen, 1985). 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 for approving an ineffective drug based on PTE efficacy is 1.25%, regardless of the result for the Early Clinical Response endpoint and vice versa. An adjustment would only be required if winning on at least 1 endpoint would result in global approval which is not the case here. 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.

22.4.4 Additional Analyses of the Primary Efficacy Outcomes

Additional and sensitivity analyses of the primary efficacy outcomes (Early Clinical Response 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 Early Clinical Response 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, receipt of allowed antibacterial therapy in the 72 hours prior to study treatment and geographic region stratum by treatment group. For each PORT Risk Class stratum, each prior antibacterial therapy stratum and each geographic region stratum, a 2-sided 95% CI for the observed difference in Early Clinical Response 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.

22.5 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 (Miettinen and Nurminen, 1985). For Investigator's Assessment of Clinical Response at PTE in the ITT and CE populations 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 Early Clinical Response will 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 (Miettinen and Nurminen, 1985).

The number and percentage of subjects with an Early Clinical Response 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.

22.6 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 (Miettinen and Nurminen, 1985).

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 temperature (no fever or hypothermia), SBP (≥ 90 mm Hg), heart rate (< 90 bpm), RR (< 20 breaths/minutes), PaO_2 (> 60 mm Hg by ABG), physical exam findings (no findings of pulmonary consolidation), WBC count (< 12,000 cells/mm^3 or ≥ 4,000 cells/mm^3) 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.

A concordance analysis of Early Clinical Response and Investigator's Assessment of Clinical Response at PTE in the ITT analysis set will also be presented.

22.6.1 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.

22.6.1.1 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.

22.6.1.2 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.

22.6.1.3 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.

22.6.1.4 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.

22.6.2 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)
- duration (days) and number of doses on iv therapy (test article)
- duration (days) and number of outpatient iv doses per type of facility (test article)
- duration (days) and number of doses on po therapy (test article)

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

22.6.3 Pharmacokinetics

Population PK analysis will be conducted to characterize PK parameters. A population PK data set including subjects with 1 or more quantified omadacycline concentration determinations will

be constructed from the dates and times of the doses and blood samples along with all the bioanalytical determinations and subject background information. If the actual date or time for a blood sample or dose is missing, the related bioanalytical determination of the PK concentration will be excluded from all analyses. Omadacycline concentrations below the limit of quantification will be treated as missing data in summary statistics and for the calculation of PK parameters.

Variables including age (years), body weight (kg), gender, and race/ethnicity along with other covariates previously determined to be important will be incorporated into the population PK database. Based on the subjects in the population analysis data set, descriptive summaries at Screening for these variables will be reported. Outliers may be excluded from the analysis. These will be determined by a scatter plot of the observed concentration versus time post dose and reported. The distribution of the number of samples contributed per subject to the model-based analysis will be tabulated. Also, simple summary descriptive statistics for the concentration of samples by study day or week will be computed.

22.6.3.1 Population PK Modeling

Results from Phase 1 studies indicate that omadacycline PK is linear and that following iv infusion, plasma concentration-time profiles show a 3-compartmental disposition. Therefore, the probable structural PK model would be a 3-compartment model with zero order input for iv infusion and first order input for po administration. This PK model contains the parameters clearance, volume of distribution, bioavailability and absorption rate constant. The associated population models are nonlinear mixed-effects models. The population model adds random effects and covariates for the PK parameters in order to recognize differences among individuals and similarities across observations corresponding to the same subject. At the time of the population modeling, previously reported structural PK models will be considered first. A residual error model combining additive error and proportional error will also be initially considered. Simplifications (eg, fewer random effects, or an alternative residual error model) may be appropriate if the diagnostics for the model suggest false convergence. Additional covariates will be investigated graphically (gender, race/ethnicity, age) as part of the model diagnostics and some may be retained in the final model and additional ones in a competing model to deliver estimates of arguably insignificant effects. Scatter plots of the observed concentrations versus population-estimated and individually estimated concentrations will be used as part of the overall assessment of the overall quality of the fit. During modeling, the broad principles outlined by the FDA will be followed (FDA, 1999).

The individual model-based exposure measures at steady state (area under the Concentration/Time curve [$AUC_{0\text{-}24,ss}$], time to maximum plasma concentration [$T_{max,ss}$], maximum plasma concentration [$C_{max,ss}$]) will be computed and summarized.

22.6.4 Pharmacogenetics/Pharmacogenomics

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

22.6.5 Biomarkers

Not applicable.

22.6.6 PK/PD

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.

22.7 Sample Size Calculation

The study is designed to show NI in the primary efficacy outcome of Early Clinical Response 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 the historical data regarding the treatment effect of antibiotics in pneumonia.

In the ceftaroline clinical studies which enrolled only PORT Risk Class III and IV, the rates for clinical success based on Investigator's Assessment of Clinical Response at the PTE visit ranged from 77%-87% in the modified ITT and CE populations, with the rates in the modified ITT population lower than those in the CE population (Teflaro full prescribing information, 2013). Thus, it is reasonable to assume clinical success rates of 79% in the ITT and 85% in the CE populations.

For the Investigator's Assessment of Clinical Response at PTE endpoint in the ITT population (PORT Risk Class III and IV) assuming an outcome rate of 79% in both treatment groups, NI margin of 10%, 80% power and a 1-sided alpha level of 0.0125 (since 1 CABP study is being conducted), using the sample size determination method of Farrington and Manning (Farrington and Manning, 1990), a total of 638 subjects (PORT Risk Class III and IV) are required. Assuming an 80% evaluability rate, 510 subjects will be available in the CE population. Assuming an 85% response rate in both treatment groups, a 10% NI margin, 1-sided alpha level of 0.0125, there is 81% power to show NI for Investigator's Assessment of Clinical Response at PTE in the CE population. If 15% of subjects are in PORT Risk Class II, a total of 750 subjects are required.

No clinical study has been conducted using Early Clinical Response as the primary efficacy outcome. However, retrospective analyses of clinical study data (Talbot, et al., 2012) indicate the point estimates for Early Clinical Response at Day 4 range from 72%-81%. Thus, it is reasonable to assume that in a prospective study of subjects with moderate to severe CABP, the rate of Clinical Success at an early time point will be approximately 79%.

For the Early Clinical Response primary efficacy endpoint, with 750 subjects in the ITT population, a response rate of 79% for both treatment groups, NI margin of 10%, a 1-sided alpha level of 0.025, there is a 92% power to show NI. Assuming the microbiological evaluability rate is 27%, a total of 202 subjects are expected to be in the microITT population.

Thus, 750 subjects provides 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 8.

Table 8 Sample Size and Power Calculations

	Primary Outcome (Early Clinical Response)	Secondary Outcome (Early Clinical Response)	Secondary Outcome (Investigator's Assessment of Clinical Response at PTE)	
Population	ITT	microITT	ITT	CE
NI Margin	10%	15%	10%	10%
Evaluability Rate	N/A	27%	N/A	80%
Outcome Rate	79%	80%	79%	85%
PORT Risk Class II	N/A	N/A	15%	15%
N	750	202	638	510
Power	92%	74%	80%	81%

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

22.8 Interim Analyses

No interim analyses of efficacy are planned. However, a DSMC will review safety data (eg, AEs and SAEs, laboratory data, ECG, and vital signs assessments) at regular time points while the study is ongoing.

22.9 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, 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 will be conducted in which subjects with an Indeterminate response are considered Clinical Successes.

For the secondary outcome measure of Investigator's Assessment of Clinical Response at PTE in the ITT population (co-primary for EMA analysis), 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 9 provides a summary of the handling of missing/indeterminate outcomes for the Investigator's Assessment of Clinical Response at PTE.

Table 9 Investigator's Assessment of Clinical Response at PTE Determination Given Missing Data

EOT Visit	PTE Visit	Overall Assessment of 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.

23 SUBJECT IDENTIFICATION

Each subject in the study is assigned a unique subject number and must keep that number throughout the study even if he/she transfers to another site. A subject who discontinues participation or is withdrawn before receiving a treatment assignment code, and who re-enrolls at a later time will be assigned a new subject number and recorded as rescreened. The investigator must maintain a subject master log of all subjects.

24 TEST ARTICLE ACCOUNTABILITY, RECONCILIATION, AND RETURN

The investigator must maintain a complete and current dispensing and inventory record of test article that has been supplied by the sponsor.

All unused test article must be returned in the original containers. Empty test article containers may be destroyed after the sponsor has performed accountability. Test article destruction must be documented on the dispensing and inventory record.

24.1 Supply, Storage and Tracking of Study Treatment

Test article must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the unblinded pharmacist or unblinded study personnel and designated assistants have access. Upon receipt, all test article should be reconciled with the shipping information and stored according to the instructions specified on the medication labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. In addition, they will include storage conditions for the medication.

The unblinded pharmacist or designee should maintain an accurate record of the shipment and dispensing of test article in the study specific medication accountability ledger. Monitoring of medication accountability will be performed by the unblinded field monitor during site visits and at the completion of the study. Subjects will be asked to return all unused test article and packaging at each visit and at the end of the study, last study visit or at the time of test article discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, with instruction from the sponsor, the unblinded pharmacist or designee will destroy on site or return unused test article, packaging, medication labels, and a copy of the completed medication accountability ledger to the monitor or to the address provided to the investigator.

25 RANDOMIZATION AND BLINDING

25.1 Treatment Assignment

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 (via phone or web) after confirming that the subject fulfills all the inclusion criteria and 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 (II or III/IV), receipt of an allowed antibacterial therapy (See Appendix 1) in the 72 hours prior to study treatment, and geographic region as defined in the IxRS specifications and SAP. Subjects randomized into the study will be assigned the treatment corresponding to the next available number in the respective stratum of the computer-generated randomization schedule. The subject is considered randomized when the IxRS provides the test article assignment, regardless of whether the subject actually receives any medication. Randomization of subjects with a PORT Risk Class of II will be capped at 15% of the subjects randomized. 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.

25.2 Dispensing the 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 moxifloxacin, 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 include active omadacycline tablets or matched placebo tablets, and active moxifloxacin over-encapsulated tablets or matched placebo over-encapsulated tablets. The unblinded pharmacist will provide the appropriate kit to the study coordinator/staff who instructs the subject on the use of po test article. The procedures are detailed in the Pharmacy Manual.

25.3 Treatment Blinding

The investigator and sponsor will be blinded to treatment arm assignments throughout the study. The iv and po phases of the study will be double-blind.

During the iv treatment period, subjects assigned to omadacycline will receive test article q24h for the first 2 doses, followed by 100 mg iv q24h (starting 24 hours after the first dose). Subjects assigned to moxifloxacin will receive test article q24h, with a single placebo infusion (the subject's second infusion 12 hours after the first dose) to match the omadacycline dosing regimen (see Table 1).

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 double-dummy 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 a potentially unblinded administrator will be required. Personnel identified as potentially unblinded administrators should 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-dummy design will also be used to ensure the blind. Subjects on the omadacycline arm active omadacycline tablets and over-encapsulated moxifloxacin placebo tablets. Subjects on the moxifloxacin arm will receive omadacycline placebo tablets and over-encapsulated active 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, from the documents containing blinded information.

Randomization data are kept strictly confidential until the time of database lock and unblinding at the end of the study.

All eCRFs must be completed, entered and checked; all safety 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.

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
- potentially unblinded administrator(s)

Plasma samples for subjects receiving omadacycline may be analyzed during the course of the study. To permit the sponsor to review the drug concentration data prior to locking the dataset and without unblinding, any PK data provided prior to unblinding will be re-coded by the bioanalytical laboratory to avoid revealing the individual subject numbers.

Unblinding is only to occur in the case of subject emergencies (see Section 25.4) and at the conclusion of the study.

25.4 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 strongly 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.

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 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.

In the event of a medical emergency in which the investigator judges that the subject cannot be managed safely without unblinding, the investigator may obtain the treatment allocation directly from the research pharmacist or designee. 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.

26 SUBJECT DISCONTINUATION OR WITHDRAWAL

Reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to, AE, subject request, protocol violation, subject noncompliance, and 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 (unless that subject withdraws informed consent) should NOT be considered withdrawn from the study. The date and primary reason for discontinuation of study treatment should be recorded in source documents. Subjects who discontinue the study treatment should have the EOT visit and the procedures listed for that visit in the STUDY FLOWCHART, a PTE visit and a Final Follow-up assessment, if possible. The site should also collect subject safety information through the Final Follow-up assessment.

Site personnel should 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.

Subjects who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled subjects.

27 STUDY SUSPENSION, TERMINATION, AND COMPLETION

27.1 Study Completion and Post-Study Test Article

A subject will have successfully completed the study after planned iv and po test article has been administered, and all assessments and visits have been made. Visits include the final follow-up visit (Final Follow-up). The study will be completed when the last subject has either discontinued or completed the Final Follow-up visit.

No long-term follow-up of subjects is planned, with the exception of pregnancies, as described in Section 21.5, and SAEs described in Section 21.1.

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 will be allowed to continue in the study.

Upon study completion, the investigator will provide the sponsor, IRB/IEC, 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 within 3 months after the completion or termination of the study. A sample of this final study report can be found in the Study Reference Manual.

27.2 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 26 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 Independent Ethics Committees (ECs) of the early termination of the study.

If the investigator suspends or terminates the study, the investigator will promptly inform the sponsor and the IRB/IEC and provide them with a detailed written explanation. Subjects should be seen as soon as possible and treated as described in Section 26 for prematurely withdrawn subjects. The investigator will also return all test article, containers, and other study materials to the sponsor.

28 ETHICAL CONSIDERATIONS

28.1 Regulatory and Ethical Compliance

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

28.2 Informed Consent Procedures

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.

28.3 Responsibilities of the Investigator and IRB/IEC/REB

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.

29 PROTOCOL ADHERENCE

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

29.1 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.

30 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 IB, the 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.

31 DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

31.1 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 1572 will be filed with the sponsor for any changes in the study personnel reported in the current form 1572.

31.2 Sponsor

The data is entered into an electronic database via eCRFs. The sponsor's 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.

32 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.

33 PRESTUDY DOCUMENTATION

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

- Completed and signed form 1572.
- 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 form 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.

34 RECORDS RETENTION

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 study drug has been approved or the sponsor has discontinued its research with respect to such drug 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.

35 PUBLICATION 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 multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter 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.

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15. **Teflaro**. Full Prescribing Information. Revision 12/2013. Forest Pharmaceuticals, Inc. St. Louis, MO.

Appendix 1: Allowed and Disallowed Prior Antibiotics

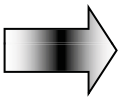
Allowed Antibiotics (One dose within 72 hours prior to randomization*)		**Disallowed Antibiotics**
Penicillins		
Amoxicillin	Nafcillin	Benzathine/Penicillin-G Procaine
Amoxicillin-Clavulanate	Oxacillin	
Amoxicillin-Sulbactam	Penicillin-G or -V	
Ampicillin	Piperacillin	
Ampicillin-Sulbactam	Piperacillin-Tazobactam	
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 Meropenem		Ertapenem
Glycopeptides		
Televancin Vancomycin		Dalbavancin Oritavancin
Fluoroquinolones		
Ciprofloxacin		Levofloxacin Moxifloxacin
Macrolides		
Clarithromycin Erythromycin		Azithromycin Clarithromycin XL
Tetracyclines		
Doxycycline (100 mg) Minocycline		Doxycycline (200 mg) Minocycline Extended Release Tigecycline
Oxazolidinones		
Linezolid		Tedizolid
Miscellaneous		
Clindamycin Metronidazole Trimethoprim-sulfamethoxazole/Co-trimoxazole		

*Prior (within 72 hours prior to randomization) administration of potentially effective systemic antibacterial therapy is an exclusion criterion (Section 12.2); 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. 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 2: PORT Risk Class Calculation

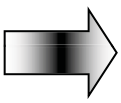
Adapted from Fine, et al., 1997.

Step 1: Stratify to Risk Class I vs. Risk Classes II-V	
Presence of:	
Over 50 years of age	Yes/No
Altered mental status	Yes/No
Pulse ≥125/minute	Yes/No
Respiratory rate >30/minute	Yes/No
Systolic blood pressure <90 mm Hg	Yes/No
Temperature <35°C or ≥40°C	Yes/No
History of:	
Neoplastic disease	Yes/No
Congestive heart failure	Yes/No
Cerebrovascular disease	Yes/No
Renal disease	Yes/No
Liver disease	Yes/No
If any "Yes", then proceed to Step 2	
If all "No" then assign to **Risk Class I**	



NOTE: Subjects stratified to Risk Class I, will **not** be eligible for enrollment in this study.

Step 2: Stratify to Risk Class II vs III vs IV vs V	
Demographics	**Points Assigned**
If Male	+Age (yr)
If Female	+Age (yr) - 10
Nursing home resident	+10
Comorbidity	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical Exam Findings	
Altered mental status	+20
Pulse ≥125/minute	+20
Respiratory rate >30/minute	+20
Systolic blood pressure <90 mm Hg	+15
Temperature <35°C or ≥40°C	+10
Lab and Radiographic Findings	
Arterial pH <7.35	+30
Blood urea nitrogen ≥30 mg/dl (9 mmol/liter)	+20
Sodium <130 mmol/liter	+20
Glucose ≥250 mg/dl (14 mmol/liter)	+10
Hematocrit <30%	+10
Partial pressure of arterial O2 <60mmHg	+10
Pleural effusion	+10
∑ 51-70 = **Risk Class II**	
∑ 71-90 = **Risk Class III**	
∑ 91-130 = **Risk Class IV**	
∑ >130 = **Risk Class V**	



NOTE: Subjects stratified to Risk Class V, will **not** be eligible for enrollment in this study.

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

Appendix 4: Equations and Conversions

1. Cockcroft-Gault equation to calculate creatinine clearance (CrCl):

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

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

2. $mm^3 = \mu L$
3. cc = mL

PROTOCOL PTK0796-CABP-1200

Study Title	A Phase 3 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)
IND Numbers:	75,928 73,431
EudraCT Number:	2013-004071-13
Protocol Number:	PTK0796-CABP-1200
Indication:	Community-Acquired Bacterial Pneumonia
Phase:	3
Investigational Drug:	Omadacycline (PTK 0796)
Dose Form(s):	Intravenous and oral
Sponsor:	Paratek Pharma, LLC A wholly-owned subsidiary of Paratek Pharmaceuticals, Inc. 75 Park Plaza, 4th Floor Boston, MA 02116 USA 1000 First Ave Suite 400 King of Prussia, PA, 19406 P.O. Box 120828 Boston, MA 02111 Tel: +1 617-275-0040
Protocol Version:	Version 2.0
Date:	27-OCT-2015

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1 DISCLOSURE STATEMENT

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: Paul Eckburg, MD, Global Medical Monitor
Phone (during business hours):
Phone (after business hours):
E-mail (not for emergencies):
Address:

Name/Title: Philippe Vitou, MD, Regional Medical Monitor
Phone (during business hours):
Phone (after business hours):
E-mail (not for emergencies):
Address:

Name/Title: Stephen Villano, MD, Paratek Pharma, LLC, VP, Clinical and Medical Affairs
Phone (during business hours):
Phone (after business hours):
E-mail (not for emergencies):
Address:

2.2 Additional Contacts

Serious Adverse Event (SAE) contact information
E-Mail:
Fax:

3 SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Stephen Villano, MD VP of Clinical and Medical Affairs Paratek Pharma, LLC	04 Jan 2016 Date of Signature (DD-MMM-YYYY)	13:00 ET Time (24-hour clock, time zone)

4 INVESTIGATOR AGREEMENT

I have read the foregoing protocol (PTK0796-CABP-1200) and agree to the following:

The protocol contains all necessary details for carrying out this study;
I will conduct the study as detailed in the protocol and will abide by all its provisions;
I will conduct the study in compliance with the most current versions of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP), all applicable government regulations and the requirements of the IRB/IEC/REB that approved the study.
I will train and supervise all individuals delegated to assist me in conducting this study, including providing copies of the protocol and all pertinent information and discussing the material with them to ensure they are fully informed regarding the investigational drug, the protocol and their responsibilities and obligations.
I will use only the informed consent form (ICF) approved by PARATEK (or their designee) and by the IRB/IEC/REB responsible for this study.
I will fulfill all requirements for submitting pertinent information to the IRB/IEC/REB and to PARATEK, including reportable serious adverse events (SAEs).
I will provide PARATEK (or their designee) with access to any source documents from which case report form information may have been generated.
I understand that the information in this protocol and the referenced Investigator's Brochure (IB) is confidential and that its disclosure to any third parties (other than those involved in approving or conducting the study) is prohibited. I will take the necessary precautions to protect this information from loss, inadvertent disclosure or access by third parties.
I will complete the study within the time designated.
My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the ICH Guideline for GCP, the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature	Date of Signature (DD-MMM-YYYY)	Time (24-hour clock, time zone)

Investigator Name and Title (print)

