Clinical Trial Protocol: PTK0796-CABPPO-19109

Study Title:	A Phase 1 Multi-Center Study to Measure the Pharmacokinetics of Oral Omadacycline in Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP)
Study Number:	PTK0796-CABPPO-19109
Study Phase:	1b
Product Name:	Omadacycline (PTK 0796)
IND Number:	75,928 73,431
Indication:	Community Acquired Bacterial Pneumonia
Investigators:	Multicenter
Sponsor:	Paratek Pharma, LLC. A wholly-owned subsidiary of Paratek Pharmaceuticals, Inc. 75 Park Plaza, 4th Floor Boston, MA 02116
Sponsor Contact:	1000 First Ave Suite 200 King of Prussia, PA 19406 Tel: +1 617-275-0040
Global Medical Monitor:	[redacted]

Original Protocol Version 1.1: 26 August 2019

Confidentiality Statement

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

SYNOPSIS

Sponsor:
Paratek Pharma, LLC.

Name of Finished Product:
Omadacycline oral tablet, 150 mg

Name of Active Ingredient:
Omadacycline

Study Title:
A Phase 1 Multi-Center Study to Measure the Pharmacokinetics of Oral Omadacycline in Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP)

Study Number:
PTK0796-CABPPO-19109

Study Phase: 1b

Study Rationale:
Omadacycline is an aminomethylcycline, a tetracycline class antibiotic, for intravenous (IV) or oral administration. NUZYRA® (omadacycline) has been approved by the United States (US) Food and Drug Administration (FDA) for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms.

This study is intended to evaluate the pharmacokinetics (PK) of an oral dosing regimen on Days 1 and 2 in adults with CABP.

Primary Objective:
To evaluate the PK of per oral (po) only omadacycline in adults with CABP.

Secondary Objectives:
- To evaluate the safety of omadacycline in the treatment of adults with CABP.

Exploratory Objectives:
- To evaluate the efficacy of oral only omadacycline in the treatment of adults with CABP.

Study Design:
This is an open-label Phase 1b study evaluating oral omadacycline in the treatment of adults with CABP.

Subjects will initiate treatment with an oral loading dose of 300 mg BID on Day 1 followed by 300 mg QD on subsequent days.

Following a screening period of up to 24 hours, eligible subjects will be assigned to receive 7 to 10 days of po treatment. Subjects with baseline bacteremia (ie, confirmed from local blood culture drawn at screening) can receive up to 14 days of omadacycline treatment after consultation with the medical monitor.

Subjects may receive oral treatment in either inpatient or outpatient settings, provided that all assessments can be completed at the timepoints required by protocol.

Eligible subjects will be assigned to the following treatment group.

Test Article	Study Day 1	Study Day 2	Study Days 3-10
Omadacycline	300 mg po BID	300 mg po QD	300 mg po QD

po = per oral, a dosing day is a 24-hour day not a calendar day
a The total duration of treatment is 7 to 10 days. Treatment duration can be extended to up to 14 days for subjects with bacteremia that, in the opinion of the investigator, requires more than 10 days of treatment.

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

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

The planned length of subject participation in the study is up to 37 days.

Rationale for Omadacycline Dose Regimen Selection:

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

A regimen of 200 mg omadacycline administered by IV infusion OR 100 mg omadacycline administered by IV infusion every 12 hours (q12h) on Day 1 followed by 100 mg of omadacycline administered by IV infusion once daily OR 300 mg of omadacycline administered orally once daily has been approved by US FDA for the treatment of adult patients with CABP and acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible microorganisms. In addition, an oral only regimen of 450 mg for Days 1 and 2, followed by 300 mg has been approved by US FDA for ABSSSI.

The total approved treatment duration is 7 to 14 days. The oral-only regimen is also being studied for the treatment of uncomplicated urinary tract infections (UTI).

The duration for the po only regimen in this study will be 7 to 10 days. The shorter regimen is supported by the efficacy observed in the previously completed CABP Phase 3 study which included Pneumonia Outcomes Research Team (PORT) Risk Classification II, III, and IV subjects, PTK0796-CABP-1200, where by Day 7 of treatment, > 80% of patients in the omadacycline treatment group had symptom improvement (as defined by the Early Clinical Response endpoint) and had reached clinical stability. The current study will be limited to PORT Risk Class II and III subjects only.

Approximate Number of Subjects/Sites:

Up to 30 subjects will be enrolled at approximately 5 sites in the US to ensure that at least 20 subjects complete all PK sample collections. The number may be adjusted as needed to meet this requirement.

Approximate Duration of the Study:

The study is expected to be complete in approximately 6 months.

Main Criteria for Inclusion:

1. Written and signed informed consent must be obtained before any protocol specific assessment is performed.
2. Male or female, 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 2 (regardless of total peripheral WBC count)
6. Has disease categorized as being PORT Risk Class II or III at Screening where initiation of antibiotics with oral therapy is appropriate in the opinion of the investigator, whether inpatient or outpatient setting (see PORT Risk Class calculation in Appendix 4).
7. Radiographically-confirmed pneumonia, ie, new or progressive pulmonary infiltrate(s) on chest X-ray (CXR) or chest computed tomography (CT) scan consistent with acute bacterial pneumonia within 48 hours prior to the first dose of test article.
8. Ability to swallow up to 3 tablets in succession.
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, oral contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal, or vasectomized partner) from Screening through PTE. Males must agree to use an acceptable method of birth control with female partner(s) and must not donate sperm from Screening through PTE.

Main Criteria for Exclusion:

1. Has received more than 24 hours (ie, a single dose of a daily therapy or the recommended daily frequency of a short acting therapy) 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*).

2. Is known or suspected to have CABP caused by a pathogen that may be resistant to test article (eg, *Pseudomonas aeruginosa*, *Proteus* spp., *Morganella morganii*, *Providencia* spp., *Pneumocystis jiroveci*, obligate anaerobes, mycobacteria, fungal pathogens).
3. Suspected or confirmed empyema (a parapneumonic pleural effusion is not an exclusion criterion) or lung abscess.
4. Subjects who reside in a long-term care or subacute/intermediate healthcare facility (eg, nursing home) or a subject diagnosed with pneumonia following a recent hospitalization (overnight admission within 90 days prior to current admission).
5. Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia) within the 3 months prior to Screening or presents with a tachyarrhythmia (excluding sinus tachycardia).
6. Has any of the following at Screening:
   - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × upper limit of normal (ULN)
   - total bilirubin > 1.5 × ULN
   - suspected or confirmed clinical evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy)
7. Requires any form of dialysis (eg, hemodialysis, peritoneal dialysis), has a history or evidence of severe renal disease, or has a calculated creatinine clearance (CrCl) of < 30 mL/minute, using the Cockcroft-Gault equation (see calculation in Appendix 2).
8. Significant immunological compromise 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 Appendix 2) Exception: Systemic corticosteroids administered within 24 hours of treatment group

assignment or any time after treatment group assignment as adjunctive therapy for the current episode of CABP (at any dosage) is allowed.

9. PORT Risk Class I, IV, or V patients.
10. Known or suspected primary or metastatic neoplastic lung disease, aspiration pneumonia, active tuberculosis, cystic fibrosis, bronchiectasis, bronchial obstruction (eg, post-obstructive pneumonia), chronic neurological disorder preventing clearance of pulmonary secretions, or severe chronic obstructive pulmonary disease (COPD) (severe COPD is defined as known forced expiratory volume in 1 second [FEV_1] < 50% of predicted in a patient with FEV_1/forced vital capacity [FVC] < 70%; note that spirometry or pulmonary function testing is not required during Screening).
11. Has a life expectancy of less than or equal to 3 months.
12. Pregnant or nursing (breastfeeding) women.
13. Has any contraindication to receiving a tetracycline, including:
    - History of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline, or tigecycline).
    - History of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
    - History of systemic lupus erythematosus or lupus-like syndrome.
    - Current clinical suspicion or diagnosis of pancreatitis.
14. Use of other investigational drugs 30 days prior to Screening.
15. Has previously been treated with omadacycline within 30 days of screening or previously enrolled in this study.
16. Any planned medical intervention that might interfere with the ability to comply with the study requirements.
17. Has any concomitant condition that, in the opinion of the investigator, is likely to interfere with evaluation of the response of the infection under study, determination of AEs, or completion of the expected course of treatment.