5 LIST OF ABBREVIATIONS

ABG	Arterial Blood Gas
ABSSSI	Acute Bacterial Skin and Skin Structure Infections
ACM	All-Cause Mortality
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
AUC	Area Under the (Concentration/Time) Curve
BMI	Body Mass Index
BP	Blood Pressure
bpm	beats per minute
CABP	Community-Acquired Bacterial Pneumonia
cc	cubic centimeter
CD4	Cluster of differentiation 4
CE	Clinically Evaluable
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine phosphokinase
C_{max}	Maximum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
CrCL	Creatinine Clearance
CSA	Clinical Study Agreement
CSR	Clinical Study Report
cSSSI	Complicated Skin and Skin Structure Infection
CT	Computed Tomography
CXR	Chest X-ray
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

EMA	European Medicines Agency
EMEA	Agency for the Evaluation of Medicinal Products
EOT	End of Treatment
FDA	Food and Drug Administration
FD&C	Food, Drug, and Cosmetic Act
g	Gravity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
HAP	Hospital-Acquired Pneumonia
HCAP	Healthcare-Associated Pneumonia
HDPE	High-Density Polyethylene
hERG	human Ether-à-go-go-Related Gene
β-hCG	beta – human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPFB	Health Products and Food Branch
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
IxRS	Interactive Voice Response System/Interactive Web Response System
LC/MS/MS	Liquid Chromatography/Tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
lpf	Low Power Field

MDR-SP	Multi-drug Resistant *Streptococcus pneumoniae*
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
microITT	Microbiological Intent-To-Treat
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
NI	Non-Inferiority
NS	Normal Saline (0.9% sodium chloride)
PaO_2	Partial pressure of arterial oxygen
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PORT	Pneumonia Outcomes Research Team
PT	Preferred Term (MedDRA)
PTE	Post Therapy Evaluation (visit)
PVC	Polyvinyl Chloride
q12h	Every 12 hours
q24h	Every 24 hours
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
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SOC	System Organ Class (MedDRA)
spp.	species (plural)
ss	steady state

TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
TGA	Therapeutic Goods Administration
T_{max}	Time to Maximum Plasma Concentration
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell

6 DEFINITIONS

Term	Definition
Regulation	The term *regulation* refers to all applicable regulations, laws, and guidelines. The regulations may be international, national, or local and may include but are not limited to the Code of Federal Regulations (CFR); the Good Clinical Practice (GCP); Consolidated Guideline (Canada); the International Conference on Harmonisation Guideline for Good Clinical Practice; the Therapeutic Goods Administration Annotated International Conference on Harmonisation Guidelines (Australia); the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.
Regulatory agency	The term *regulatory agency* refers to all health and regulatory agencies with oversight responsibility for the study. These may be international, national, or local and may include but are not limited to the Australian Therapeutic Goods Administration (TGA), the Canadian Health Products and Food Branch (HPFB), the European Agency for the Evaluation of Medicinal Products (EMEA), the United States (US) Food and Drug Administration (FDA).
Sponsor	The term *sponsor* refers to, but is not limited to the sponsor listed in the front of this document and any contract research organization that is being used for the study.
Test article	Any study drug, device, biologic agent, or comparator (including placebo) used in sponsor studies. For test article accountability, this term applies to the above articles when they are required by the protocol and supplied (shipped) by the sponsor (including diluents such as normal saline [NS] for injection).
Adverse Event	An adverse event (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.

7 PROTOCOL SYNOPSIS

Study Title	A Phase 3 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)
Clinical Phase	3
Study Rationale	PTK 0796 (hereafter referred to as omadacycline) is the first member of the aminomethylcycline class of antibiotics, which are semi-synthetic 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. Omadacycline was evaluated in a Phase 2 study of 219 subjects with complicated skin and skin structure infection (cSSSI) and a sponsor-terminated Phase 3 study that enrolled 143 subjects with cSSSI. Omadacycline was well-tolerated and demonstrated efficacy similar to an established comparator (linezolid). Omadacycline has been shown to have *in vitro* activity against the most common typical and atypical causes of CABP. Further, it has been shown to be effective in animal models of lower respiratory tract infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae.* It is expected that omadacycline will achieve levels in the lower respiratory tract comparable to related tetracyclines (doxycycline and tigecycline) which have been used to successfully treat subjects with CABP. Omadacycline has demonstrated activity against the most common CABP pathogens, including isolates resistant to standards of care. 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 adults with CABP.
Study Objective(s)	**Primary objective:** The primary objective of this study is to demonstrate that omadacycline 100 mg iv every 12 hours (q12h) for 2 doses, followed by 100 mg iv/300 mg po once every 24 hours (q24h) is non-inferior to moxifloxacin 400 mg iv/po q24h in the treatment of adults with 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 (Pneumonia Outcomes Research Team [PORT] Risk Class II, III, or IV). Both iv and po phases of the study will be double-blind. Enrollment of subjects with disease characterized as PORT Risk Class II will be limited to no more than 15% of randomized subjects. Enrollment of subjects who have received a single dose of an allowed short-acting antibiotic (see Appendix 1) within the 72 hours prior to the first dose of test article will be limited to no more than 25% of randomized subjects.
Approximate Duration of Subject Participation	Subjects will participate in the study for approximately 30 days. Following Screening, eligible subjects will be randomly assigned to receive 7 to 14 days of treatment with either omadacycline or moxifloxacin. A post therapy evaluation visit will occur approximately 5 to 10 days after the last dose of test article and a follow-up telephone contact will occur approximately 30 to 37 days after the first dose of test article.
Approximate Duration of Study	The study is expected to be clinically complete in approximately 18 months.
Approximate Number of Subjects	750 randomized subjects.
Approximate Number of Study Centers	150
Diagnosis and Main Criteria for Inclusion	1. Written and signed informed consent must be obtained before any protocol specific assessment is performed. 2. Male or female, age 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 systolic blood pressure (SBP) < 90 mm Hg • Heart rate > 90 beats per minute (bpm) • Respiratory rate (RR) > 20 breaths/minute 5. Has at least 1 clinical sign or laboratory finding associated with

	CABP: • Hypoxemia (partial pressure of arterial oxygen [PaO_2] < 60 mm Hg by arterial blood gas [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, see % bands calculation in Appendix 4, regardless of total peripheral WBC count) 6. 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 24 hours prior to the first dose of test article. 7. Has disease categorized as being PORT Risk Class II, III, or IV at Screening (see PORT Risk Class calculation in Appendix 2). 8. Is expected to require a minimum of at least 3 days of iv therapy for the initial treatment of CABP. 9. Females must have a negative urine 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 post therapy evaluation (PTE). Males must agree to use an acceptablemethod 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 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 1). 2. Is known or suspected to have CABP caused by a pathogen that may

be resistant to either test article (eg, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *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. Subjects with known or suspected hospital-acquired pneumonia (HAP) or healthcare-associated pneumonia (HCAP). HAP is defined as pneumonia with onset of clinical signs and symptoms ≥ 48 hours after hospitalization in an acute in-subject health care facility. HCAP is defined as pneumonia acquired in a long-term care or subacute/intermediate healthcare facility (eg, nursing home) or in a subject admitted with pneumonia following a recent hospitalization (discharged within 90 days of current admission and previously hospitalized for ≥ 48 hours).
5. Has known or is clinically suspected to have 1 or more of the following prior to randomization:
   - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2 × Upper Limit of Normal (ULN),
   - total bilirubin > 1.5 × ULN, or
   - evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy).
6. Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to Screening.
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, and/or present with tachyarrhythmia.
8. Requires any form of dialysis (eg, hemodialysis, peritoneal dialysis).
9. History or evidence of severe renal disease or has a calculated creatinine clearance (CrCl) of < 30 mL/minute, using the Cockcroft-Gault equation (see equation in Appendix 4).
10. Evidence of 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

- 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 (see equivalent corticosteroid doses in Appendix 4)

11. Requires acute pharmacologic intervention to stabilize blood pressure (BP) and/or adequate tissue perfusion, OR has evidence of septic shock defined by ALL of the following:
    - Fever or hypothermia documented by the investigator (temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
    - Heart rate > 90 beats/minute
    - RR > 20 breaths/minute
    - WBC > 12,000 cells/mm^3 or < 4,000 cells/mm^3 or > 10% immature (band) forms, see % bands calculation in Appendix 4, regardless of the total peripheral WBC count
    - Hypotension with SBP < 90 mm Hg despite an iv fluid challenge of 20-30 cc/kg over a 30 minute period
    - Perfusion abnormalities that may include, but are not limited to, lactic acidosis (blood lactate concentration ≥ 4 mmol/L), oliguria, or acute alteration in mental status.
12. 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).
13. Pregnant or nursing (breastfeeding) women.
14. Has a history of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or to any fluoroquinolone antibiotic.
15. Has a history of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
16. Has a history of systemic lupus erythematosus or lupus-like syndrome.
17. Has current evidence of pancreatitis.
18. Has a history of a central nervous system disorder that may predispose to seizures or lower the seizure threshold.
19. Use of other investigational drugs within 5 half-lives or 30 days prior

	to Screening, whichever is longer. 20. Has previously been treated with omadacycline or previously enrolled in this study. 21. Any planned medical intervention that might interfere with the ability to comply with the study requirements. 22. 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 adverse events (AEs), or completion of the expected course of treatment.
Prior and Concomitant Treatment	No systemic prior or concomitant antibacterial therapy is allowed, other than a single dose of a short-acting antibacterial (see Exclusion Criterion number 1 and Appendix 1), within the 72 hours prior to the first dose of test article. All other medications not prohibited by the protocol and considered necessary for the subject's welfare may be administered and/or continued under the supervision of the investigator.
Test Article(s)	Subjects will be randomized (1:1) to 1 of the following 2 treatment arms: • Omadacycline • Moxifloxacin
Dosage and Administration	• Omadacycline 100 mg iv q12h for 2 doses followed by 100 mg iv q24h (starting 24 h after first dose), with the option to switch to 300 mg po q24h after a minimum of 3 days (4 doses) of iv treatment. • Moxifloxacin 400 mg iv q24h (with a single placebo infusion to match the omadacycline dosing regimen 12 hours after the first dose on Day 1) with the option to switch to 400 mg po q24h after a minimum of 3 days (4 doses) of iv treatment.
Safety Evaluation	• Physical exams • AEs and SAEs • Vital signs • Laboratory assessments • Electrocardiogram (ECG) • Pregnancy assessments
Efficacy Evaluation	• In order to satisfy different health authority requirements, the primary variables assessing efficacy will be tested with 2 response endpoints: ❖ Successful Early Clinical Response (72-120 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. ❖ Successful Investigator's Assessment of Clinical Response 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 • Assessment of clinical response
Health Outcomes Assessment	• Resource utilization
Pharmacokinetics	• Population PK analysis
Statistical Analysis	A number of subject populations have been defined for the various analyses of efficacy and safety, as follows: • The intent-to-treat (ITT) population will consist of all randomized subjects. • The microbiological intent-to-treat (microITT) 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 *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 early clinical 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), 97.5% 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, changes in vital signs, ECGs, and laboratory results obtained from blood samples taken during the study. **Data and Safety Monitoring Committee:** A Data and Safety Monitoring Committee (DSMC) (independent of the sponsor) will provide ongoing monitoring of safety data. Data will be provided to the DSMC as treatment A and treatment B.
Rationale for Number of Subjects	The study is designed to show NI in the primary efficacy outcome of Early Clinical Response 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 the historical data regarding the treatment effect of antibiotics in pneumonia. The sample size determination is based on ensuring sufficient power for the secondary efficacy analyses of Investigator's Assessment of Clinical Response at PTE in the CE and ITT populations (co-primary efficacy outcomes for EMA) as well as the primary efficacy analysis of Early Clinical Response (efficacy outcome for FDA). For the Investigator's Assessment of Clinical Response at PTE endpoint in the ITT population (PORT Risk Class III and IV) assuming an outcome rate of 79% in both treatment groups, NI margin of 10%, 80% power and a 1-sided alpha level of 0.0125 (since 1 CABP study is being conducted), using the sample size determination method of Farrington and Manning (Farrington and Manning, 1990), a total of 638 subjects (PORT Risk Class III and IV) are required. Assuming an 80% evaluability rate, 510 subjects will be available in the CE population. Assuming an 85% response rate in both treatment groups, a 10% NI margin, 1-sided alpha level of 0.0125, there is 81% power to show NI for Investigator's Assessment of Clinical Response at PTE in the CE population. If 15% of enrolled subjects are assumed to have CABP of PORT Risk Class II, a total of 750 subjects are required. For the Early Clinical Response primary efficacy endpoint, with 750 subjects in the ITT population, a response rate of 79% for both treatment groups with a NI margin of 10%, a 1-sided alpha level of 0.025, there is a 92% power to show NI. Assuming the microbiological evaluability rate is 27%, a total of 202 subjects are expected to be in the microITT population.

	Thus, 750 subjects provides sufficient power for the primary efficacy analyses for both the FDA and EMA regulatory authorities.
Ethical Considerations	This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. The institutional review board (IRB)/independent ethics committee (IEC)/research ethics board (REB) must review and approve the protocol and informed consent form (ICF) before any subjects are enrolled. The subject must be consented using the approved ICF before any procedures specified in the protocol are performed.

8 STUDY FLOWCHART

Study Phase	**Screening**[b]	**Double-Blind Phase**										**Follow-up Phase**	
	-	iv Treatment Phase				iv or po Treatment Phase							
Study Day[a]		Day 1		Day 2	Day 3	Day 4	Day 5	Day 6[c]	Day 7	Day 10[c]	EOT[d]	PTE[e]	Final Follow-up[f]
		iv dose 1	iv dose 2										
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	
Chest X-ray or CT scan[i]	X												
PORT Risk Class, ABG (or pulse oximetry)[j]	X												
Blood and urine samples for local lab hematology/chemistry/urine tests/pregnancy[k]	X												
Review of Inclusion and Exclusion criteria/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		
Physical examination[m]	X			X	X	X	X	X	X	X	X	X	
Vital signs[n]	X	X[o]	X[o]	X[o]	X	X	X	X	X	X	X	X	
12-lead ECG	X	X[p]		X[p]					X		X		

Study Phase	**Screening**[b]	**Double-Blind Phase**										**Follow-up Phase**	
	-	iv Treatment Phase				iv or po Treatment Phase							
Study Day[a]		Day 1		Day 2	Day 3	Day 4	Day 5	Day 6[c]	Day 7	Day 10[c]	EOT[d]	PTE[e]	Final Follow-up[f]
		iv dose 1	iv dose 2										
Blood for Central Lab tests: hematology/chemistry/pregnancy	X[q]					X			X	X	X[q]	X[q]	
Adverse Events[r]	X	X----------X											
Prior & Concomitant Medications[s]	X	X----------X											
Plasma samples (in heparin) for PK analyses[t]		X	X	X	X	X	X	X	X				
Assessment for po Switch or need for continued therapy[u]						X	X	X	X	X			
Investigator's Assessment of Clinical Response											X	X	
Microbiological Procedures													
Blood culture[v]	X	As Clinically Indicated											
Respiratory culture & Gram stain[w]	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; eCRF = electronic case report form; EOT = end of treatment; ICF = informed consent form;

IxRS = Interactive Voice Response System/Interactive Web Response System; PK = pharmacokinetics; PORT = Pneumonia Outcomes Research Team; PTE = post-therapy evaluation; 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, with the exception of the blood culture sample collection and radiographic confirmation of pneumonia, should be completed within the 24 hours prior to randomization. The blood culture sample collection and radiographic confirmation of pneumonia should be completed within the 24 hours prior to the first dose of test article.

[c] The Day 6 visit is optional for subjects that have been switched to po test article and have been discharged from a hospital setting. A Day 10 visit should be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the EOT visit.

[d] 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.

[e] To be conducted 5 to 10 days after the subject's last day of therapy.

[f] To be conducted 30 to 37 days after the start of the first infusion 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 Successes 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.

[g] Written and signed ICF must be obtained before any 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 in Appendix 3.

[i] Subjects must have a confirming CXR or CT scan consistent with acute bacterial pneumonia within the 24 hours prior to the first dose of test article.

[j] Only subjects with a PORT Risk Class of II, III or IV are eligible for enrollment, see Appendix 2.

[k] Local laboratory hematology and chemistry evaluations required for assessing subject eligibility, urine dipstick test, a urine pregnancy test (for women only), serum transaminase or bilirubin levels.

[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 at least 7 days and no more than 14 days. 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 of iv medication and review the pharmacist's records. Oral test article may be dispensed and reconciled by blinded or unblinded personnel. Monitoring of oral medication accountability will be performed by the blinded or unblinded field monitor. Subjects discharged with po test article will be asked to return all unused test article and packaging at each visit (see Section 24). At the EOT visit subjects discharged with po test article will return any remaining unused po test article and site staff will peform accountability.

[m] A full physical examination will be completed at Screening (see Section 14.2.2), thereafter only changes from Screening measurements should be recorded as AEs in the eCRFs.

[n] Vital signs include body temperature, BP, pulse/heart rate, and RR.

[o] For the first 3 doses of test article, heart rate and BP should be recorded at the following times: just prior to the first infusion, within 30-90 minutes after the start of the first infusion, and at 3.5-5.5 hours after the start of the first infusion (see Table 1 and Section 16.1.2).

[p] A 12-lead ECG should be performed just prior (within 30 minutes) and 30-90 minutes after the start of the first infusion of the first and third doses of test article (see Section 16.1.4.1).

[q] 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.

[r] A subject's AEs and SAEs will be recorded and reported from signing of the ICF to the Final Follow-up assessment.

[s] Treatments that have been administered within the 7 days prior to the date of signing the ICF or during the Screening phase will be recorded in the eCRF. All medications and significant non-drug therapies administered after the first dose of test article must be recorded in the eCRF (see Section 13).

[t] Up to 4 samples will be collected per subject between study Days 1 to 7. The PK sample collection schedule for the individual subject will be provided by the sponsor (see Section 19).

[u] At any time after the first 3 days of iv treatment (after 4 iv doses) the subject may be switched to po medication based upon determination of clinical stability. Refer to protocol Section 14.3.1.2 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. At the investigator's discretion, all therapy may be discontinued after the seventh day of treatment, when the infection is considered clinically cured (based on normalization of the clinical signs and symptoms of infection and the investigator's clinical assessment that continued systemic antibacterial therapy is no longer needed).

[v] If bacteria are isolated from baseline blood cultures, repeat blood cultures should 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. (see Section 16.1.4.3)

[w] 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 (see Section 17.2.2.1).

9 INTRODUCTION

9.1 Background

Community Acquired Bacterial Pneumonia (CABP) is a leading cause of morbidity and mortality in the United States (US) and throughout the world (Mandell, et al., 2007). 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) (Niederman, et al., 1998). Furthermore, there is increasing resistance to antibiotics among common pathogens, with a resulting critical need for new antibiotics (Spellberg, et al., 2008). 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* (MRSA) and multi-drug resistant *Streptococcus pneumoniae* (MDR-SP) 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 (Paterson DL, 2004). 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.

The investigational product – PTK 0796 (hereafter referred to as omadacycline) – is the first member of the aminomethylcycline class of antibiotics, which are semi-synthetic derivatives of the tetracycline class (Noel, et al., 2012). 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.

Omadacycline is very active *in vitro* against most Gram-positive pathogens. It also exhibits activity against atypical pathogens (eg, *Legionella* species (spp.), *Chlamydophila* spp.), and some anaerobic and Gram-negative pathogens. The drug is active against strains expressing both mechanisms of tetracycline resistance, as well as strains that are resistant to currently available antibiotics, including methicillin, vancomycin, erythromycin, and ciprofloxacin (Omadacycline Investigator's Brochure [IB], Paratek, 2014).

Omadacycline has been shown to have *in vitro* activity against the most common typical and atypical causes of CABP including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and *Legionella pneumophila*. Omadacycline has potent activity against each of these pathogens and is not affected by tetracycline, penicillin, macrolide (inducible or constitutive ribosome methylation or efflux), or quinolone resistance in *Streptococcus pneumoniae*, nor penicillin or macrolide resistance in *Haemophilus influenzae*. Omadacycline has potent activity against methicillin-susceptible *Staphylococcus aureus* (MSSA) and is equally

potent against multi-drug resistant MRSA. In addition, omadacycline has demonstrated activity against *Chlamydophila pneumoniae* using a macrophage culture system and is expected to be active against *Mycoplasma pneumoniae* based on mechanism of action, intracellular penetration, and the activity of the tetracycline family. The *in vitro* activity of omadacycline was not affected by serum or lung surfactant, an important characteristic that is consistent with potential utility in infections involving the lower respiratory tract. Further, it has been shown to be effective in animal models of lower respiratory tract infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. It is expected that omadacycline will achieve levels in the lower respiratory tract comparable to related tetracyclines (doxycycline and tigecycline) which have been used to successfully treat subjects with CABP.