Test Article; Dose; and Mode of Administration:

Test Article	Study Day 1	Study Day 2	Study Days 3-10
Omadacycline	300 mg po BID	300 mg po QD	300 mg po QD

po = per oral, a dosing day is a 24-hour day not a calendar day

a The total duration of treatment is 7 to 10 days. Treatment duration can be extended to up to 14 days for subjects with bacteremia that, in the opinion of the investigator, requires more than 10 days of treatment.

Duration of Treatment:

The total duration of po treatment is 7 to 10 days. Subjects with baseline bacteremia (ie, confirmed from local blood culture drawn at screening) can receive up to 14 days of treatment after consultation with the medical monitor.

Pharmacokinetic Assessments

Blood Collection (plasma):

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

- Day 1: within an hour prior to Dose 1, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 hours (12 hour taken immediately before Dose 2);

  Dose 2 administered (times relative to Dose 1); 13, 13.5, 14, 14.5, 15, 16, 24 hours post dose
- Day 2: within an hour prior to dose, 1, 1.5, 2, 2.5, 3, 4, 6 hours
- Day 3: prior to the Day 3 dose
- EOT: anytime during the visit

Safety Assessments:

- Physical examinations;
- Vital signs (body weight, blood pressure, heart rate, pulse oximetry, respiratory rate (RR) and body temperature);
- Laboratory tests (Hematology, serum chemistry);
- AEs, and serious adverse events (SAEs);
- Concomitant medications;
- Urinalysis and Pregnancy assessments (Screening only).

Efficacy Assessments:

- Investigator's assessment of clinical response at EOT and PTE visits. Clinical success is defined as resolution of signs and symptoms of the infection to the extent that further antibacterial therapy is not necessary
- Clinical Stability
- Final Follow-up Assessment of signs and symptoms of CABP by the investigator

Resource Utilization:

- Hospital admission
- Emergency Department and Physician visits

Statistical Methods:

The following subject populations have been defined for the various analyses:

- The PK population will consist of all assigned subjects who receive omadacycline and have PK samples collected.
- The Safety population will consist of all assigned subjects who receive at least one dose of omadacycline.
- The intent-to-treat (ITT) population will consist of all assigned subjects.

Demography and Baseline Characteristics: Subject disposition, demographics, and baseline characteristics will be summarized overall for all subjects in the ITT population.

Pharmacokinetic Analyses: The observed omadacycline concentration-time data after an oral dosing regimen, BID on Day 1 and QD on Day 2, in CABP patients will be evaluated. 300mg administered orally is the dose that provided equivalent total exposure as measured by AUC relative to the 100mg IV dose (CPTK796-A2104). The oral bioavailability of omadacycline is 34%.

Using the superposition principle, the AUC of a single 100mg IV dose on Day 1 for n=63 healthy subjects were totaled to evaluate the $AUC_{(0-48)}$ of the established omadacycline IV dosing regimen (q12h on Day 1 followed by q24h on Day 2). $AUC_{(0-48)}$ values are then summarized and serve as the comparator for this current study. Safety and efficacy in CABP patients were demonstrated for this dosing regimen (PTK796-CABP-1200), but only sparse PK sampling was conducted. The final population PK model for omadacycline, which includes CABP patients from the PTK0796-CABP-1200 study, generated similar $AUC_{(0-48)}$ values for the 100mg IV dosing regimen.

The comparative bioavailability assessment between the test, 300mg po in CABP patients, and the reference, 100mg IV in healthy subjects, will be based on 90% confidence intervals (CIs) for the geometric mean ratios (GMR) of $AUC_{(0-48)}$ for the two dosing regimens being within 80% and 125%.

Individual plasma concentration, time deviation data and PK parameters will be presented in data listings. Plasma concentration data and PK parameters will be summarized by time point using descriptive statistics (number of subjects, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum). Mean and individual plasma concentration versus time profiles will be presented in figures on both linear and semilogarithmic scales. Geometric means will be included for area under the concentration-time curve (AUC) and maximum observed plasma concentration (C_{max}).

Safety Analyses: Adverse events will be coded by preferred term (PT) and system organ class (SOC) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). All AE data will be presented in a data listing. All AEs will be summarized

overall, as well as by severity, and relationship to study drug. Any serious AEs and AEs leading to discontinuation of study drug will also be presented in a data listing.