Omadacycline has been developed for both intravenous (iv) and oral (po) administration and has been well characterized in 16 Phase 1 studies. In addition, omadacycline has been evaluated in a randomized Phase 2 safety and efficacy study of 219 subjects with complicated skin and skin structure infections (cSSSI) and in a sponsor-terminated (for administrative reasons) randomized Phase 3 study that enrolled 143 subjects with cSSSI. Within the limits of the study sizes, omadacycline demonstrated numerical efficacy similar to an established comparator (linezolid) (Noel, et al., 2012; Paratek, 2014).

In the Phase 1 studies, 536 subjects were exposed to omadacycline iv or po formulations and 83 were exposed to placebo. Single iv doses up to 600 mg and single po doses up to 600 mg have been investigated. Multiple iv doses of 100 mg once daily and 200 mg once daily for up to 14 and 7 consecutive days, respectively, have been investigated. Multiple po doses of 200 mg once daily and 300 mg once daily for up to 10 consecutive days have also been investigated. In a Phase 2 study, 219 subjects with cSSSI were treated with omadacycline (n = 111) or linezolid (n = 108) for a mean of 10 and maximum of 20 days. In the sponsor-terminated Phase 3 study, 140 subjects with cSSSI were treated with omadacycline (n = 68) or linezolid (n = 72) for a mean of 10 and maximum of 20 days for omadacycline and 22 days for linezolid.

In Phase 1 studies, there were no discontinuations due to drug-related adverse events (AEs) in any subject who received multiple doses of omadacycline. An increased incidence of gastrointestinal (GI) AEs, particularly nausea, was noted in early po studies.

In iv studies in healthy subjects, modest and reversible alanine aminotransferase (ALT) increases were seen most notably with iv doses of 300 mg or greater (3 × higher than the therapeutic dose of 100 mg iv). There were no differences in ALT changes in the Phase 2 study compared to linezolid. Transient increases in heart rate were observed following administration of single and multiple doses of omadacycline, with a dose dependent mean increase of up to 15-20 beats per minute (bpm) compared to placebo for the first 4 hours after dosing. The increases in heart rate were not reported as AEs and not associated with any other cardiac findings. These increases were observed most consistently during the 2 hours immediately post-infusion. Beyond 6 hours after the start of the infusion, heart rate in all subjects, including controls, were comparable. A listing of all Phase 1 AEs is provided in Appendix I of the IB (Paratek, 2014).

In the Phase 2 study, omadacycline was well-tolerated. The most frequently reported AEs were GI-related occurring in 21 (18.9%) of 111 omadacycline-treated, and 18 (16.7%) of 108 linezolid-treated subjects. Nausea and vomiting were reported in 11 (9.9%) and 5 (4.5%), respectively, of omadacycline-treated subjects primarily during po treatment, compared to 8 (7.4%) and 4 (3.7%), respectively, of linezolid-treated subjects. Premature discontinuation of treatment due to an AE was very infrequent, occurring in 0.9% and 1.9% of omadacycline and linezolid-treated subjects, respectively.

There was no pattern of adverse changes in laboratory safety parameters among subjects treated with omadacycline or linezolid; changes in omadacycline-treated subjects were comparable to those observed with linezolid. In particular, there was no clinical or statistical difference between the treatment groups in ALT values or in other liver function tests (LFTs).

An increase in mean heart rate was observed, but to a much lesser extent than what was observed in Phase 1 studies. During the first 4 hours following the start of the first infusion of omadacycline there was a mean increase in heart rate from Baseline of 2.5 bpm for omadacycline (range from -20 to 40 bpm), peaking at 4 hours, as compared to a slight decrease of -0.1 bpm effect on heart rate for the linezolid treatment arm (range from -21 to 22 bpm), $p = 0.005$. This effect was transient and no QT prolongation was observed, consistent with the omadacycline thorough corrected QT interval (QTc) and human Ether-à-go-go-Related Gene (hERG) studies. Three subjects treated with omadacycline had AEs of tachycardia; 1 other subject reported palpitations. All 4 of these AEs were mild in intensity, all were assessed as either unrelated or unlikely related to test article, and none resulted in discontinuation of study treatment. Three of these AEs occurred during the first week of treatment; 1 AE occurred 8 days after completing therapy and was associated with a new infection (at a different site).

A Phase 3 cSSSI study enrolled 143 subjects prior to being discontinued due to a change in the Food and Drug Administration (FDA) Guidance for the development of antimicrobials for acute bacterial skin and skin structure infections (ABSSSI). The overall incidence of reported AEs in this study was comparable between the 2 treatment groups. The most commonly reported AEs (≥ 10% frequency in either treatment group) were nausea (26.5% omadacycline, 26.4% linezolid), headache (23.5% omadacycline, 6.9% linezolid), vomiting (8.8% omadacycline, 15.3% linezolid), diarrhea (4.4% omadacycline, 18.1% linezolid), and dizziness (10.3% omadacycline, 8.3% linezolid). Creatine phosphokinase (CK) elevation was reported in 8.8% of omadacycline-treated subjects compared to 2.8% for linezolid. AEs associated with ALT increases were reported in 4 linezolid-treated subjects (5.6%) compared to 1 omadacycline subject (1.5%). Six linezolid subjects (8.3%) reported rash compared to 1 subject (1.5%) on omadacycline. Four subjects experienced serious adverse events (SAEs) (3 omadacycline and 1 linezolid). The 3 omadacycline SAEs consisted of small bowel obstruction, large left pleural effusion, and worsening depression. The 1 linezolid SAE consisted of worsening right hand cellulitis.

For full details of safety findings in nonclinical and clinical studies, see the IB (Paratek, 2014).

Omadacycline has demonstrated activity against the most common CABP pathogens, including isolates resistant to standards of care. 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 CABP.

10 STUDY OBJECTIVES

10.1 Primary Objective

The primary objective of this study is to demonstrate that omadacycline 100 mg iv once every 12 hours (q12h) for 2 doses, followed by 100 mg iv/300 mg po once every 24 hours (q24h) is non-inferior to moxifloxacin 400 mg iv/po q24h in the treatment of adults with CABP.

10.2 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.

11 STUDY DESIGN

11.1 Description

This is a randomized (1:1), double-blind, active comparator-controlled, Phase 3 study comparing omadacycline and moxifloxacin for the treatment of adults with CABP. The number of subjects in Pneumonia Outcomes Research Team (PORT) Risk Class II will be limited to no more than 15% of randomized subjects. Subject randomization will be stratified by PORT Risk Class (II or III/IV), receipt of an allowed antibacterial therapy (see Appendix 1) in the 72 hours prior to study treatment, and geographic region as defined in the Interactive Voice Response System/Interactive Web Response System (IxRS) specifications and statistical analysis plan (SAP) (see Section 25.1). All subjects are expected to present with CABP severe enough to require a minimum of at least 3 days of iv treatment.

The study will consist of 3 phases: Screening, Double-Blind Treatment and Follow-up. Following the signing of an ICF, all Screening evaluations, with the exception of the blood culture sample collection and radiographic confirmation of pneumonia, should be completed within the 24 hours prior to randomization. The blood culture sample collection and radiographic confirmation of pneumonia should be completed within the 24 hours prior to the first dose of test article. Subjects who meet inclusion criteria, and do not meet exclusion criteria will be randomly assigned to a treatment group, and should receive their first dose of test article within 4 hours after randomization.

11.2 Rationale of Study Design

The study was designed in accordance with the FDA (FDA, 2014) and European Medicines Agency (EMA) (EMA 2011; EMA 2013) guidance on developing antimicrobial drugs for the treatment of CABP, in addition to the guidelines created jointly by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (Mandell, et al., 2007).

11.3 Rationale for Choice of Comparator

Given the wide acceptance of fluoroquinolone monotherapy as a safe, first-line option for treating subjects with CABP, the comparator drug for this study was selected to be moxifloxacin (400 mg iv q24h with the option to transition to 400 mg po q24h). 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.

11.4 Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 30 days. Following Screening, eligible subjects will be randomly assigned to receive 7 to 14 days of treatment with omadacycline or moxifloxacin. A follow-up office visit will occur 5 to 10 days after the last dose of test article, and another follow-up telephone contact will occur approximately 30 to 37 days after the first dose of test article.

11.5 Approximate Duration of Study

This study will be clinically complete in approximately 18 months.

11.6 Approximate Number of Subjects

Approximately 750 subjects will participate in this study at up to approximately 150 sites.

12 SELECTION OF SUBJECTS

Each subject must participate in the informed consent process and sign and date an institutional review board (IRB) or independent ethics committee (IEC) or research ethics board (REB) approved informed consent form (ICF) before any procedures specified in this protocol are performed.

12.1 Inclusion Criteria

To be eligible for randomization in this study, a subject must fulfill ALL of the following criteria:

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 systolic blood pressure (SBP) < 90 mm Hg
    - Heart rate > 90 bpm
    - Respiratory rate (RR) > 20 breaths/minute.
5. Has at least 1 clinical sign or laboratory finding associated with CABP:
    - Hypoxemia (partial pressure of arterial oxygen [PaO_2] < 60 mm Hg by arterial blood gas [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, see % bands calculation in Appendix 4, regardless of total peripheral WBC count).
6. 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 24 hours prior to the first dose of test article.
7. Has disease categorized as being PORT Risk Class II, III, or IV at Screening (see PORT Risk Class calculation in Appendix 2).
8. Is expected to require a minimum of at least 3 days of iv therapy for the initial treatment of CABP.
9. Females must have a negative urine 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 post therapy evaluation (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.

12.2 Exclusion Criteria

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 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 1).

2. Is known or suspected to have CABP caused by a pathogen that may be resistant to either test article (eg, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *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. Subjects with known or suspected hospital-acquired pneumonia (HAP) or healthcare-associated pneumonia (HCAP). HAP is defined as pneumonia with onset of clinical signs and symptoms ≥ 48 hours after hospitalization in an acute in-subject health care facility. HCAP is defined as pneumonia acquired in a long-term care or subacute/intermediate healthcare facility (eg, nursing home) or in a subject admitted with pneumonia following a recent hospitalization (discharged within 90 days of current admission and previously hospitalized for ≥ 48 hours).
5. Has known or is clinically suspected to have 1 or more of the following prior to randomization:
    - ALT or aspartate aminotransferase (AST) ≥ 2 × Upper Limit of Normal (ULN),
    - total bilirubin > 1.5 × ULN, or
    - evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy).
6. Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to Screening.
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 and/or present with tachyarrhythmia.
8. Requires any form of dialysis (eg, hemodialysis, peritoneal dialysis).
9. History or evidence of severe renal disease or has a calculated creatinine clearance (CrCL) < 30 mL/minute, using the Cockcroft-Gault equation (see equation in Appendix 4).
10. Evidence of significant immunologic 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

- 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 (see equivalent corticosteroid doses in Appendix 4).

11. Requires acute pharmacologic intervention to stabilize blood pressure (BP) and/or adequate tissue perfusion, OR has evidence of septic shock, defined by ALL of the following:
    - Fever or hypothermia documented by the investigator (temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
    - Heart rate > 90 beats/minute
    - RR > 20 breaths/minute
    - WBC > 12,000 cells/mm^3 or < 4000 cells/mm^3 or > 10% immature [band] forms, see % bands calculation in Appendix 4, regardless of the total peripheral WBC count
    - Hypotension with SBP < 90 mm Hg despite an iv fluid challenge of 20-30 cc/kg over a 30 minute period
    - Perfusion abnormalities that may include but are not limited to lactic acidosis (blood lactate concentration ≥ 4 mmol/L), oliguria, or acute alteration in mental status.
12. 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).
13. Pregnant or nursing (breastfeeding) women.
14. Has a history of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or to any fluoroquinolone antibiotic.
15. Has a history of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
16. Has a history of systemic lupus erythematosus or lupus-like syndrome.
17. Has current evidence of pancreatitis.
18. Has a history of a central nervous system disorder that may predispose to seizures or lower the seizure threshold.
19. Use of other investigational drugs within 5 half-lives or 30 days prior to Screening, whichever is longer.
20. Has previously been treated with omadacycline or previously enrolled in this study.
21. Any planned medical intervention that might interfere with the ability to comply with the study requirements.
22. 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.

12.3 Screen Failures

Subjects who sign the ICF but withdraw or are withdrawn from the study before random assignment to a 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 electronic case report form (eCRF) or IxRS system for screen failures.

13 PRIOR AND CONCOMITANT TREATMENT

Treatments that have been administered within the 7 days prior to the date of informed consent, or during the Screening period, 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 recorded as concomitant medications/significant non-drug therapies in the eCRF.

13.1 Permitted Treatment

Any concomitant treatment that is not prohibited explicitly in the protocol is permitted. A single dose of a short-acting potentially effective systemic antibacterial agent (see list in Appendix 1) administered within the 72 hours prior to the first dose of test article will be allowed for 25% or less of randomized subjects. Subjects requiring additional or alternative antibacterial therapy for 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.

13.2 Prohibited Treatment

The following treatments are prohibited:

All investigational medications or devices used during the 30 days prior to Screening are prohibited. Long-acting systemic antibacterial agents potentially effective for CABP are prohibited for 72 hours prior to randomization through End of Treatment (EOT), except in cases of clinical failure (see list in Appendix 1).

During po treatment, subjects will be instructed to avoid taking antacids and multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc).

13.3 Prohibited Concomitant Medications that may Interact with Moxifloxacin

Use of proarrhythmic or QT prolonging medications is prohibited through the Final Follow-up assessment. 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.

14 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 should then be assigned a study subject number. AEs must be recorded from the time the ICF is signed. Subjects who have been pre-screened and 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.

14.1 Visit Schedule and Assessments

Refer to STUDY FLOWCHART for the study procedures and their time points. There are 3 protocol defined phases of the study: Screening, Double-Blind Treatment and Follow-up. The study will have the following protocol-defined evaluations:

- Visits will be conducted daily on study Days 1 through 7. The Day 6 visit is optional for subjects that have been switched to po test article and have been discharged from a hospital setting. A Day 10 visit should be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the End of Treatment (EOT) visit.
- End of Treatment: to 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 before completion, the EOT visit should be conducted.
- PTE: to be performed 5 to 10 days after the subject's last day of therapy.
- Final Follow-up assessment: Study Day 30 to 37 (after start of first infusion of test article).

Subjects who discontinue study treatment prematurely should have the EOT visit and the procedures listed for that visit in the STUDY FLOWCHART, a PTE visit and a Final Follow-up assessment, if possible. The site should also collect subject safety information through the Final Follow-up assessment.

14.2 Screening Phase

Due to the nature of the disease under study, the Screening period should be completed within 1 day (24 hour period). The Screening will be used to establish subject eligibility and Baseline characteristics for each subject. Subjects are eligible for Screening if they present with CABP. Following the signing of an ICF, site personnel will collect the following information:

- Demographics
- Medical/surgical history and current medical conditions
- Physical examination
- Vital signs
- Review of inclusion/exclusion criteria

- Local and Central Laboratory tests: hematology, chemistry, urine tests, pregnancy test (for women only)
- 12-lead electrocardiogram (ECG)
- Concomitant medications (past 7 days)
- AEs and SAEs since the signing of the ICF
- Assessment of CABP symptom severity (cough, sputum production, pleuritic chest pain, dyspnea) (See Appendix 3 for symptom severity scale)
- Radiologic (CXR or CT scan) evaluation of pneumonia
- ABG (or pulse oximetry) and PORT Risk Class Assessment
- Microbiological assessments (blood culture, respiratory culture & Gram stain, local lab urine antigen tests, and blood for Central Lab testing)

14.2.1 Subject Demographics/Other Baseline Characteristics

Subject demographic and Baseline characteristic data to be collected on all subjects include: date of birth, gender, race, ethnicity and childbearing potential. Medical history/current medical condition data includes data until the signing of informed consent. Whenever possible, diagnoses are to be recorded.

The investigator will perform a comprehensive history and physical examination at the Screening evaluation with particular attention to items indicated below.

14.2.1.1 Medical History Relating to the Infection Under Study

- 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.).
- History of pneumococcal vaccination (eg, Pneumovax, Prevnar 13).
- All systemic antimicrobials from onset of the infection will be recorded under concomitant medications.

14.2.2 Physical Examination

At Screening, the physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams may be performed. Height and body weight will be measured.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of test article must be included in the subject's eCRF.

14.2.3 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 (see Section 12.1).

14.2.4 Radiologic Evaluation of Pneumonia

A CXR or CT scan will be obtained for all subjects at Screening (within 24 hours prior to the first dose of test article). 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.

14.2.5 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 2). As part of the Inclusion Criteria to this study, all subjects must have disease characterized as PORT Risk Class of II, III, or IV at randomization.

14.2.6 Urine Tests

A urine dipstick test will be performed locally at Screening. Urine dipstick results will be recorded on the eCRF. A urine pregnancy test will be performed locatlly during Screening for all women and the results will be recorded on the eCRF. Urine will also be tested locally at Screening for the presence of *Legionella pneumophila* and *Streptococcus pneumoniae* antigens and the results will be recorded on the eCRF.

14.3 Double-blind Treatment Phase

14.3.1 Assessments While on Test Article

The double-blind treatment period is up to 14 days in duration. Subjects who met inclusion criteria and did not meet exclusion criteria will be randomly assigned to a treatment group, and should receive their first dose of test article within 4 hours after randomization.

The following assessments (see STUDY FLOWCHART) will be done:

- Vital signs
- Physical examinations (worsening of observations since the Screening examination will be recorded as AEs)
- AEs and SAEs
- Concomitant treatments
- CABP symptom severity scale (performed by the investigator) (Appendix 3)
- Microbiological assessments
- 12-lead ECG (should be performed just prior [within 30 minutes] and 30-90 minutes after the start of the first infusion of the first and third doses of test article, at the Day 7 visit, at the EOT visit, and as otherwise clinically indicated)
- Blood for Central Laboratory assessments: hematology, chemistry, pregnancy (for women only)
- Test article administration and accountability
- Assessment for po switch or need to continue therapy
- Investigator's assessment of clinical response

14.3.1.1 Intravenous Treatment Phase (Test Article)

The iv treatment phase (minimum of 3 days, 4 doses) will follow a double-dummy design with placebo infusions matched to active omadacycline and moxifloxacin infusions as shown in Table 1. Infusions of omadacycline and matched placebo will be administered continuously over approximately 30 minutes. During the first 24 hours of iv treatment, subjects on the moxifloxacin treatment arm will receive a placebo infusion to match the t = 12 h infusion in the omadacycline arm as shown in Table 1.

Infusions of moxifloxacin and matched placebo will be administered continuously over approximately 60 minutes. All infusion start and stop times are to be recorded in 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. If gravity administration is not the standard of care then an infusion pump may be used. If an infusion pump is used then a potentially unblinded administrator will be required (see Section 25.3). All subjects should remain in a hospital setting while on iv test article (for a minimum of 3 days, 4 doses). Thereafter, subjects should not be discharged from the hospital prior to completion of protocol specified assessments, except in circumstances where the Principal Site Investigator has clearly identified that sufficient resources and processes are available to complete all study procedures as defined in the protocol

and the sponsor has reviewed and approved the process for outpatient iv test article administration.

Table 1 Treatment Regimens for IV Test Article

Infusion Regimen[a]	Omadacycline Arm[b,c]	Moxifloxacin Arm[b,c]
t = 0 h[d]	omadacycline 100 mg in 100 mL NS 250 mL NS placebo	100 mL NS placebo moxifloxacin 400 mg in 250 mL 0.8% saline
t = 12 h	omadacycline 100 mg in 100 mL NS	100 mL NS placebo
t = 24 h[d]	omadacycline 100 mg in 100 mL NS 250 mL NS placebo	100 mL NS placebo moxifloxacin 400 mg in 250 mL 0.8% saline
t = 48 h[d]	omadacycline 100 mg in 100 mL NS 250 mL NS placebo	100 mL NS placebo moxifloxacin 400 mg in 250 mL 0.8% saline
t = 72 h[e], then q24h[d]	omadacycline 100 mg in 100 mL NS 250 mL NS placebo	100 mL NS placebo moxifloxacin 400 mg in 250 mL 0.8% saline

t = time; NS = Normal saline (0.9% sodium chloride) for injection; q12h = every 12 hours; q24h = every 24 hours.

[a] The start time of the first infusion is designated time 0 (t = 0 h), followed by 2 q12h doses (t = 12 h, t = 24 h), and then all subsequent doses are q24h for a minimum of 3 days, 4 doses of iv treatment (through t = 48 h). See Section 14.3.1.1.2 for allowed adjustments in iv dosing schedules.

[b] All 100 mL infusions of omadacycline or 100 mL NS placebo are administered continuously over 30 minutes (at least 30 minutes and not more than 45 minutes).

[c] All 250 mL infusions of moxifloxacin or 250 mL NS placebo are administered continuously over approximately 60 minutes.

[d] At these time points a 100 mL infusion will be administered first, followed by a 250 mL infusion. It is important to follow this sequence of administration.

[e] Beginning with the fifth dose (t = 72 h), based on the investigator decision the therapy could be iv or switch to po therapy. Note, the first po dose should be administered in the morning, 12-24 hours after the last iv dose, therefore the first po dose may occur as early as t = 60 h, see Section 14.3.1.3.

14.3.1.1.1 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 based on the overall clinical assessment of the subject:

- continue iv test article;
- switch to po test article (after a minimum of 3 days [4 doses] of iv therapy) Note, the first po dose should be administered in the morning, 12-24 h after the last iv dose, therefore the first po dose may occur as early as t = 60 h, see Section 14.3.1.3;
- discontinue test article – this decision will prompt the EOT evaluation.

Each daily decision is to be recorded on source documents and the information transferred to eCRFs by blinded study site personnel.

Note the following:

- At all times during the study the decision to continue iv, switch to po, or discontinue test article is made based on the clinical judgment of the investigator.
- The investigator may use the culture and susceptibility results from the local microbiology laboratory to help guide therapy; however, decisions to continue or discontinue test article should be based on clinical response rather than susceptibility results (as omadacycline susceptibility testing is not available at the local site). If the CABP is caused by a microorganism that is not susceptible to moxifloxacin *in vitro,* the decision to continue or discontinue study treatment should be based on the subject's clinical course and the investigator's clinical judgment. These cases should be discussed with the Medical Monitor. The rationale for this decision should be recorded in source documents.

14.3.1.1.2 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, 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.

14.3.1.2 Switch to Oral Treatment

The decision to switch to po treatment should be made by the investigator. For a subject to be considered clinically stable and meet criteria for transition to a po regimen, they must have the following findings 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 ≥ 95 mm Hg
- Oxygen saturation ≥ 90% as measured by pulse oximetry or PaO_2 ≥ 60 mm Hg by ABG
- No worsening of CABP symptoms (cough, sputum production, pleuritic chest pain, dyspnea) compared to Screening
- Normal mental status ("absence of confusion" or pre-illness Baseline for subjects who did not have normal mental status before onset of pneumonia)
- Ability to maintain po intake.

Switch to po will NOT be permitted until after the subject has completed at least the first 3 days of iv treatment (after 4 iv doses).

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. For subjects that have been switched to po test article and discharged from the hospital prior to study Day 6, visits must be conducted on study Days 4 and 5, while a study Day 6 visit is optional.

14.3.1.3 Oral Treatment Phase (Test Article)

Treatment regimens for po dosing are shown in Table 2. 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 iv dose.

The po treatment phase will employ a double-blind, double-dummy design using omadacycline placebo comparator tablets of matching size and shape to active omadacycline tablets and matching over-encapsulated placebo and active moxifloxacin tablets.

To maintain investigator and subject blinding, subjects on both arms will receive 2 tablets and 1 over-encapsulated tablet in the morning as shown in Table 2 below.

Table 2 Treatment Regimens for Oral Test Article

Time of Dosing	Omadacycline Arm	Moxifloxacin Arm	Dosing Condition[a,b]
Morning	Two 150 mg tablets and 1 over-encapsulated placebo tablet resembling moxifloxacin	One 400 mg over-encapsulated tablet and 2 placebo tablets resembling omadacycline tablets	Fasting overnight (no food or drink except water for at least 6 hours) before dosing; after dosing, no food for 2 hours, no dairy products for 4 hours

[a] All doses of po test article should be taken with water.
[b] All subjects will be instructed to avoid taking antacids and multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) while taking po 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 7-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.

14.3.1.3.1 Management while on Oral Test Article

While the subject is receiving po therapy, the investigator should assess the subject on study Day 7, 10 and 14 and choose 1 of the following actions:

- continue po test article;

- discontinue test article – this decision will prompt the EOT evaluation.

The date, time and the decision of the investigator will be recorded on source documents and the information transferred to eCRFs by study site personnel.

The investigator may use the culture and susceptibility results from the local microbiology laboratory to help guide therapy; however, decisions to continue or discontinue test article should be based on clinical response rather than susceptibility results (as omadacycline susceptibility testing is not available at the local site). If the CABP is caused by a microorganism that is not susceptible to moxifloxacin *in vitro,* the decision to continue or discontinue study treatment should be based on the subject's clinical course and the investigator's clinical judgment. These cases should be discussed with the Medical Monitor. The rationale for this decision should be recorded in the source documents.

14.3.2 Permitted Dose Adjustments and Interruptions of Test Article

None.

14.4 Follow-up Phase

Subjects will be evaluated at 2 visits after the completion of treatment: at the PTE 5 to 10 days after the last treatment day and at a Final Follow-up assessment 30 to 37 days after the first dose of treatment (see STUDY FLOWCHART). 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 AEs or clinically significant laboratory or ECG abnormalities noted at or after the PTE visit. Otherwise, this assessment is to be performed with an in person study visit.

14.5 Total Volume of Blood Collected

The total volume of blood collected from each subject for this protocol will be up to approximately 170 mL depending on the subject's duration of study participation.

15 TEST ARTICLE AND ADMINISTRATION

Test article will be supplied by Paratek Pharma, LLC (the sponsor). Test article will be labeled according to regulations.

The test article 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.

15.1 Test Article Administration

Subjects will be randomized (1:1) to 1 of the following 2 treatment arms:

- Investigational therapy: omadacycline, 100 mg iv q12 h (first 2 doses), followed by 100 mg iv q24h (starting 24 hours after first dose), with the option to switch to 300 mg (two 150 mg omadacycline tablets and 1 over-encapsulated placebo tablet matching moxifloxacin) po q24h after at least 3 days (4 doses) of iv treatment.
- Reference therapy: moxifloxacin, 400 mg iv q24h (with a single placebo infusion to match the omadacycline dosing regimen 12 hours after the first dose on Day 1) with the option to switch to 400 mg (one 400 mg moxifloxacin over-encapsulated tablet and 2 placebo tablets matching omadacycline tablets) po q24h after at least 3 days (4 doses) of iv treatment.

All subjects should receive at least 7 days and at most 14 days (iv and po combined) of test article therapy.

15.1.1 Identity of the Investigational Product

Table 3 Intravenous Formulation

Active ingredient	Omadacycline
[redacted]	[redacted]

Table 4 Oral Formulation

Active ingredient	Omadacycline
[redacted]	[redacted]

Table 4 Oral Formulation

Active ingredient	Omadacycline
[redacted]	[redacted]

15.2 Investigational and Comparator Test Article

15.2.1 Investigational Test Article: Omadacycline

- 100 mg iv q12 h for first 2 doses followed by 100 mg iv q24h (starting 24 h after first dose)
- 300 mg po q24h after completion of at least 3 days (4 doses) of iv treatment at the discretion of the investigator and meeting minimum criteria for po switch as outlined in Section 14.3.1.2
- Total treatment duration of 7 to 14 days

15.2.2 Comparator Test Article: Moxifloxacin

- 400 mg iv q24h (with a single placebo infusion to match the omadacycline dosing regimen 12 hours after the first dose on Day 1)
- 400 mg po q24h after completion of at least 3 days (4 doses) of iv treatment at the discretion of the investigator and meeting minimum criteria for po switch as outlined in Section 14.3.1.2
- Total treatment duration of 7 to 14 days

15.3 Subject Compliance while on Oral Test Article

Intravenous administration and compliance will be managed by study personnel prior to switching to po test article. Study personnel at the site, should monitor po test article compliance at each study visit, by comparing the returned test article with the dosing information reported in the subject charts and subject diaries. 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 and subject diaries.

16 SAFETY

Any subject who receive test article will be included in the evaluation for safety.

Safety is assessed by the following measures:

- Physical exams
- AEs and SAEs
- Vital signs
- Laboratory assessments
- 12-lead ECG
- Pregnancy assessments

16.1.1 Physical Examinations

After Screening, a physical examination should be conducted on the study days indicated in the STUDY FLOWCHART and at the EOT and PTE visits. Any abnormalities or changes in intensity noted during the review of the body systems should be documented in the source documents. If a new clinically significant finding occurs (ie, not noted at Screening) after the Screening exam, it must be captured as an AE. In addition, resolution of any clinically significant abnormal findings that have been reported as an AE will be noted in the medical record and the AE eCRF.

16.1.2 Vital Signs

Vital signs including body temperature, BP, pulse/heart rate, and RR should be recorded prior to each dose while the subject is on iv treatment. Thereafter vital signs should be recorded at all visits, with the exception of the Final Follow-up visit.

- In addition, for the first 3 doses of test article (t = 0 hours, t = 12 hours, t = 24 hours; see Table 1) heart rate and BP should be recorded at the following times: just prior to the first infusion, within 30-90 minutes after the start of the first infusion, and again 3.5-5.5 hours after the start of the first infusion.

All vital signs should be captured after 10 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 validated device, with an appropriately sized cuff.

Pulse will be measured using an automated validated device, when available. If not available, pulse will be measured manually.

In addition to the above, BP and heart rate may be measured whenever clinically indicated at the discretion of the treating physician. Any subject who experiences an AE of non-pleuritic cardiac chest pain, palpitations, or tachyarrhythmia while on study should have an ECG and an evaluation by the investigator (see Section 16.1.4.1).

Temperature will be obtained using an electronic (rapid reading) device whenever possible.

RR will be determined by observation.

Once the subject is discharged from the hospital, vital signs will be recorded at each return clinical visit by blinded study personnel.

16.1.3 Laboratory Evaluations

Blood samples for hematology, chemistry and coagulation (prothrombin time only) should be drawn at Screening, Day 4, Day 7, Day 10, EOT, and PTE (see STUDY FLOWCHART). At Screening only, 1 sample will be analyzed at a local laboratory for confirmation of eligibility criteria and a second sample will be shipped to the Central Laboratory for analysis. At all other visits samples should be shipped to the Central Laboratory for analysis.

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 meeting inclusion/exclusion criteria, it is expected that local laboratory testing will be used in circumstances where this testing is needed to assess a subject's WBC count or differential, serum transaminase or bilirubin levels, serum creatinine or pregnancy testing (for women only).

16.1.3.1 Hematology

The analytes listed in the table below (Table 5) will be measured at the Central Laboratory.

Table 5 Hematology Panel

Hematocrit	White blood cell differential (as % cell counts)
Total red blood cell count	-Neutrophils
Hemoglobin	-Lymphocytes
Mean cell hemoglobin	-Monocytes
Mean cell hemoglobin concentration	-Eosinophils
Mean cell volume	-Basophils
WBC count	
Platelet count	

Table 5 Hematology Panel

16.1.3.2 Clinical Chemistry

The analytes indicated in the table below (Table 6) below will be measured at the Central Laboratory.

Table 6 Clinical Chemistry Panel

Blood glucose	ALT	LDH
Urea	AST	CK
Creatinine	AP	(CK isoenzyme testing as required)
Sodium	Total bilirubin	Calcium
Potassium	Total protein	Phosphate
Chloride	Magnesium	Cholesterol
Bicarbonate	Albumin	Uric Acid
		GGT
		Amylase
		Lipase

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AP = alkaline phosphatase; LDH = lactate dehydrogenase; CK = creatine phosphokinase; GGT = gamma-glutamyl transpeptidase.

16.1.3.3 Other laboratory tests

Table 7 Additional Laboratory Tests

Category	Test	Note
Coagulation	INR	Prothrombin time only
Female endocrinology	β-hCG (for women only)	See Section 16.1.4.2 below. Done both locally (urine) and centrally (serum)

INR = international normalized ratio; β-hCG = beta – human chorionic gonadotropin.

16.1.4 Safety Studies to be Performed Locally

16.1.4.1 Electrocardiogram

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

- Screening
- Just prior (within 30 minutes) to the start of the first infusion of the first dose of test article (t = 0 h on Table 1)
- 30-90 minutes after the start of the first infusion of the first dose of test article

- Just prior (within 30 minutes) to the start of the first infusion of the third dose of test article (t = 24 h on Table 1)
- 30-90 minutes after the start of the first infusion of the third dose of test article
- At the Day 7 visit
- At the EOT visit
- In any case in which a subject develops an AE of non-pleuritic cardiac chest pain, palpitations, tachyarrhythmia or as otherwise clinically indicated (see Section 16.1.2)

Reading and interpretation of the ECG will be performed centrally and provided to the investigator. The investigator is responsible for reviewing interpretations and for retaining hard copies of the reports.

16.1.4.2 Pregnancy and Assessments of Fertility

All women will have a urine pregnancy test at the site at the Screening visit. Urine pregnancy test kits will be provided by the sponsor through the Central Laboratory. If a positive urine pregnancy test result is obtained at the site, the woman is not to be randomized. A serum sample for β-hCG testing will be collected at the Screening visit and sent to the Central Laboratory for confirmation of the urine pregnancy results. Serum samples for β-hCG testing at the Central Laboratory also will be collected at EOT and PTE. If a positive β-hCG result is reported by the Central Laboratory after a woman is enrolled, test article administration should be discontinued (see Section 21.6).

16.1.4.3 Blood Cultures

Two sets of blood cultures (first set = 1 aerobic bottle + 1 anaerobic bottle, second set = 2 aerobic bottles) 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 15-30 minutes apart. If bacteria are isolated from baseline blood cultures, repeat blood cultures should 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 (see Section 17.2.2.1).

16.1.4.4 Additional Local Laboratory Tests

The investigator may order additional local laboratory tests consistent with his/her routine standard of care.

16.2 Appropriateness of Safety Measurements

The safety assessments selected are standard for this indication and subject population.

17 EFFICACY

17.1 Primary and Secondary Efficacy Variables

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

- Successful Early Clinical Response (72-120 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.
- Successful Investigator's Assessment of Clinical Response 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.

The Early Clinical Response endpoint will be the primary efficacy outcome supporting registration with the FDA in the US and this will be tested in the intent-to-treat (ITT) analysis population. The Investigator's Assessment of Clinical Response at PTE endpoint will be the primary efficacy outcome supporting registration with the EMA in the European Union (EU) and will be tested in the ITT and clinically evaluable (CE) populations (co-primary endpoints). The analysis of the Investigator's Assessment of Clinical Response at PTE as the primary efficacy outcome will be detailed in a separate SAP for the EMA.

Secondary efficacy variables will include:

- Response category for Early Clinical Response
- Clinical Response category for Investigator's Assessment of Clinical Response at EOT and PTE
- Clinical Response category according to the identified causative pathogen

17.2 Key Assessments

The following is a list of key assessments that will be performed:

- Assessment of signs and symptoms of CABP by the investigator
- Microbiological assessment of the infection
- Assessment of clinical response

Each of the key assessments is described in further detail below.

17.2.1 Assessment of CABP Symptom Severity

The assessment of CABP symptoms observed by the investigator should be conducted at every scheduled evaluation with the exception of the Final Follow-up assessment (see STUDY FLOWCHART) The investigator will specifically assess the 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 scores into the eCRF. For subjects that have been switched to po test article and discharged from the hospital prior to study Day 6, visits must be conducted on study Days 4 and 5, while a study Day 6 visit is optional.

17.2.2 Microbiological Assessments

17.2.2.1 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 STUDY FLOWCHART). 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 low power field (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 low power field (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.

In addition, Gram stained slides of specimens, particularly those of sputum samples, will be submitted to the Central Laboratory. If it is necessary, based on local laboratory requirements, a duplicate slide of the primary specimen can be prepared for the purposes of retaining 1 at the local laboratory.

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

17.2.2.2 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.

17.2.2.3 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.

17.2.3 Assessment of Clinical Outcome

Assessment of clinical outcome will occur at Early Clinical Response assessment (programmatically), EOT, and PTE as described below.

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

The formal determination of the response to therapy at the Early Clinical Response 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 Early Clinical Response 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 17.2.1 and STUDY FLOWCHART). For subjects that have been switched to po test article and discharged from the hospital prior to study Day 6, visits must be conducted on study Days 4 and 5, while a study Day 6 visit is optional.

Clinical Success: at the Early Clinical Response 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 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 Early Clinical Response.

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 Early Clinical Response 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 1 under study.
- Discontinued study therapy due to an AE and received alternative antibacterial treatment for CABP prior to the Early Clinical Response assessment,.
- Death prior to the Early Clinical Response 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, were lost to follow-up, other reason (specify).
- Other specified reason.

17.2.3.2 Clinical Evaluation of the Infection Under Study at EOT

EOT 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 whether or not the subject meets the criteria of 1 of the following clinical outcomes:

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:

- Subject is receiving antibacterial therapy that may be effective for the infection under study for a different infection from the 1 under study.
- Death prior to EOT visit.

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

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

17.2.3.3 Clinical Evaluation of the Infection Under Study 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 whether or not the subject meets the criteria of 1 of the following clinical outcomes:

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).

- The subject is receiving antibiotics that may be effective for the infection under study for a different infection from the 1 under study.
- Death prior to PTE.

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

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

18 OTHER ASSESSMENTS

18.1 Resource Utilization

The number of hospital days for all hospital admissions during the study period will be calculated. Hospital days will be specified from date of admission to date of discharge.

19 PHARMACOKINETIC PLASMA SAMPLES FOR OMADACYCLINE CONCENTRATION

19.1 Selection of Sites for PK Studies

Pharmacokinetic data will be analyzed using a population PK model. In order to maximize the number of subjects who participate so that this analysis is optimal, 1 criterion for selection of sites in this study will be the site's ability to participate in the PK portion of the study. To assure the quality and accuracy of the PK samples, samples will be obtained only from subjects participating at a center that has the appropriate facilities and capabilities and has been specifically trained by the sponsor.

19.2 Collection of PK Samples

PK samples will be collected using a sparse sampling method for the population PK model. The number of samples and collection schedule will vary for individual subjects. The sponsor will notify the site of the PK sample collection schedule for the individual subject. Up to 4 samples will be collected per subject between study Days 1 to 7 (see STUDY FLOWCHART).

The sponsor will provide heparin tubes for the collection of PK blood samples and will provide freezer tubes for storing the plasma. Blood will be collected either by fresh venipuncture or via a cannula used SOLEY for that purpose; blood for PK samples must NOT be drawn through the same iv access used for administration of test article.

The dates and times for all doses of test article and PK sample collections will be recorded. For intravenously administered doses of test article, the start and stop times for each infusion shall be recorded. The identification of the subject and the time of the sample collection to the nearest

minute should be immediately recorded on the tube. The tube will be centrifuged at 1500 × *g* for 10 minutes and the separated plasma transferred in 2 equal aliquots into pre-labeled tubes; and the tubes frozen at -70ºC within 60 minutes of collection. The time the sample is frozen should be recorded to the nearest minute.

19.3 Storing and Shipping of PK Samples

After all of the PK samples from a single subject have been collected and frozen at -70ºC, 1 sample from each time point can be batched together with corresponding complete sample sets from other subjects and be carefully packaged and shipped frozen at -70ºC to the Central Laboratory. Samples are to be shipped with sufficient dry ice to remain frozen during transit (up to a possible 4-day period). The Central Laboratory will process these samples and forward them at -70ºC to the Analytical Laboratory designated by the sponsor. For each subject and time point, the remaining stored aliquots will be retained on-site at –70ºC until released or requested by the sponsor.

19.4 Analysis of PK Samples

The Analytical Laboratory will assay the samples for omadacycline using a specific, sensitive and validated Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS) method approved by the sponsor.

20 OTHER BIOMARKERS

None.

21 SAFETY MONITORING

21.1 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.

A 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 cancer.
- 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 1 of the outcomes listed 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, 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.

In addition, a hospitalization for a preexisting condition that has not worsened does not constitute an SAE.

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.

A protocol-related AE is an AE occurring during a clinical study 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.

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.

21.2 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 faxing a completed SAE Report Form to the fax number below or emailing a completed SAE Report Form to the e-mail address below.

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

21.3 Overdose

Any administration of omadacycline of greater than 600 mg (iv or po) 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 moxifloxacin of greater than 2.8 grams in 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 24-hours. 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. The IxRS will also provide a confirmation report of the drug assignment to site personnel. The site personnel will retain this confirmation report.

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

21.4 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 faxingor emailing the Clinical Test Article Error Incident Report Form as indicated in the Emergency Contacts (See Section 2).

21.5 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 within 30 days 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?" Signs and symptoms should be recorded using standard medical terminology.

Any unanticipated risks to the subjects must be reported promptly to the IRB/IEC/REB.

21.6 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.

21.7 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee (DSMC), independent of the sponsor, will provide ongoing monitoring of safety data on an approximately quarterly basis. The DSMC will review the data as treatment A and treatment B. The charter for the DSMC will clearly outline 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 sponsor will be maintained, in addition to the procedures that ensure the independence and objectivity of the DSMC's activities. As the DSMC will be reviewing safety data for this study, it may require reports indicating treatment assignment to assist in clinical interpretation of its findings. Therefore, the DSMC charter will provide a detailed explanation of the processes by which the DSMC 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.

22 DATA ANALYSIS

All analyses of data for this study will comply with International Conference on Harmonisation 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).

A SAP incorporating the sections below and with mock table, figure and listing (TFL) shells will be prepared prior to the start of the study and approved and finalized by the sponsor prior 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. As a consequence of differing regulatory requirements for the choice of the primary efficacy outcome and statistical analyses, 2 separate SAPs will be prepared (FDA and EMA). The sections below indicate the overall structure and approach of the analyses.

Inferential statistical analyses of the primary and secondary outcomes will be conducted as outlined below. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations (SD), medians, minimums, and maximums for continuous variables will be provided. All comparisons will be for omadacycline versus moxifloxacin. Exploratory analyses may also be performed. Listings of individual subject's data will be produced.

22.1 Analysis Populations

A number of subject populations have been defined for the various analyses of efficacy and safety, as follows:

- The ITT population will consist of all randomized subjects.
- The microbiological intent-to-treat (microITT) 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 *Chlamydophila 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 at Screening.
- The Safety population will consist of all randomized subjects who receive test article.

22.2 Subject 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/m^2)
- 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).

22.3 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.

22.4 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 (see Section 25.1).

22.4.1 Early Clinical Response Efficacy Variable

The Early Clinical Response can be Clinical Success, Clinical Failure or Indeterminate (defined in Section 17.2.3.1).

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.

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

This is defined as the Investigator's Assessment of Clinical Response at the PTE visit with outcomes of Clinical Success, Clinical Failure or Indeterminate (defined in Section 17.2.3.3) 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.

22.4.3 Statistical Model, Hypothesis, and Method of Analysis

To demonstrate 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 Early Clinical Response endpoint will be assessed in the ITT population as follows:

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

H_{ai}: $\theta_T - \theta_C > -\Delta$

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 Early Clinical Response (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 (Miettinen and Nurminen, 1985). 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 97.5% 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 those subjects with a PORT Risk Class of III or higher. The 97.5% CI will be calculated using the stratified (for the randomization stratification factors) method proposed by Miettinen and Nurminen (Miettinen and Nurminen, 1985). 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 for approving an ineffective drug based on PTE efficacy is 1.25%, regardless of the result for the Early Clinical Response endpoint and vice versa. An adjustment would only be required if winning on at least 1 endpoint would result in global approval which is not the case here. 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.

22.4.4 Additional Analyses of the Primary Efficacy Outcomes

Additional and sensitivity analyses of the primary efficacy outcomes (Early Clinical Response 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 Early Clinical Response 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, receipt of allowed antibacterial therapy in the 72 hours prior to study treatment and geographic region stratum by treatment group. For each PORT Risk Class stratum, each prior antibacterial therapy stratum and each geographic region stratum, a 2-sided 95% CI for the observed difference in Early Clinical Response 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.

22.5 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 (Miettinen and Nurminen, 1985). For Investigator's Assessment of Clinical Response at PTE in the ITT and CE populations 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 Early Clinical Response will 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 (Miettinen and Nurminen, 1985).

The number and percentage of subjects with an Early Clinical Response 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.

22.6 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 (Miettinen and Nurminen, 1985).

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), PaO_2 (≥ 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/mm^3 or ≥ 4,000 cells/mm^3) 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.

A concordance analysis of Early Clinical Response and Investigator's Assessment of Clinical Response at PTE in the ITT analysis set will also be presented.

22.7 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.

22.7.1 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.

22.7.2 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.

22.7.3 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.

22.7.4 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.

22.8 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)

- 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)

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

22.9 Pharmacokinetics

Population PK analysis will be conducted to characterize PK parameters. A population PK data set including subjects with 1 or more quantified omadacycline concentration determinations will be constructed from the dates and times of the doses and blood samples along with all the bioanalytical determinations and subject background information. If the actual date or time for a blood sample or dose is missing, the related bioanalytical determination of the PK concentration will be excluded from all analyses. Omadacycline concentrations below the limit of quantification will be treated as missing data in summary statistics and for the calculation of PK parameters.

Variables including age (years), body weight (kg), gender, and race/ethnicity along with other covariates previously determined to be important will be incorporated into the population PK database. Based on the subjects in the population analysis data set, descriptive summaries at Screening for these variables will be reported. Outliers may be excluded from the analysis. These will be determined by a scatter plot of the observed concentration versus time post dose and reported. The distribution of the number of samples contributed per subject to the model-based analysis will be tabulated. Also, simple summary descriptive statistics for the concentration of samples by study day or week will be computed.

22.9.1 Population PK Modeling

Results from Phase 1 studies indicate that omadacycline PK is linear and that following iv infusion, plasma concentration-time profiles show a 3-compartmental disposition. Therefore, the probable structural PK model would be a 3-compartment model with zero order input for iv infusion and first order input for po administration. This PK model contains the parameters clearance, volume of distribution, bioavailability and absorption rate constant. The associated population models are nonlinear mixed-effects models. The population model adds random effects and covariates for the PK parameters in order to recognize differences among individuals and similarities across observations corresponding to the same subject. At the time of the population modeling, previously reported structural PK models will be considered first. A residual error model combining additive error and proportional error will also be initially considered. Simplifications (eg, fewer random effects, or an alternative residual error model) may be appropriate if the diagnostics for the model suggest false convergence. Additional covariates will be investigated graphically (gender, race/ethnicity, age) as part of the model diagnostics and some may be retained in the final model and additional ones in a competing model to deliver estimates of arguably insignificant effects. Scatter plots of the observed concentrations versus population-estimated and individually estimated concentrations will be

used as part of the overall assessment of the overall quality of the fit. During modeling, the broad principles outlined by the FDA will be followed (FDA, 1999).

The individual model-based exposure measures at steady state (area under the Concentration/Time curve [$AUC_{0\text{-}24,ss}$], time to maximum plasma concentration [$T_{max,ss}$], maximum plasma concentration [$C_{max,ss}$]) will be computed and summarized.

22.10 Pharmacogenetics/Pharmacogenomics

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

22.11 Biomarkers

Not applicable.

22.12 PK/PD

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.

22.13 Sample Size Calculation

The study is designed to show NI in the primary efficacy outcome of Early Clinical Response 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 the historical data regarding the treatment effect of antibiotics in pneumonia.

In the ceftaroline clinical studies which enrolled only PORT Risk Class III and IV, the rates for clinical success based on Investigator's Assessment of Clinical Response at the PTE visit ranged from 77%-87% in the modified ITT and CE populations, with the rates in the modified ITT population lower than those in the CE population (Teflaro full prescribing information, 2013). Thus, it is reasonable to assume clinical success rates of 79% in the ITT and 85% in the CE populations.

For the Investigator's Assessment of Clinical Response at PTE endpoint in the ITT population (PORT Risk Class III and IV) assuming an outcome rate of 79% in both treatment groups, NI margin of 10%, 80% power and a 1-sided alpha level of 0.0125 (since 1 CABP study is being conducted), using the sample size determination method of Farrington and Manning (Farrington and Manning, 1990), a total of 638 subjects (PORT Risk Class III and IV) are required. Assuming an 80% evaluability rate, 510 subjects will be available in the CE population. Assuming an 85% response rate in both treatment groups, a 10% NI margin, 1-sided alpha level of 0.0125, there is 81% power to show NI for Investigator's Assessment of Clinical Response at PTE in the CE population. If 15% of subjects are in PORT Risk Class II, a total of 750 subjects are required.

Retrospective analyses of clinical study data (Talbot, et al., 2012) indicate the point estimates for Early Clinical Response at Day 4 range from 72%-81%. In addition, a recent clinical study of oral solithromycin compared to moxifloxacin found 78% of subjects had an Early Clinical Response rate of success. Thus, it is reasonable to assume that in a prospective study of subjects with moderate to severe CABP, the rate of Clinical Success at an early time point will be approximately 79%.

For the Early Clinical Response primary efficacy endpoint, with 750 subjects in the ITT population, a response rate of 79% for both treatment groups, NI margin of 10%, a 1-sided alpha level of 0.025, there is a 92% power to show NI. Assuming the microbiological evaluability rate is 27%, a total of 202 subjects are expected to be in the microITT population.

Thus, 750 subjects provides 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 8.

Table 8 Sample Size and Power Calculations

	Primary Outcome (Early Clinical Response)	Secondary Outcome (Early Clinical Response)	Secondary Outcome (Investigator's Assessment of Clinical Response at PTE)	
Population	ITT	microITT	ITT	CE
NI Margin	10%	15%	10%	10%
Evaluability Rate	N/A	27%	N/A	80%
Outcome Rate	79%	80%	79%	85%
PORT Risk Class II	N/A	N/A	15%	15%
N	750	202	638	510
Power	92%	74%	80%	81%

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

22.14 Interim Analyses

No interim analyses of efficacy are planned. However, a DSMC will review safety data (eg, AEs and SAEs, laboratory data, ECG, and vital signs assessments) at regular time points while the study is ongoing.

22.15 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, 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 will be conducted in which subjects with an Indeterminate response are considered Clinical Successes.

For the secondary outcome measure of Investigator's Assessment of Clinical Response at PTE in the ITT population (co-primary for EMA analysis), 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 9 provides a summary of the handling of missing/indeterminate outcomes for the Investigator's Assessment of Clinical Response at PTE.

Table 9 Investigator's Assessment of Clinical Response at PTE Determination Given Missing Data

EOT Visit	PTE Visit	Overall Assessment of 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.

23 SUBJECT IDENTIFICATION

Each subject in the study is assigned a unique subject number and must keep that number throughout the study even if he/she transfers to another site. A subject who discontinues participation or is withdrawn before receiving a treatment assignment code, and who re-enrolls at a later time will be assigned a new subject number and recorded as rescreened. The investigator must maintain a subject master log of all subjects.

24 TEST ARTICLE ACCOUNTABILITY, RECONCILIATION, AND RETURN

The investigator must maintain a complete and current dispensing and inventory record of test article that has been supplied by the sponsor.

All unused test article must be returned in the original containers. Empty test article containers may be destroyed after the sponsor has performed accountability. Test article destruction must be documented on the dispensing and inventory record.

24.1 Supply, Storage and Tracking of Study Treatment

Test article must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location. Upon receipt, all test article should be reconciled with the shipping information and stored according to the instructions specified on the medication labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. In addition, they will include storage conditions for the medication.

The unblinded pharmacist or designee should maintain an accurate record of the shipment and dispensing of iv test article in the study specific medication accountability ledger. Monitoring of iv medication accountability will be performed by the unblinded field monitor during site visits and at the completion of the study. 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. Monitoring of oral medication accountability will be performed by the blinded or unblinded field monitor during site visits and at the completion of the study. Subjects will be asked to return all unused po test article and packaging at each visit and at the end of the study, last study visit or at the time of test article discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, with instruction from the sponsor, the unblinded pharmacist or designee will destroy on site or return unused test article, packaging, medication labels, and send a copy of the completed medication accountability ledger to the monitor or to the address provided to the investigator.

25 RANDOMIZATION AND BLINDING

25.1 Treatment Assignment

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 (via phone or web) after confirming that the subject fulfills all the inclusion criteria and 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 (II or III/IV), receipt of an allowed antibacterial therapy (See Appendix 1) in the 72 hours prior to study treatment, and geographic region as defined in the IxRS specifications and SAP. Subjects randomized into the study will be assigned the treatment corresponding to the next available number in the respective stratum of the computer-generated randomization schedule. The subject is considered randomized when the IxRS provides the test article assignment, regardless of whether the subject actually receives any medication. Randomization of subjects with a PORT Risk Class of II will be capped at 15% of the subjects randomized. 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.

25.2 Dispensing the 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 moxifloxacin, 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 include active omadacycline tablets or matched placebo tablets, and active moxifloxacin over-encapsulated tablets or matched placebo over-encapsulated 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.

25.3 Treatment Blinding

The investigator and sponsor will be blinded to treatment arm assignments throughout the study. The iv and po phases of the study will be double-blind.

During the iv treatment period, subjects assigned to omadacycline will receive test article q12h for the first 2 doses, followed by 100 mg iv q24h (starting 24 hours after the first dose). Subjects assigned to moxifloxacin will receive test article q24h, with a single placebo infusion (the subject's second infusion 12 hours after the first dose) to match the omadacycline dosing regimen (see Table 1).

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 double-dummy 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 a potentially unblinded administrator will be required. Personnel identified as potentially unblinded administrators should 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-dummy design will also be used to ensure the blind. Subjects on the omadacycline arm active omadacycline tablets and over-encapsulated moxifloxacin placebo tablets. Subjects on the moxifloxacin arm will receive omadacycline placebo tablets and over-encapsulated active 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, from the documents containing blinded information.

Randomization data are kept strictly confidential until the time of database lock and unblinding at the end of the study.

All eCRFs must be completed, entered and checked; all safety 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.

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
- potentially unblinded administrator(s)

Plasma samples for subjects receiving omadacycline may be analyzed during the course of the study. To permit the sponsor to review the drug concentration data prior to locking the dataset and without unblinding, any PK data provided prior to unblinding will be re-coded by the bioanalytical laboratory to avoid revealing the individual subject numbers.

Unblinding is only to occur in the case of subject emergencies (see Section 25.4) and at the conclusion of the study.

25.4 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. 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 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.

In the event of a medical emergency in which the investigator judges that the subject cannot be managed safely without unblinding, the investigator may obtain the treatment allocation directly from the research pharmacist or designee. 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.

26 SUBJECT DISCONTINUATION OR WITHDRAWAL

Reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to, AE, subject request, protocol violation, subject noncompliance, and 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 (unless that subject withdraws informed consent) should NOT be considered withdrawn from the study. The date and primary reason for discontinuation of study treatment should be recorded in source documents. Subjects who discontinue the study treatment should have the EOT visit and the procedures listed for that visit in the STUDY FLOWCHART, a PTE visit and a Final Follow-up assessment, if possible. The site should also collect subject safety information through the Final Follow-up assessment.

Site personnel should 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.

Subjects who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled subjects.

27 STUDY SUSPENSION, TERMINATION, AND COMPLETION

27.1 Study Completion and Post-Study Test Article

A subject will have successfully completed the study after planned iv and po test article has been administered, and all assessments and visits have been made. Visits include the final follow-up visit (Final Follow-up). The study will be completed when the last subject has either discontinued or completed the Final Follow-up visit.

No long-term follow-up of subjects is planned, with the exception of pregnancies, as described in Section 21.6, and SAEs described in Section 21.1.

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 will be allowed to continue in the study.

Upon study completion, the investigator will provide the sponsor, IRB/IEC, 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 within 3 months after the completion or termination of the study.

27.2 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 26 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 Independent Ethics Committees (ECs) of the early termination of the study.

If the investigator suspends or terminates the study, the investigator will promptly inform the sponsor and the IRB/IEC and provide them with a detailed written explanation. Subjects should be seen as soon as possible and treated as described in Section 26 for prematurely withdrawn subjects. The investigator will also return all test article, containers, and other study materials to the sponsor.

28 ETHICAL CONSIDERATIONS

28.1 Regulatory and Ethical Compliance

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

28.2 Informed Consent Procedures

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.

28.3 Responsibilities of the Investigator and IRB/IEC/REB

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.

29 PROTOCOL ADHERENCE

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

29.1 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.

30 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 IB, the 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.

31 DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

31.1 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 1572 will be filed with the sponsor for any changes in the study personnel reported in the current form 1572.

31.2 Sponsor

The data is entered into an electronic database via eCRFs. The sponsor's 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.

32 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.

33 PRESTUDY DOCUMENTATION

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

- Completed and signed form 1572.
- 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 form 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.

34 RECORDS RETENTION

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.

35 PUBLICATION 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 multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter 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.

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Appendix 1: Allowed and Disallowed Prior Antibiotics

Allowed Antibiotics (One 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 Meropenem		Ertapenem
Glycopeptides		
Televancin Vancomycin		Dalbavancin Oritavancin
Fluoroquinolones		
Ciprofloxacin		Levofloxacin Moxifloxacin
Macrolides		
Clarithromycin Erythromycin		Azithromycin Clarithromycin XL
Tetracyclines		
Doxycycline (100 mg) Minocycline		Doxycycline (200 mg) Minocycline Extended Release Tigecycline
Oxazolidinones		
Linezolid		Tedizolid
Miscellaneous		
Clindamycin Metronidazole Trimethoprim-sulfamethoxazole/Co-trimoxazole		

*Prior (within 72 hours prior to randomization) administration of potentially effective systemic antibacterial therapy is an exclusion criterion (Section 12.2); 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. 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 2: PORT Risk Class Calculation

Adapted from Fine, et al., 1997.

Subject Characteristic	**Point Assignment**
Age	
Male	Age (years)
Female	Age (years) -10
Nursing home resident[1]	+10
Coexisting illnesses	
Neoplastic disease[2]	+30
Liver disease[3]	+20
Congestive heart failure[4]	+10
Cerebrovascular disease[5]	+10
Renal disease[6]	+10
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
Laboratory and radiographic findings	
Arterial pH < 7.35	+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
PORT Score	Sum of numbers above

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

1. Subjects that reside in a nursing home or assisted living facility that provides 24-hour medical supervision are excluded from the study and should not be enrolled per Exclusion Criterion number 4.
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 12.
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 liver test abnormalities or evidence of end-stage liver disease as defined in Exclusion Criterion number 5 should not be enrolled.
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 acute congestive heart failure are excluded from the study and 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 who require dialysis or who have severely impaired renal function (CrCl < 30 mL/min) are excluded from the study and should not be enrolled per Exclusion Criteria numbers 8 or 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.

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

Appendix 4: 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. $mm^3 = \mu L$
3. cc = mL
4. Conversion of immature neutrophils (bands) in K/µL or K/mL to % bands (relevant to Inclusion Criterion number 5 and Exclusion Criterion number 11):
   [(bands K/µL)/(total WBC K/µL)] × 100 = % bands
   Or
   [(bands K/mL)/(total WBC K/mL)] × 100 = % bands
5. Corticosteroid conversions (relevant to Exclusion Criterion number 10):

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.

6. Blood urea conversion to blood urea nitrogen (BUN) (relevant to PORT Risk Class calculation)
   (blood urea in mmol/L)/0.357 = BUN in mg/dL
   OR
   (blood urea in mg/dL)/2.14 = BUN in mg/dL

ADMINISTRATIVE CHANGES		
Protocol section	**Summary of Changes**	**Rationale**
Cover page	Change of Paratek address.	Paratek moved to new corporate offices in Boston, MA and King of Prussia, PA during the summer of 2015.
Section 2.1 Section 3	Stephen Villano, MD added as an emergency contact and replaces Evan Loh, MD as Sponsor Signature.	Dr. Villano joined Paratek in September of 2015 as Vice President of Clinical and Medical Affairs.
CLARIFICATIONS		
Protocol section	**Summary of Changes**	**Rationale**
Section 5, Section 7, Section 8, Section 9.1, Section 11.1	Abbreviation corrections: CK, creatine phosphokinase; PORT, Pneumonia Outcomes Research Team	Corrections.
Section 7	In Inclusion Criterion 1 the text “protocol specific” was added.	To align with the wording of Inclusion Criterion 1 in Section 12.1.
Section 7, Section 12.1, Section 12.2, Section 14.3.1.2	In Inclusion Criterion 4, Exclusion Criterion 11 and Section 14.3.1.2 references to “oral or rectal” as the only acceptable sites of body temperature measurement were removed.	Operational clarification, body temperature measurements at body sites other than oral or rectal are acceptable.
Section 7, Section 12.1, Section 12.2, Appendix 4	Inclusion Criterion 5 and Exclusion Criterion 11 refer to immature neutrophils (band forms) as a percent of the total white blood cell count (WBC). Hyperlinked references to Appendix 4 were added to the criteria and equations below added to Appendix 4 to allow conversion of bands and total WBC in K/μL or K/mL to % bands. “Conversion of immature neutrophils (bands) in K/μL or K/mL to % bands [(bands K/μL)/(total WBC K/μL)] × 100 = % bands Or [(bands K/mL)/(total WBC K/mL)] × 100 = % bands”	Some site’s local laboratories do not provide results for immature neutrophils (bands) as a % of total white blood cells as specified in the inclusion/exclusion criteria, thus conversion equations were added to Appendix 4.
Section 7, Section 12.2	Exclusion Criterion 6: **Previous wording:** “Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, congestive heart failure, cardiac arrhythmia, etc.) within the 3 months prior to Screening.” **Current wording:** “Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart	Clarification of definition of unstable cardiac disease.

	failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to Screening."	
Section 7, Section 12.2	Exclusion Criterion 9: **Previous wording:** "History or evidence of severe renal disease or is known to have a calculated creatinine clearance (CrCl) of < 30 mL/minute, using the Cockcroft-Gault equation (see Appendix 4)." **Current wording:** "History or evidence of severe renal disease or has a calculated creatinine clearance (CrCl) of < 30 mL/minute, using the Cockcroft-Gault equation (see equation in Appendix 4)."	Clarification that exclusion may be based on history or the CrCl measured at Screening.
Section 7, Section 12.2	Exclusion Criterion 10, second bullet point: **Previous wording:** "Infection with Human Immunodeficiency Virus (HIV) and a cluster of differentiation 4 (CD4) count < 200 cells/mm^3, or another Acquired Immune Deficiency Syndrome (AIDS) defining illness" **Current wording:** "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"	Clarification that exclusion of subjects with HIV is based on known medical history and not testing at the time of screening.
Section 7	Exclusion criterion 11: Correction of body temperature from "95.5°C" to "95.5°F".	Correction.
Section 8, Section 11.1	In Section 8: Study Flowchart, footnote b and Section 11.1 the text in quotes was added: ", with the exception of the blood culture sample collection and radiographic confirmation of pneumonia, should be completed within the 24 hours prior to randomization. The blood culture sample collection and radiographic confirmation of pneumonia should be completed within the 24 hours prior to the first dose of test article."	Clarification of the timing of Screening procedures.
Section 8, Section 14.2, Section 14.2.6	"Urinalysis" was changed to "urine tests" in Section 8: Study Flowchart (in the chart and change to "urine dipstick test" in footnote k), Section 14.2 and Section 14.2.6.	The original intent of the protocol was to perform urine dipstick screen as the initial urine test, rather than urinalysis; therefore "urinalysis" was corrected to "urine test".
Section 8, Section 14.4	In Section 8: Study Flowchart, footnote f and Section 14.4 the following wording was changed: **Previous wording:** "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 AEs noted at or after the PTE visit." **Current wording:**	Clarification that the Final Follow-up visit must be conducted in person if the subject's laboratory or ECG abnormalities are being followed to resolution after the PTE visit.

	"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 AEs or clinically significant laboratory or ECG abnormalities noted at or after the PTE visit."	
Section 8, Section 24.1, Section 25.2	In Section 8: Study Flowchart, footnote l, Section 24.1 and Section 25.2 wording was added to clarify that oral test article supplies are completely blinded and thus can be transferred from the unblinded study personnel to blinded study personnel for storage, dispensation, and reconciliation.	Operational clarification.
Section 8	The following footnote n was added to the Section 8: Study Flowchart: "Vital signs include body temperature, BP, pulse/heart rate, and RR."	Operational clarification.
Section 8	Section 8: Study Flowchart, footnote p was changed to provide further information regarding ECGs on Day 1 (dose 1) and Day 2 (dose 3) only.	Operational clarification.
Section 8	In Section 8: Study Flowchart, footnote u the following was deleted: "(after 8 iv or po total doses)". The following wording was added: "The first po dose should be administered in the morning, 12-24 hours after the last iv dose."	Operational clarification. Subjects must receive at least 7 days of treatment, not a specific number of doses. The timing of first po dose was clarified.
Section 8, Section 16.1.4.3	In Section 8: Study Flowchart, footnote v and Section 16.1.4.3 the following wording was changed: **Previous wording:** "If Screening blood cultures are positive for a potential pathogen, blood cultures must be repeated at each visit or more frequently if clinically indicated until negative cultures are obtained" **Current wording:** "If bacteria are isolated from baseline blood cultures, repeat blood cultures should 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."	Operational clarification.
Section 13.2	In Section 13.2 Prohibited Treatment the following wording was changed: **Previous wording:** "Long-acting systemic antibacterial agents potentially effective for CABP are prohibited for 72 hours prior to randomization and concomitantly (see list in Appendix 1)." **Current wording:**	Operational clarification.

	"Long-acting systemic antibacterial agents potentially effective for CABP are prohibited for 72 hours prior to randomization through End of Treatment (EOT), except in cases of Clinical Failure (see list in Appendix 1)."	
Section 13.2, Section 14.3.1.3, Section 15.1.1	In Section 13.2, Section 14.3.1.3 (Table 2, footnote b), and in Section 15.1.1 (Table 4, Administration) the wording in quotes was added: antacids and/or multivitamins "containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc)".	Clarification that only antacids/multivitamins containing multivalent cations are restricted, and specific examples of multivalent cations are provided.
Section 13.3	In Section 13.3 the first sentence was changed as follows" **Previous wording:** "Use of proarrhythmic or QTc prolonging medications is prohibited." **Current wording:** "Use of proarrhythmic or QT prolonging medications is prohibited through the Final Follow-up assessment."	Clarification.
Section 14.2.6	The Section 14.2.6 wording was updated as follows: **Previous wording:** "A urine dipstick will be performed during Screening. Urine WBC results will be recorded on the eCRF. A urine pregnancy test will be performed during Screening for all women. Urine will also be tested at Screening for the presence of *Legionella pneumophila* and *Streptococcus pneumoniae* antigens." **Current wording:** A urine dipstick test will be performed locally at Screening. Urine dipstick results will be recorded on the eCRF. A urine pregnancy test will be performed locally during Screening for all women and the results will be recorded on the eCRF. Urine will also be tested locally at Screening for the presence of *Legionella pneumophila* and *Streptococcus pneumoniae* antigens and the results will be recorded on the eCRF."	Operational clarifications.
Section 14.3.1, Section 16	In Section 14.3.1 in the 7th bullet point regarding ECGs "12-lead" and "at the Day 7 visit" were added. In Section 16 in the 5th bullet point "12-lead" was added.	Corrections to align with Study Flowchart and Section 16.1.4.1.
Section 8, Section 14.3.1.1, Section 14.3.1.1.1, Section 14.3.1.3	Section 8 (Study Flowchart, footnote u), Section 14.3.1.1 (Table 1, footnote e), Section 14.3.1.1.1 (second bullet point) and Section 14.3.1.3 (Table 2) were updated to emphasize that the first oral test article dose must be administered in the morning.	To ensure that subjects in both treatment arms receive continuous active test article therapy and to facilitate the fasting requirements for omadacycline oral dosing.

Section 14.3.1.3, Section 15.1.1	In Section 14.3.1.3 (Table 2) "at least 6 hours" was added in reference to the required length of overnight fasting prior to morning oral doses. In Section 15.1.1 (Table 4) the fasting requirement prior to omadacycline oral dosing was changed from "overnight" to "at least 6 hours".	Clarification of the required length of fasting prior to omadacycline oral dose administration.
Section 15.1.1	In Section 15.1.1, Table 4, Omadacycline oral formulation, excipients the following corrections were made: [redacted] changed to [redacted] and [redacted] changed to [redacted].	These changes are corrections of a typographical error and a spelling error and do not represent changes in the omadacycline oral formulation.
Section 15.3	In Section 15.3 the wording in quotes was added: subject charts "and subject diaries".	Clarification that subject diaries will be checked for compliance during oral treatment.
Section 16.1.2	In Section 16.1.2, Vital Signs, in the first sentence "infusion" was changed to "dose".	Clarification that vital signs should be checked prior to each dose on iv treatment. Some doses require 2 infusions due to the double-dummy design. Vital signs do not need to be re-checked prior to the second infusion given for the same dose.
Section 16.1.3.1	In Section 16.1.3.1, Hematology, in Table 5 "Hemoglobin" was added.	Correction, hemoglobin is being measured as part of the hematology panel.
Section 16.1.4.1	In Section 16.1.4.1, Electrocardiogram (ECG), a bullet point for "Screening" was added to the list of visits when ECGs will be performed.	Correction to align with the Study Flowchart.
Section 17.2.2.1	Wording was added to reflect that collection of a sputum or other respiratory specimen should be "attempted from all subjects".	Production of purulent sputum is not required for inclusion of a subject in the study. Per Inclusion Criterion 3 a subject may have a cough without purulent sputum production and still be eligible for the study if dyspnea and pleuritic chest pain are also present. While an adequate quality sputum specimen may not be obtained from each eligible subject, the collection should be attempted from each subject.
Section 17.2.2.1	Wording was added to indicate that details concerning Gram stains, cultures and criteria for isolates to be shipped to the Central Laboratory are supplied in the Local/Regional Clinical Microbiology Laboratory Manual.	Operational clarification as there are both local/regional and central clinical microbiology laboratory manuals for the study.
Section 17.2.2.2	The wording "and the results will be recorded on the eCRF" was added.	Operational clarification.
Section 17.2.3.1	One of the criteria for Clinical Failure (bullet point 5) at the Early Clinical Response Assessment was clarified as follows: **Previous wording:** "Discontinued study therapy due to an AE prior to Early Clinical Response assessment," **Current wording:** "Discontinued study therapy due to an AE and received alternative antibacterial treatment for CABP prior to the Early Clinical Response assessment."	Clarification.

Section 17.2.3.3	The following sentences were removed from the first paragraph: "Only subjects determined to be a Clinical Success at EOT or Indeterminate due to missing the EOT visit will be considered for evaluation as Clinical Success at PTE. Subjects assessed as Clinical Failures at EOT or Indeterminate for reasons other than missing the EOT visit, will have this outcome carried forward."	The "carrying forward" of clinical outcomes for the analysis of the Investigator's Assessment of Clinical Response is discussed in Section 22.15, Table 9, and in the SAP. The investigator should assess the subject for Clinical Response at PTE according to the criteria listed in Section 17.2.3.3.
Section 21.2	In Section 21.2, Serious Adverse Event Reporting, the wording in quotes was added: must be reported within 1 business day "or 24 hours as required by local regulations"	To comply with regional regulatory requirements.
Section 22.6	In the third paragraph the following was changed: "SBP (≥ 90 mm Hg)" corrected to "SBP (> 90 mm Hg)".	Correction.
Section 22.8	In Section 22.8 Resource Utilization, bullet point 3, the words "per type of facility" were removed.	The variable "duration (days) and number of outpatient iv doses (test article)" will be analyzed, but not per type of facility.
Section 25.3	In Section 25.3 in the first sentence of the second paragraph "will receive test article q24h for the first 2 doses" was changed to "will receive test article q12h for the first 2 doses".	Correction.
Section 25.4	In Section 25.4, Emergency Unblinding of Treatment Assignment, the wording of the last sentence in paragraph 1 was changed as follows: **Previous wording:** "It is strongly 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." **Current wording:** "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. However, if required the investigator can unblind without consulting the Medical Monitor."	To comply with regional regulatory requirements.
Section 27.1	In Section 27.1, Study Completion and Post-Study Test Article, the following sentence was deleted: "A sample of this final study report can be found in the Study Reference Manual"	Operational change.
Section 34	In Section 34, Records Retention, references to "study drug" were changed to "investigational test article".	Clarification.
Appendix 2	The PORT Risk Class Calculation table was corrected, simplified and footnotes were added for clarification of criteria that effect subject eligibility for the study.	Corrections to align with the PORT score determination criteria in Fine et al. 1997, NEJM and clarifications to provide guidance to investigators.

Appendix 4	The title of Appendix 4 "Equations and Conversions" was changed to "Equations and Conversion Factors" and references to the Inclusion or Exclusion Criteria that the equation or conversion factors are relevant to were provided.	Clarification.
Appendix 4	Conversion equations from blood urea to blood urea nitrogen (BUN) were added.	Some site's local laboratories report only blood urea, however BUN is required for the calculation of PORT scores.
MODIFICATIONS		
Protocol section	**Summary of Changes**	**Rationale**
Section 7, Section 8, Section 12.1, Section 14.2, Section 22.6	Pulse oximetry measurement of oxygen saturation was added as an acceptable method to determine hypoxemia. In Section 7 and Section 12.1 the wording of Inclusion Criterion 5 was changed as follows: **Previous wording:** • Hypoxemia (partial pressure of arterial oxygen [PaO_2]) < 60 mm Hg by arterial blood gas (ABG) **Current wording:** • Hypoxemia (partial pressure of arterial oxygen [PaO_2] < 60 mm Hg by arterial blood gas [ABG] or oxygen saturation < 90% by pulse oximetry) In Section 8 in the Study Flowchart the row heading "PORT Risk Class, ABG[i]" was changed to "PORT Risk Class, ABG or pulse oximetry[i]". In Section 14.2 the 12th bullet point was changed from "ABG and PORT Risk Class Assessment" to "ABG (or pulse oximetry) and PORT Risk Class Assessment". In Section 22.6 "PaO_2 (> 60 mm Hg by ABG)" was changed to "PaO_2 (≥ 60 mm Hg by ABG or oxygen saturation ≥ 90% by pulse oximetry)"	The original PORT study allowed for pulse oximetry as an acceptable alternative to ABG (Fine et al. 1997, NEJM).
Section 7, Section 12.1	Inclusion Criterion 9: **Previous wording:** "Females must have a negative urine pregnancy test at Screening and agree to comply with using a highly effective form of birth control (eg, abstinence, po contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, or vasectomized partner) from Screening through post therapy evaluation (PTE). Males must agree to use a highly effective method of birth control with female	A "highly effective method" changed to "an acceptable method" because of different regional definitions of highly effective methods of birth control. Postmenopausal added as a method of birth control.

<table>
<tr><td></td><td>partner(s) and must not donate sperm from Screening through PTE.”
<u>Current wording:</u>
“Females must have a negative urine 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 post therapy evaluation (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.”</td><td></td></tr>
<tr><td>Section 7, Section 12.2</td><td>Exclusion Criterion 7:
<u>Previous wording:</u>
“Are diagnosed with long corrected QT interval (QTc) syndrome, use drugs of potential proarrhythmic or QTc prolonging effect, and/or present with tachyarrhythmia.”
<u>Current wording:</u>
“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, and/or present with tachyarrhythmia.”</td><td>Specific QT interval thresholds were added for clarification.</td></tr>
<tr><td>Section 7, Section 12.2, Appendix 4</td><td>Exclusion Criterion 10, third bullet point:
Regarding the receipt of corticosteroids equivalent to prednisone, a reference and hyperlink to Appendix 4 was added.

The following chart was added to Appendix 4:
“Corticosteroid conversions (relevant to Exclusion Criterion number 10):
<table>
<tr><th colspan="2">The following have equivalent glucocorticoid activity</th></tr>
<tr><td>Hydrocortisone</td><td>160 mg</td></tr>
<tr><td>Prednisone</td><td>40 mg</td></tr>
<tr><td>Prednisolone</td><td>40 mg</td></tr>
<tr><td>Methylprednisolone</td><td>32 mg</td></tr>
<tr><td>Triamcinolone</td><td>32 mg</td></tr>
<tr><td>Dexamethasone</td><td>6 mg</td></tr>
</table>
“</td><td>To provide guidance to investigators.</td></tr>
<tr><td>Section 7, Section 12.2</td><td>Exclusion criterion 12:
Added known or suspected “active tuberculosis”.</td><td>Listed in the 2014 FDA CABP Draft Guidance as a recommended exclusion.</td></tr>
</table>

Section 7, Section 16, Section 22.1	The Safety population definition was updated: **Previous wording:** "The Safety population will consist of all randomized subjects who receive at least one dose test article." **Current wording:** "The Safety population will consist of all randomized subjects who receive test article."	Subjects who receive any amount of test article, including less than one complete dose, will be included in the Safety population.
Section 8, Section 11.1, Section 14.3.1	In Section 8: Study Flowchart, footnote l, Section 11.1 and Section 14.3.1 the following was added: "Subjects should receive their first dose of test article within 4 hours after randomization."	Operational change to ensure that subjects receive timely treatment for their infection.
Section 8, Section 19.2	Section 8: Study Flowchart, footnote t and Section 19.2 were updated to reflect that blood samples for PK analysis will be collected on Days 1 to 7.	Operational change in the Population PK sample schedule.
Section 8, Section 17.2.2.1	In Section 8: Study Flowchart, Study Flowchart footnote w and Section 17.2.2.1 language was added to indicate that at the PTE visit a respiratory specimen culture and Gram stain should be obtained only for subjects who are clinical failures and require alternative antibacterial treatment for the infection under study.	To assess whether infections present at the PTE visit are caused by persistence of the original pathogen, caused by a pathogen resistant to either test article, caused by a new pathogen, etc.
Section 8, Section 17.2.2.2	In Section 8: Study Flowchart and Section 17.2.2.2 Urine antigen screening for *Legionella pneumophila* and *Streptococcus pneumoniae* was removed at the PTE visit.	Urine antigen testing is useful only as an initial, non-quantitative diagnostic test. Follow-up antigen tests do not provide additional information (eg, no impact on clinical management or treatment).
Section 17.2.2.1	In Section 17.2.2.1 the criteria for an adequate quality sputum specimen were changed. **Previous wording:** "1. < 10 Squamous epithelial cells/low power field (lpf) (ie, 100×) 2. > 10 Polymorphonuclear cells/lpf (ie, 100×)" **Current wording:** "1. < 10 Squamous epithelial cells/low power field (lpf) (ie, 100×) 2. > 25 Polymorphonuclear cells/lpf (ie, 100×)"	To align with standard clinical practice and the 2014 FDA CABP Draft Guidance.
Section 22.13	In Section 22.13 Sample Size Calculation, paragraph 4 the following sentence was removed: "No clinical study has been conducted using Early Clinical Response as the primary efficacy outcome." The following sentence was added: "In addition, a recent clinical study of oral solithromycin compared to moxifloxacin found 78% of subjects had an Early Clinical Response rate of success."	Update. The results of Cempra's solithromycin oral CABP study were reported after the finalization of V1.0 of this protocol.

Statistical Analysis Plan: PTK0796-CABP-1200

Study Title:	A Phase 3 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-1200
Study Phase:	3
Sponsor:	Paratek Pharma, LLC A wholly-owned subsidiary of Paratek Pharmaceuticals, Inc. 75 Park Plaza, 4th Floor Boston, MA 02116 USA Tel: +1 617-275-0040
Version:	Final 1.0
Date:	17-MAR-2017

Confidentiality Statement

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LIST OF TABLES

LIST OF APPENDICES

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACM	all-cause mortality
AE	adverse event
BMI	body mass index
CABP	community-acquired bacterial pneumonia
CI	confidence interval
CE	clinically evaluable
CN	clinically notable
CT	computed tomograpy
CXR	chest X-ray
eCRF	electronic case report form
ECR	Early Clinical Response
EMA	European Medicines Agency
EOT	End of Treatment
FDA	Food and Drug Administration
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
IxRS	Interactive Response System
lpf	Low Power Field
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MDRSP	multi-drug resistant *Streptococcus pneumoniae*
mg	milligram
MIC	minimum inhibitory concentration
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
NDA	New Drug Application
NI	non-inferior

PNSSP	Penicillin-nonsusceptible *Streptococcus pneumoniae*
PORT	Pneumonia Outcomes Research Team
PSSP	Penicillin-susceptible *Streptococcus pneumoniae*
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	orally
PR	Interval from the P wave (atrial contraction or depolarization) to the onset of the Q wave in the measurement of electrical activity of the myocardium
PTE	post therapy evaluation
QTc	QT, corrected
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	standard deviation
SI	International System
spp	species (plural)
SIRS	Systemic Inflammatory Response Syndrome
TEAE	treatment emergent adverse event
UAT	urinary antigen test
ULN	upper limit of normal
US	United States

3 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the protocol PTK0796-CABP-1200, "A Phase 3 Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Moxifloxacin IV/PO for Treating Community-Acquired Bacterial Pneumonia (CABP)." The statistical plan described is an *a priori* plan and no analysis prior to the preparation of this plan has been conducted. This SAP summarizes the study design and objectives, and provides details of the outcome definitions and statistical methods that will be used to analyze the data from protocol PTK0796-CABP-1200.

The study has been designed to address both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory requirements; however, a separate SAP will be developed to address the different primary efficacy outcome and analyses for the EMA. While the EMA supports the assessment of clinical response by the Investigator at a Post Therapy Evaluation (PTE) visit (which is scheduled to occur 5 to 10 days after the last dose of test article) as the primary endpoint, the FDA guidelines require using an earlier primary endpoint (Day 3 to Day 5 after the first dose of test article) based on improvement in pneumonia symptoms.

4 TRIAL OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is to demonstrate that omadacycline 100 mg iv once every 12 hours (q12h) for 2 doses, followed by 100 mg iv/300 mg po once every 24 hours (q24h) is non-inferior to moxifloxacin 400 mg iv/po q24h in the treatment of adults with CABP.

4.2 Secondary Objectives

The secondary objectives are as follows:

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

5 STUDY DESIGN CONSIDERATIONS

5.1 Study Design

This is a randomized (1:1), double-blind, active comparator-controlled, Phase 3 study comparing 7 to 14 days of treatment with either omadacycline or moxifloxacin for the treatment of adults with CABP. The number of subjects in Pneumonia Outcomes Research Team (PORT) Risk Class II will be limited to no more than 15% of randomized subjects. Subject randomization will be stratified across treatment groups by PORT Risk Class (II and III/IV), receipt of an allowed antibacterial therapy in the 72 hours prior to study treatment (yes and no) and geographic region (Western Europe/North America, Eastern Europe, and Rest of World). All subjects are expected to present with CABP severe enough to require a minimum of at least 3 days of intravenous (iv) treatment. After a minimum of 3 days of iv treatment, the investigator can switch the subject to oral (po) treatment if the subject is considered clinically stable and meets the criteria for transition to a po regimen.

Screening assessments will be performed within 24 hours before the first infusion of test article. The day of the first infusion of test article is defined as Day 1 and the day prior is Day-1; there is no Day 0. The study will have the following protocol-defined evaluations:

- Visits will be conducted daily on Days 1 through 7. The Day 6 visit is optional for subjects that have been switched to po test article and have been discharged from a hospital setting. A Day 10 visit should be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the End of Treatment (EOT) Visit.
- EOT Visit: to 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 before completion, the EOT Visit should be conducted.
- PTE Visit: to be performed 5 to 10 days after the subject's last day of study therapy
- Final Follow-up assessment: Study Day 30-37 (after start of first infusion of test article)

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

5.1.1 Sample Size

The study is designed to show NI in the primary efficacy outcome for the FDA of Early Clinical Response (ECR) at 72 to 120 hours following the first dose of test article in the intent to treat (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 the historical data regarding the treatment effect of antibiotics in pneumonia.

The study has also been designed to show NI in the co-primary efficacy outcomes for the EMA of Investigator assessment of clinical response at the PTE visit in the ITT and CE-PTE

populations. A separate SAP will be developed to address the different primary efficacy outcome and analyses for the EMA.

In the ceftaroline clinical studies which enrolled only subjects of PORT Risk Class III and IV, the rates for clinical success based on Investigator's Assessment of Clinical Response at the PTE visit ranged from 77%-87% in the modified ITT and clinically evaluable (CE) populations, with the rates in the modified ITT population lower than those in the CE population (Teflaro, 2013). Thus, it is reasonable to assume clinical success rates of 79% in the ITT and 85% in the CE populations.

For the Investigator's Assessment of Clinical Response at PTE endpoint in the ITT population (PORT Risk Class III and IV) assuming an outcome rate of 79% in both treatment groups, NI margin of 10%, 80% power and a 1-sided alpha level of 0.0125 (since 1 CABP study is being conducted), using the sample size determination method of Farrington and Manning (1990), a total of 638 subjects (PORT Risk Class III and IV) are required. Assuming an 80% evaluability rate, 510 subjects will be available in the CE population. Assuming an 85% response rate in both treatment groups, a 10% NI margin, 1-sided alpha level of 0.0125, there is 81% power to show NI for Investigator's Assessment of Clinical Response at PTE in the CE population. If 15% of subjects are in PORT Risk Class II, a total of 750 subjects are required.

Retrospective analyses of clinical study data (Talbot, et al., 2012) indicate the point estimates for Early Clinical Response at Day 4 range from 72% to 81%. In addition, a recent clinical study of oral solithromycin compared to moxifloxacin found 78% of subjects had an Early Clinical Response of success. Thus, it is reasonable to assume that in a prospective study of subjects with moderate to severe CABP, the rate of Clinical Success at an early time point will be approximately 79%.

For the Early Clinical Response primary efficacy endpoint, with 750 subjects in the ITT population, a response rate of 79% for both treatment groups, NI margin of 10%, a 1-sided alpha level of 0.025, there is a 92% power to show NI. Assuming the microbiological evaluability rate is 27%, a total of 202 subjects are expected to be in the microITT population.

Thus, 750 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 1.

Table 1. Sample Size and Power Calculations

	Primary Outcome (Early Clinical Response)	Secondary Outcome (Early Clinical Response)	Secondary Outcome (Investigator's Assessment of Clinical Response at PTE)	
Population	ITT	microITT	ITT	CE
NI Margin	10%	15%	10%	10%
Evaluability Rate	N/A	27%	N/A	80%
Outcome Rate	79%	80%	79%	85%
PORT Risk Class II	N/A	N/A	15%	15%
N	750	202	638	510
Power	92%	74%	80%	81%

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

5.1.2 Randomization and Masking

All eligible subjects will be randomized via an Interactive Response System (IxRS) that assigns them to 1 of the 2 treatment arms omadacycline and moxifloxacin (in a 1:1 ratio). The site delegate will contact the IxRS (via web) after confirming that the subject fulfills all the inclusion criteria and has none of the exclusion criteria. The IxRS will assign a test article to the subject based on a computer-generated randomization schedule. The randomization will be a blocked randomization sequence stratified by PORT Risk Class (II and III/IV), receipt of an allowed antibacterial therapy in the 72 hours prior to study treatment (yes and no), and geographic region (Western Europe/North America, Eastern Europe and Rest of World). Subjects randomized into the study will be assigned the treatment corresponding to the next available number in the respective stratum of the computer-generated randomization schedule. The subject is considered randomized when the IxRS provides the test article assignment (ie, completes a randomization transaction), regardless of whether the subject actually receives any medication. Randomization of subjects with a PORT Risk Class of II will be capped at 15% of the total number of subjects randomized. Randomization of subjects who have received an allowed antibacterial therapy in the 72 hours prior to study treatment will be capped at 25% of the total number of subjects randomized.

5.2 Efficacy Measures

5.2.1 Primary Efficacy Outcome

The primary efficacy outcome is the determination of the response to therapy at the Early Clinical Response assessment (72 to 120 hours after administration of the first dose of test article) and will be determined programmatically using the investigator's assessment of the subject's symptoms associated with CABP entered into the eCRF. The severity of the subject's CABP symptoms of cough, sputum production, pleuritic chest pain, and dyspnea will be evaluated on a 4-point scale (absent, mild, moderate, or severe) based upon the

Community-Acquired Bacterial Pneumonia Subject Symptom Severity Guidance Framework for Investigator Assessment in Table 2.

Table 2. Community-Acquired Bacterial Pneumonia Subject Symptom Severity Guidance Framework for Investigator Assessment

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

The categories of Early Clinical Response are defined as follows:

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

Clinical Failure: meeting any of the following criteria:

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

- Any of the 4 CABP symptoms is worse (by at least 1 level) compared to baseline (Screening).
- The subject requires alternative (rescue) antibacterial treatment for CABP prior to the Early Clinical Response 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 prior to the Early Clinical Response assessment.
- Death prior to the Early Clinical Response assessment.

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

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

Subjects with missing data such that an Early Clinical Response cannot be determined will be considered an indeterminate response. Subjects who did not have at least 2 symptoms of CABP at baseline will also be considered an indeterminate response. Since subjects with an indeterminate response are included in the denominator of the calculation of Clinical Success, these subjects are essentially Clinical Failures. For the ITT population, the proportion of ITT subjects with a Clinical Success is defined using the following formula:

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

5.2.2 Secondary Efficacy Outcomes

5.2.2.1 Investigators Assessment of Clinical Response

The investigator will make an assessment of Clinical Response at the EOT and PTE Visits, based on the definitions below. The secondary efficacy outcome is the overall assessment of clinical response at PTE (derived from the investigator assessments at the EOT and PTE Visits) in the ITT and CE-PTE populations as defined in Table 3.

EOT Visit

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

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

Clinical Failure: the subject requires alternative antibacterial treatment for CABP prior to EOT related to either (a) progression or development of new symptoms to 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 prior to the EOT. Other reasons for clinical failure are:

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

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

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

PTE Visit

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

Clinical Success: survival after completion of a test article regimen without receiving any systemic antibacterial therapy other than test article, resolution of signs and symptoms of the infection present at Screening with no new symptoms or complications attributable to CABP and no need for further antibacterial therapy.

Clinical Failure: the subject requires alternative antibacterial treatment for CABP prior to PTE related to either (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:

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

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

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

Overall Clinical Response at PTE (based on the investigator's assessment) is determined as follows from the investigator's assessments at the EOT and PTE Visits:

Table 3. Investigator's Assessment of Clinical Response

EOT Visit	PTE Visit	Overall Assessment of Clinical Response at PTE Visit
Success	Success	Success
Success	Failure	Failure
Success	Indeterminate	Indeterminate
Failure	Success	Failure
Failure	Failure	Failure
Failure	Indeterminate	Failure
Indeterminate	Success	Indeterminate
Indeterminate	Failure	Failure
Indeterminate	Indeterminate	Indeterminate

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

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

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

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

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

5.2.2.2 Microbiologic Outcomes

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

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

Table 4. Per-Pathogen Microbiological Response Definitions at the EOT and PTE Visits

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

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

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

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

Table 5. Per-Pathogen Microbiologic Response

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

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

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

The overall per-subject microbiologic response at PTE is determined from the per-subject microbiologic responses at the EOT and PTE Visits in the same manner as the per-pathogen microbiologic response in Table 5. For subjects with a per-subject favorable response at the EOT Visit, the overall microbiologic response at PTE of eradication, presumed eradication, persistence, and presumed persistence are based on the response at the PTE Visit. For subjects with a per-subject unfavorable response at the EOT Visit, the overall microbiologic response at PTE of persistence and presumed persistence are based on the response at the EOT Visit except for when the response at the PTE Visit is unfavorable. In this case, the overall microbiologic response at PTE of persistence and presumed persistence are based on the response at the PTE Visit. For subjects with a per-subject indeterminate response at the EOT Visit and unfavorable at the PTE Visit, the overall microbiologic response at PTE of persistence and presumed persistence are based on the response at the PTE Visit.

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

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

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

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

Microbiological response definitions of superinfection and new infection are presented in Table 6 below:

Table 6. Microbiological Response Definitions: Superinfection or New Infection

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

Abbreviations: CABP = community-acquired bacterial pneumonia.

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

5.3 Safety Measures

The safety parameters include AEs, clinical laboratory evaluations, vital signs, and ECG findings. AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 17.1 or higher to the System Organ Class and Preferred Term levels.

5.4 Pharmacokinetic Parameters

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

6 STUDY POPULATIONS

6.1 Analysis Populations

6.1.1 Intent-to-Treat (ITT) Population

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

6.1.2 Safety Population

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

6.1.3 Microbiological Intent-to-Treat (microITT) Population

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

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

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

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

The following isolates will always be considered a pathogen:

Streptococcus pneumoniae

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

Haemophilus influenzae

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

Staphylococcus aureus

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

Moraxella catarrhalis

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

Legionella pneumophila

- Positive BAL, bronchoscopy, pleural fluid, or blood culture; or
- Positive sputum culture, regardless of Gram stain findings; or
- Positive acute (baseline) or positive convalescent (PTE) IgM (Euroimmun IgM ELISA OD ratio of ≥ 1.1)
- Negative acute (baseline) and positive or indeterminate convalescent (PTE) IgG (Euroimmun IgG ELISA OD ratio of ≥ 1.1)
- A positive urine antigen test

Mycoplasma pneumoniae

- Positive acute (Baseline) or positive convalescent (PTE) IgM (Euroimmun IgM ELISA OD ratio of ≥ 1.1)
- Negative acute (Baseline) and positive or indeterminate convalescent (PTE) IgG (Euroimmun IgG ELISA OD ratio of ≥ 1.1)

Chlamydophila pneumoniae

- Positive acute (Baseline) or positive convalescent (PTE) IgM (SeroCP™ IgM cut-off index of > 1.5)
- Negative acute (Baseline) and positive or indeterminate convalescent (PTE) IgG (SeroCP™ IgG cut-off index of > 1.1)

The following isolates are considered as contaminants from respiratory specimens rather than pathogens of CABP: fungi, *Enterococcus* spp., viridans streptococci, coagulase-negative staphylococci, *Micrococcus* spp., *Neisseria* spp. other than *N. meningitidis*, *Corynebacterium* spp. and other coryneforms, *Lactobacillus* spp., *Vibrio* spp., *Capnocytophaga* spp., *Cardiobacterium* spp., *Flavobacterium* spp.

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

An expanded microITT population will also be analyzed. The expanded microITT population will be defined using the same criteria as for the microITT population except an adequate Gram stain will be defined as > 10 PMNs/LPF and < 10 SECs/LPF for determination of whether an isolate from a sputum culture is a pathogen or not.

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

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

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

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

6.1.4 Clinically Evaluable (CE) Populations

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

6.1.4.1 Diagnosis of CABP

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

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

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

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

- Fever or hypothermia documented by the investigator (po or rectal temperature > 38.0ºC [100.4ºF] or < 36.0ºC [95.5ºF])

- Hypotension with systolic blood pressure (SBP) < 90 mmHg
- Heart rate > 90 bpm
- Respiratory rate (RR) > 20 breaths/minute.

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

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

Inclusion Criterion 6: 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 24 hours prior to the first dose of test article.

If the imaging study is done more than 24 hours prior to the first dose of test article but within 48 hours, the subject will be included in the CE populations as long as the imaging study shows a new or progressive pulmonary infiltrate(s) consistent with acute bacterial pneumonia.

Inclusion Criterion 7: Have disease categorized as being PORT Risk Class II, III, or IV at Screening:

The Sponsor Medical Monitor will also review those subjects with a concomitant illness identified after baseline that could have presented at baseline as pneumonia. If it is determined that the subject does not have pneumonia but had another condition such as lung cancer at baseline, the subject will not be evaluable for the CE populations.

6.1.4.2 Prior Antibiotic Therapy

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

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

causes of CABP [eg, *Streptococcus pneumoniae, Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus, Legionella pneumophila*]). EXCEPTION: Subjects may be eligible despite prior antibacterial therapy if they have been treated with a single dose of a short-acting antibacterial (ie, an antibacterial whose standard dosing regimen is more frequent than once per day, see Appendix 1 of the protocol). Enrollment of subjects who received a single dose of an allowed short-acting antibiotic within the 72 hours prior to the first dose of test article will be limited to no more than 25% of randomized subjects.

6.1.4.3 Concomitant Antibiotic Therapy

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

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

6.1.4.4 Test Article Therapy

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

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

6.1.4.5 Clinical Outcome Assessment

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

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

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

6.1.4.6 Baseline Medical Events

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

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

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

Exclusion Criterion 4: Subjects with known or suspected hospital-acquired pneumonia (HAP) or healthcare-associated pneumonia (HCAP). HAP is defined as pneumonia with onset of clinical signs and symptoms ≥ 48 hours after hospitalization in an acute in-subject health care facility. HCAP is defined as pneumonia acquired in a long-term care or subacute/intermediate healthcare facility (eg, nursing home) or in a subject admitted with pneumonia following a recent hospitalization (discharged within 90 days of current admission and previously hospitalized for ≥ 48 hours.

Exclusion 11: Requires acute pharmacologic intervention to stabilize blood pressure (BP) and/or adequate tissue perfusion, OR has evidence of septic shock defined by ALL of the following:

- Fever or hypothermia documented by the investigator (po or rectal temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
- Heart rate > 90 beats/minute

- RR > 20 breaths/minute
- WBC > 12,000 cells/mm^3 or < 4,000 cells/mm^3 or > 10% immature (band) forms regardless of the total peripheral WBC count
- Hypotension with SBP < 90 mmHg despite an iv fluid challenge of 20-30 cc/kg over a 30-minute period
- Perfusion abnormalities that may include, but are not limited to, lactic acidosis (blood lactate concentration ≥ 4 mmol/L), oliguria, or acute alteration in mental status.

Exclusion Criterion 12: Known or suspected primary or metastatic neoplastic lung disease, aspiration pneumonia, cystic fibrosis, bronchiectasis, bronchial obstruction (eg, post-obstructive pneumonia), chronic neurological disorder preventing clearance of pulmonary secretions, or severe chronic obstructive pulmonary disease (COPD).

6.1.5 Microbiologically Evaluable (ME) Populations

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

6.2 Evaluability Review Team

6.2.1 Membership and Responsibilities

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

6.2.2 Process for Determining Inclusion in Populations

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

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

Review of data, Sponsor determination of evaluability, and final subject population classification will be performed in a blinded manner prior to database lock and unblinding with the exception of those criteria requiring the subject's actual treatment assignment (for

example, the requirement for the subject to have received the correct test article per the randomization assignment). For the criteria requiring the subject's actual treatment assignment, population determination will be completed programmatically.

6.3 Subgroups

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

Exploratory analyses in other subgroups may also be conducted.

7 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

The expanded microITT population was added and selected analyses are conducted in this population.

8 OVERALL STATISTICAL CONSIDERATIONS

8.1 General Conventions

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

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

8.2 Baseline Definition

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

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

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

8.3 Handling of Missing Data

Missing data will be handled as outlined below:

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

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

- For the primary outcome measure (Early Clinical Response at 72 to 120 hours after administration of the first dose of test article):
  - The subject will be considered to have missing data if an assessment of all of the CABP symptoms (cough, sputum production, pleuritic chest pain, and dyspnea) is not made from 72 to 120 hours after the administration of the first dose of test article, unless the subject is considered a Clinical Failure for another reason. Subjects who do not have at least 2 symptoms of CABP at baseline will also be considered to have missing data unless the subject is considered a Clinical Failure for another reason. Subjects with missing data will be defined as an Indeterminate response which is essentially a Clinical Failure for the primary analysis in the ITT population.
  - If the time of administration of the first dose of test article is missing, the subject will be defined as an Indeterminate response (unless the subject is considered a Clinical Failure for another reason) which is essentially a Clinical Failure for the primary analysis in the ITT population.
- For the secondary outcome measures (investigator's assessment of Clinical Response at the EOT and PTE Visits):
  - Subjects will be defined as an Indeterminate if the investigator cannot determine whether the subject is a Clinical Success or Failure at the EOT or PTE Visits or the subject has a missing response (see Table 1). By definition, subjects with an Indeterminate response are included in the denominator for analyses in the ITT and

microITT populations, and thus, are considered Clinical Failures. Subjects with an Indeterminate response are excluded from the CE-EOT, CE-PTE, ME-EOT and ME-PTE populations.

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

8.4 Interim Analysis

An interim analysis to assess efficacy is not planned. However, a Data and Safety Monitoring Committee (DSMC) will review safety data (eg, AEs and SAEs, laboratory data, ECG assessments) by unblinded (treatment A and treatment B) treatment assignment on approximately a quarterly basis. However the DSMC can convene unscheduled meetings as necessary. A detailed DSMC charter outlines the responsibilities of the DSMC, format and frequency of the meetings, methods of providing data to and from the DSMC, statistical issues, documentation of the meeting outcomes, and communication pathways.

8.5 Pooling Strategy for Study Sites

Data will be pooled across site and geographic region (Western Europe/North America, Eastern Europe, Rest of World). Due to the large number of sites and the small number of subjects per site, no analyses by site will be conducted. Analyses by geographic region will be conducted as well as an adjusted analysis including geographic region as a stratification factor.

8.6 Visit Windows/Unscheduled Visits

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

For each safety outcome, analyses will utilize assessments occurring during the scheduled visit windows (provided in Table 7). Thus, if a subject has a visit outside the scheduled visit window, for example, a PTE Visit occurred 20 days after the subject's last day of therapy, the assessment will not be summarized with the PTE Visit but will be considered an unscheduled assessment. If a subject does not have an assessment at a scheduled visit and an unscheduled assessment was taken within the window for the time point (for example, 5 to 10 days after the subject's last day of therapy for PTE), these assessments will be summarized in the by time point analyses. If more than one measurement is taken during the visit window, the value taken on the scheduled visit will be utilized or if no scheduled visit was done, the first (earliest) measurement in the visit window will be used. If more than one measurement is taken on the same day, the assessment closest to the start of the dose will be used for on treatment values and the last measurement on the day will be used for post-treatment values. For worst overall post-baseline analyses, all assessments including those obtained from unscheduled visits will be included.

Table 7. Scheduled Study Visits

Study Visit	Study Day	Notes
Baseline	Day -1 or Day 1	Except where indicated, last measurement prior to the first dose of test article. Screening assessments are to be taken within 24 hours prior to the first dose of test article. If no test article is taken, the date and time of randomization is used in place of the first dose of test article.
On Treatment	Day 1-Day 10	Day 6 visit is optional for subjects that have been switched to po test article and have been discharged from a hospital setting. A Day 10 visit will be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the EOT Visit.
EOT		Within 2 days following the last dose of test article
PTE		5-10 days after the subject's last day of therapy
Final Follow-up	Day 30-37	30-37 days after the start of the first infusion of test article

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

9 STATISTICAL ANALYSIS METHODS

9.1 Subject Disposition

The number of Screen Failures and reason for screen failure will be presented overall and by geographic region (Western Europe/North America, Eastern Europe, Rest of World). A listing, grouped by randomization stratum (PORT Risk Class, receipt of prior antibiotics, and geographic region), will be provided that indicates the subject's date and time of randomization, randomized treatment assignment, randomization number, and block number.

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

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

9.2 Demographics and Baseline Characteristics

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

these data were used for determination of the inclusion and exclusion criteria and will be determined from the Cockcroft-Gault equation:

$$\frac{(140\text{-age[yrs]})*\text{weight [kg]}*(Z)}{}$$

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

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

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

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

Baseline assessments of clinical symptoms, clinical signs, abnormal vital signs, and abnormal laboratory signs of CABP will be presented for the ITT, Safety, microITT, and CE-PTE populations. The number and percentage of subjects with each of the CABP symptoms (cough, pleuritic chest pain, dyspnea, and phlegm/sputum production) by severity (absent, mild, moderate, severe) will be presented by treatment group. The number and percentage of subjects with the presence by severity (ie, absent, mild, moderate, severe) of the following clinical signs will be provided by treatment group: rales, rhonchi, dullness on percussion, bronchial breath sounds, wheezing, decreased breath sounds, and egophony. The number

and percentage of subjects with fever (defined as body temperature > 38°C [100.4°F] oral or rectal), hypothermia (defined as body temperature < 36°C [95.5°F] oral or rectal), hypotension with systolic blood pressure < 90 mmHg, heart rate > 90 bpm, respiratory rate > 20 breaths/min, hypoxemia (defined as PaO_2 < 60 mmHg by arterial blood gas or oxygen saturation < 90% by pulse oximetry), elevated total WBC count (> 12,000 cells/mm^3), leucopenia (WBC < 4,000 cells/mm^3), elevated immature neutrophils (> 15% band forms regardless of total peripheral WBC count) and any of elevated total WBC count, leucopenia or elevated immature neutrophils will be summarized by treatment group. Differences between treatment groups will be tested for statistical significance using Fisher's exact test.

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

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

9.2.1 Microbiology

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

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

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

1. > 25 PMNs and < 10 SECs
2. 10-25 PMNs and < 10 SECs
3. < 10 PMNs and < 10 SECs
4. >25 PMNs and 10-25 SECs
5. 10-25 PMNs and 10-25 SECs
6. < 10 PMNs and 10-25 SECs
7. > 25 PMNs and > 25 SECs
8. 10-25 PMNs and > 25 SECs
9. < 10 PMNs and > 25 SECs

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

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

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

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

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

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

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

The distribution of disk diffusion zone diameters (mm) will be provided for the test article received, by treatment group.

9.3 Treatment Compliance and Exposure

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

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

10 EFFICACY PARAMETERS

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

10.1 Primary Analysis

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

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

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

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

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

The 2-sided 95% CI for non-inferiority testing based on the difference of Early Clinical Success rates at the Early Clinical Response Assessment (72 to 120 hours after the first infusion of test article), will be computed using the method proposed without stratification by Miettinen and Nurminen (1985). For notation purposes, assume 1 represents the omadacycline group (Group 1) and 2 represents the moxifloxacin group (Group 2).

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

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

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

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

where n_1 = number of subjects in Group 1; n_2 = number of subjects in Group 2; $\tilde{p}_1 = \tilde{p}_2 + RD$; and $\tilde{p}_2$ is the maximum likelihood estimate for p_2 as a function of RD and under the constraint $p_1 = p_2 + RD$.

As stated above, the 2-sided 95% CI for the difference in rates is given by the roots for $RD = p_1 - p_2$ from the equation above, but this equation does not allow for explicit solution for RD . Therefore, a numerical algorithm will be used to obtain the 2 roots (CI) for RD . This CI approach corresponds to the non-inferiority test (a p-value approach) proposed by Farrington and Manning (1990).

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

10.2 Sensitivity and Additional Analyses of the Primary Efficacy Outcome

If the null hypothesis of inferiority is rejected for Early Clinical Response 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 95% 2-sided CI for the treatment difference is greater than 0.00, omadacycline will be considered superior to moxifloxacin.

Sensitivity analyses of the primary outcome include:

- Determination of the 95% CI adjusted for PORT Risk Class (II vs III/IV), prior use of antibiotics (yes and no), and geographic region (Western Europe/North America, Eastern Europe, and Rest of World). If there are < 20 subjects within a stratum and treatment group or there is a 0 count within a stratum for a treatment group and outcome, the geographic regions of Eastern Europe and Rest of World will be combined. If the combining of the geographic regions is not sufficient to complete the adjusted analysis,

receipt of prior antibiotics (yes vs no) will be combined. The 95% CI interval will be computed using the stratified methodology of Miettinen and Nurminen (1985). Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI as follows, where n_{1i} = number of subjects in Group 1 in the ith stratum; n_{2i} = number of subjects in Group 2 in the ith stratum:

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

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

10.3 Secondary Analysis

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

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

Early Clinical Response and the overall assessment of Clinical Response at the PTE Visit by baseline pathogen will be determined as the proportion of subjects with a Clinical Success, for each pathogen isolated at baseline. The number and percentage of subjects in each treatment group with a Clinical Success (based on Early Clinical Response and investigator's assessment of response) will be tabulated per pathogen for the microITT, ME-PTE (for Investigators assessment only), and the expanded microITT 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 (ie, included in the numerator and denominator of the calculation) but will be presented separately on the summary table. An additional analysis in the ITT

population of ACM will be completed that includes only those subjects whose status is known at 15 and 30 days after the first dose of study drug.

10.4 Additional Analyses

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

Clinical Outcomes

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

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

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

A concordance analysis of the primary efficacy outcome (Early Clinical Response at 72 to 120 hours) with the overall assessment of Clinical Response at the PTE Visit (based on the investigator's assessment) will be conducted in the ITT population. A concordance analysis of overall assessment of Clinical Response (based on the investigator's assessment) and microbiological response at the PTE Visit will be conducted in the microITT population.

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

Microbiological Outcomes

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

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

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

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

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

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

10.5 Interim Analysis

No interim analysis of efficacy is planned.

10.6 Subgroup Analyses

The primary analysis (ECR) results will be assessed separately across PORT Risk Class, use of prior antibiotics and geographic region stratum by treatment group for both the as randomized strata and the actual strata as indicated on the eCRF. For each PORT Risk Class stratum, prior antibiotic stratum and each geographical region stratum, a 2-sided 95% CI for the observed difference in the Early Clinical Success rates will be calculated for the ITT population. If a clinically meaningful treatment group-by-PORT Risk Class, treatment group-by-prior antibiotic use, or treatment group-by-geographical region result in the opposite direction of the overall result is noted, an inferential test may be performed as a descriptive statistic.

Results of the overall assessment of Clinical Response at the PTE Visit (based on the investigator's assessment at the EOT and PTE Visits) will also be assessed across PORT Risk Class, use of prior antibiotics, and geographic region strata by treatment group for both the as randomized strata and the actual strata as indicated on the eCRF. Separately for each PORT Risk Class stratum, use of prior antibiotics stratum and for each geographical region stratum, 2-sided 95% CIs for the observed difference in clinical response in the ITT and CE-PTE populations will be calculated. If a clinically meaningful treatment group-by-PORT Risk Class, treatment group-by-prior antibiotic use, or treatment group-by-geographical region result in the opposite direction of the overall result is noted, an inferential test may be performed as a descriptive statistic.

11 SAFETY AND TOLERABILITY

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

11.1 Adverse Events

Verbatim descriptions of AEs will be coded using Version 17.1 or higher of MedDRA. Summary tables will be provided for all treatment-emergent adverse events (TEAEs) but all AEs will be provided in a listing. A treatment-emergent AE is defined as any AE that newly appeared, increased in frequency, or worsened in severity on or after the initiation of active test article. An AE is considered treatment emergent if the AE start date and time is on or after the start date and time of the first infusion of active test article. If time of the AE is missing and it occurred on the same date as the first infusion of active test article, the AE will be defined as treatment emergent. If the start date of the AE is partial or missing and it cannot be determined if the AE occurred prior to or after the first dose of test article, the AE should be defined as treatment emergent.

Subjects assigned to the moxifloxacin arm receive placebo as their first infusion of test article. The AEs of subjects who experience an AE during this placebo infusion and prematurely discontinue from test article prior to receiving moxifloxacin, will only be presented in a listing.

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

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

reported for the same subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to test article.

The table of all TEAEs occurring while on treatment and post-treatment will be summarized by system organ class and preferred term for those subjects who received at least 4 days of iv test article. TEAEs occurring (ie, with a start date and time) during the time period subjects are on treatment, and separately for the time period subjects are on iv and po test article will be summarized by system organ class and preferred term.

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

11.2 Vital Signs

Blood pressure (systolic and diastolic), respiratory rate, temperature, and pulse/heart rate will be summarized using descriptive statistics at the following time points: prior to each infusion while the subject is on iv treatment, EOT Visit, PTE Visit, and highest and lowest post-baseline value. Heart rate and blood pressure will be summarized for the following additional time points: for the first 3 doses of test article, just prior to the first infusion, within 30 to 90 minutes after the start of the first infusion and 3.5 to 5.5 hours after the start of the first infusion. Descriptive statistics of the change from baseline to each post-baseline time point and the highest and lowest post-baseline value will also be provided. Baseline is defined as the value closest to but prior to the initiation of test article administration. If no value is available prior to the initiation of test article administration, a value within 2 hours after initiation of test article administration.

Post-baseline vital signs will be defined as clinically notable (CN) if they meet the criterion value or both the criterion value and the change from baseline criterion listed in Table 8. The incidence of CN vital signs will be summarized by time point and treatment group, and will be listed and flagged in by-subject listings. The overall post-baseline incidence of CN values for each vital sign parameter, which includes values from unscheduled post-baseline visits, will also be summarized. A listing will also be provided of subjects with a CN vital sign and will list all values for a vital sign noted as CN.

Table 8. Criteria for Treatment Emergent Clinically Notable Vital Signs

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

11.3 Electrocardiogram

A central vendor with readers blinded to treatment assignment will perform the reading of the ECGs. The central ECG results will be used for the statistical analyses.

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) at baseline, 30 to 90 minutes after the start of the first infusion of the first and third doses of test article, Day 7 (+1 day), and at the EOT Visit, and the change from baseline will be presented by treatment group. The QTc interval will be presented by both the Bazett ($QTcB = QT/(RR)^{1/2}$) and the Fridericia ($QTcF = QT/(RR)^{1/3}$) corrections. The change from baseline to the minimum and maximum post-baseline values will also be summarized by treatment group. Baseline is defined as the value closest to but prior to the initiation of test article administration. If no value is available prior to the initiation of test article administration, a value within 2 hours after initiation of test article administration.

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

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

11.4 Laboratory Values

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

Table 9. Laboratory Parameters and Organ Class

Organ Class	Laboratory Parameter
Renal	Creatinine
Renal	Urea
Liver	Alkaline phosphatase (ALP)
Liver	ALT
Liver	AST
Liver	Total Bilirubin
Liver	GGT
Electrolytes	Bicarbonate
Electrolytes	Calcium
Electrolytes	Chloride
Electrolytes	Magnesium
Electrolytes	Potassium
Electrolytes	Sodium
Other	Albumin
Other	Amylase
Other	Blood glucose
Other	Cholesterol
Other	CK
Other	LDH
Other	Lipase
Other	Phosphate
Other	Total protein
Other	Uric acid

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

Several analyses of the laboratory data will be presented. Descriptive statistics (based on International System [SI] units) for chemistry, hematology and coagulation values, and the change from baseline will be summarized by treatment group at each time point (Day 4 [+/1 1 day], Day 7 [+1 day], Day 10, EOT Visit and PTE Visit), and for the overall worst value

post-baseline (which includes unscheduled visits). Appendix 4 provides the directionality of the worst values for each laboratory parameter.

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

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

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

11.5 Physical Examinations

Subject listings of all physical examination results by body system will be provided. Physical examination results will be coded using MedDRA Version 17.1. Any changes from baseline will be recorded as adverse events.

12 RESOURCE UTILIZATION ANALYSES

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

- Number of days in the hospital from the time of initiation of test article until discharge. Analyses will be completed only for those subjects admitted to the hospital and separately for all subjects. For the latter, subjects who are not admitted to the hospital will be assigned a value of 0 for number of days in the hospital. Analyses will also be completed by country.
- Number of days in the hospital from the time of initiation of rescue antibiotic (ie, a second antibiotic) therapy until discharge. Analyses will be completed only for those subjects admitted to the hospital and who required a second antibiotic therapy (ie, were treatment failures) and separately for all subjects. For the latter, subjects who are not admitted to the hospital or who did not require a second antibiotic therapy will be assigned a value of 0 for number of days in the hospital. Analyses will also be completed by country.
- Number of days in the hospital from the time of admission for CABP until discharge. Analyses will be completed only for those subjects admitted to the hospital and separately for all subjects. For the latter, subjects who are not admitted to the hospital will be assigned a value of 0 for number of days in the hospital. Analyses will also be completed by country.
- Duration (days) of test article.
- Other test article exposure variables are described in Section 9.3.

13 OTHER RELEVANT DATA ANALYSES/SUMMARIES

13.1 Protocol Deviations

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

13.2 Prior and Concomitant Medications

All medications taken within 7 days prior to the date of informed consent through the Final Follow-up Visit will be recorded on the eCRF. Prior medications will be summarized by WHODRUG (Version 01 Dec 2014) Anatomical Therapeutic Chemical Classification (ATC) level 3 (third level indicates the therapeutic/pharmacologic subgroup) and generic medication name. Medications are considered prior if taken prior to the first infusion of test article or if their start date is unknown. Subjects will be counted only once for an ATC class and generic medication name. Concomitant medications taken during and after the study treatment period will be similarly summarized. Medications are considered concomitant if taken on or after the first infusion of test article, or if their stop date is unknown or marked as continuing.

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

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

14 REFERENCES

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15 APPENDICES

Appendix 1 Schedule of Assessments and Procedures

Study Phase		Double-Blind Phase										Follow-up Phase	
		iv Treatment Phase				iv or po Treatment Phase							
Study Day[a]	Screening[b]	Day 1 iv dose 1	Day 1 iv dose 2	Day 2	Day 3	Day 4	Day 5	Day 6[c]	Day 7	Day 10[c]	EOT[d]	PTE[e]	Final Follow-up[f]
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	
Chest X-ray or CT scan[i]	X												
PORT Risk Class, ABG[j]	X												
Blood and urine samples for local lab hematology/chemistry/ urinalysis/pregnancy[k]	X												
Review of Inclusion and Exclusion criteria/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		
Physical examination[m]	X			X	X	X	X	X	X	X	X	X	
Vital signs	X	X[n]	X[n]	X[n]	X	X	X	X	X	X	X	X	
12-lead ECG[o]	X	X		X					X		X		
Blood for Central Lab tests: hematology/chemistry/pregnancy	X[p]					X			X	X	X[p]	X[p]	
Adverse Events[q]	X	X----------											----------X
Prior & Concomitant Medications[r]	X	X----------											----------X
Plasma samples (in heparin) for PK analyses[s]				X	X	X	X						
Assessment for po Switch or need for continued therapy[t]						X	X	X	X	X			

Study Phase		Double-Blind Phase										Follow-up Phase	
		iv Treatment Phase				iv or po Treatment Phase							
Study Day[a]	Screening [b]	Day 1 iv dose 1	Day 1 iv dose 2	Day 2	Day 3	Day 4	Day 5	Day 6[c]	Day 7	Day 10[c]	EOT[d]	PTE[e]	Final Follow-up [f]
Investigator's Assessment of Clinical Response											X	X	
Microbiological Procedures													
Blood culture[u]	X	As Clinically Indicated											
Respiratory culture & Gram stain[v]	X										X		
Urine for Local lab *Legionella pneumophila* and *Streptococcus pneumoniae* antigen test	X											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; eCRF = electronic case report form; EOT = end of treatment; ICF = informed consent form; IxRS = Interactive Voice Response System/Interactive Web Response System; PK = pharmacokinetics; PTE = post-therapy evaluation; 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 should be completed within the 24 hours prior to the first dose of test article.

[c] The Day 6 visit is optional for subjects that have been switched to po test article and have been discharged from a hospital setting. A Day 10 visit should be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the EOT visit.

[d] 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.

[e] To be conducted 5 to 10 days after the subject's last day of therapy.

[f] To be conducted 30 to 37 days after the start of the first infusion 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 Successes and had no AEs noted at or after the PTE visit. Otherwise, the visit must be conducted in person.

[g] Written and signed ICF must be obtained before any 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 in Appendix 3 of the protocol.

[i] Subjects must have a confirming CXR or CT scan consistent with acute bacterial pneumonia within the 24 hours prior to the first dose of test article.

[j] Only subjects with a PORT Risk Class of II, III or IV are eligible for enrollment, see Appendix 2 of the protocol.

[k] Local laboratory hematology and chemistry evaluations required for assessing subject eligibility, urinalysis for WBC, a urine pregnancy test (for women only), serum transaminase or bilirubin levels.

[l] The total duration of test article therapy (iv plus po) for all subjects will be at least 7 days and no more than 14 days. The pharmacist or designee will be unblinded to prepare appropriate doses of the IxRS identified test article. An unblinded monitor will perform drug accountability and review the pharmacist's records. Subjects discharged with po test article will be asked to return all unused test article and packaging at each visit (see Section 24 of the protocol). 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 (see Section 14.2.2 of the protocol), thereafter only changes from Screening measurements should be recorded as AEs in the eCRFs.

[n] For the first 3 doses of test article heart rate and BP should be recorded at the following times: just prior to the first infusion, within 30-90 minutes after the start of the first infusion, and at 3.5-5.5 hours after the start of the first infusion (see Table 1 and Section 16.1.2 of the protocol).

[o] A 12-lead ECG should be performed just prior (within 30 minutes) and 30-90 minutes after the start of the first infusion of the first and third doses of test article, at the Day 7 visit, at the EOT visit, and as otherwise clinically indicated (see Section 16.1.4.1 of the protocol).

[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] A subject's AEs and SAEs will be recorded and reported from signing of the ICF to the Final Follow-up assessment.

[r] Treatments that have been administered within the 7 days prior to the date of signing the ICF or during the Screening phase will be recorded in the eCRF. All medications and significant non-drug therapies administered after the first dose of test article must be recorded in the eCRF (see Section 13 of the protocol).

[s] Up to 4 samples will be collected per subject. The PK sample collection schedule for the individual subject will be provided by the sponsor (see Section 19 of the protocol).

[t] At any time after the first 3 days of iv treatment (after 4 iv doses) the subject may be switched to po medication based upon determination of clinical stability. Refer to protocol Section 14.3.1.2 of the protocol for required criteria to switch to po treatment. At the investigator's discretion, all therapy may be discontinued after the seventh day of treatment (after 8 iv or po total doses), when the infection is considered clinically cured (based on normalization of the clinical signs and symptoms of infection and the investigator's clinical assessment that continued systemic antibacterial therapy is no longer needed).

[u] If Screening blood cultures are positive for a potential pathogen, blood cultures must be repeated at each visit or more frequently if clinically indicated until negative cultures are obtained (see Section 16.1.4.3 of the protocol).

[v] Culture and Gram stain from an adequate quality sputum specimen or other respiratory specimen. At the EOT visit respiratory specimen cultures and Gram stains should be obtained only for subjects who are Clinical Failures and require alternative antibacterial treatment for CABP (see Section 17.2.2.1 of the protocol).

Appendix 2 Summary of Efficacy Analyses

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

Appendix 3 Adverse Event and Prior/Concomitant Medication Date Imputations

Adverse Event Start/Stop Date Imputation

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

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

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

Prior and Concomitant Medication Start Date Imputation

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

Appendix 4 Directionality of Worst Laboratory Parameters

Laboratory Test	Parameter	Worst Value
Hematology	Hematocrit	Lowest value
	Red blood cell count	Lowest value
	Mean cell hemoglobin	Lowest value
	Mean cell hemoglobin concentration	Lowest value
	Hemoglobin	Lowest value
	Mean cell volume	Lowest value
	White blood cell count	Lowest value
	Platelets	Lowest value
	Neutrophils	Lowest value
	Lymphocytes	Lowest value
	Monocytes	Lowest value
	Eosinophils	Highest value
	Basophils	Lowest value
Chemistry	Albumin	Lowest value
	Alkaline phosphatase	Highest value
	Alanine aminotransferase (ALT/SGPT)	Highest value
	Amylase	Highest value
	Aspartate aminotransferase (AST/SGOT)	Highest value
	Urea	Highest value
	Bicarbonate	Lowest value
	Calcium	Both highest value and lowest value
	Cholesterol	Highest value
	Chloride	Both highest value and lowest value
	Creatinine	Highest value
	Creatine kinase (CK)	Highest value
	Gamma-glutamyl transpeptidase (GGT)	Highest value
	Blood glucose	Both highest value and lowest value
	Lactate dehydrogenase (LDH)	Highest value
	Lipase	Highest value
	Magnesium	Both highest value and lowest value
	Phosphate	Both highest value and lowest value
	Potassium	Both highest value and lowest value
	Sodium	Both highest value and lowest value
	Total bilirubin	Highest value
	Total protein	Lowest value
	Uric acid	Highest value
Coagulation	International normalized ratio (INR)	Highest value

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

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

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

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

HEMATOLOGY

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

CHEMISTRY

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

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

ENZYMES

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