Clinical laboratory test results (hematology and serum chemistry) and vital sign measurements will be summarized by time point. Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary and will presented in a data listing.

Efficacy Analyses: The number and percentage of subjects with investigator assessment of clinical response will be presented at each time point (EOT and PTE). The number and percentage of subjects who achieve clinical stability will be presented for each day, EOT and PTE.

Rationale for Number of Subjects: This study is designed to evaluate the PK profile of an oral dosing regimen, BID on Day 1 and QD on Day 2, in adults with CABP. The sample size determination is based on consideration of the precision of the estimate, GMR of $AUC_{(0-48)}$ for 300mg po to 100mg IV, derived from model-based simulations of omadacycline concentration data (Phase I studies).

With 20 evaluable subjects, there will be 90% probability that the 90% CIs of the GMR for $AUC_{(0-48)}$ will be within 80% and 125%. Up to 30 subjects will be enrolled so that at least 20 subjects are evaluable for bioavailability estimation. The number may be adjusted as needed to meet this requirement.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABG	arterial blood gas
ABSSSI	acute bacterial skin and skin structure infections
AE	adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration time curve
AUC_{0-24}	AUC from time 0 to 24 hours after dosing
AUC_{last}	AUC from time 0 to the last quantifiable concentration
β-hCG	serum β-human chorionic gonadotropin
BP	blood pressure
CABP	community-acquired bacterial pneumonia
CD4	cluster of differentiation 4
CFR	Code of Federal Regulations
C_{max}	maximum observed plasma concentration
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CRF	case report form
CSA	clinical study agreement
CSR	Clinical Study Report
CT	computed tomography
CV	coefficient of variation
CXR	chest X-ray
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration

FEV_1	forced expiratory volume in one second
FFU	Follow-up visit
FVC	forced vital capacity
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
IxRS	interactive voice/web response system
LPF	low power field
MDR-SP	Multi-drug resistant *Streptococcus pneumoniae*
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
PaO_2	partial pressure of arterial oxygen
PI	Principal Investigator
PK	pharmacokinetics
po	per oral
PORT	Pneumonia Outcomes Research Team
PT	preferred term
PTE	Post Therapy Evaluation
QD	once per day
q12h	every 12 hours
RAC	accumulation factor
REB	Research Ethics Board

RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum observed plasma concentration
$T_{1/2}$	terminal-phase elimination half-life
ULN	Upper Limit of Normal
US	United States
UTI	urinary tract infection
WBC	White Blood Cell (Count)

1 DISCLOSURE STATEMENT

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2 CONTACTS

2.1 Emergency Contacts

Name/Title: [redacted]
Global Medical Monitor

Phone (during business hours): [redacted]
Phone (after business hours):
E-mail (not for emergencies):
Address:

2.2 Additional Contacts

SAE contact information:
E-Mail: [redacted]

3 INTRODUCTION

3.1 Community Acquired Bacterial Pneumonia

Community Acquired Bacterial Pneumonia (CABP) is a leading cause of morbidity and mortality in the United States (US) and throughout the world (Mandell). 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). Furthermore, there is increasing resistance to antibiotics among common pathogens, with a resulting critical need for new antibiotics (Spellberg). Bacterial resistance to the most frequently prescribed, currently available antibiotics has limited their potential to treat infections, which prevents their use as a first-line empiric monotherapy. Methicillin-resistant *Staphylococcus aureus* and multi-drug resistant *Streptococcus pneumoniae* in the community have posed treatment challenges because of resistance to penicillins (resistance rate 100% for both), cephalosporins (100% and 11%, respectively, for ceftriaxone), macrolides (83% and 86%, respectively, for azithromycin/erythromycin), and quinolones (73% and 2%, respectively, for levofloxacin), in CABP. In addition, the growing concern about, "collateral damage" associated with use of quinolone and beta-lactam class antibiotics further underscores the need for new antibiotic treatment options for CABP (Paterson). Failure of therapy due to resistance will continue to contribute to the morbidity and mortality of CABP and treatment failures of mild disease will result in increased hospitalizations and contribute to increased healthcare costs.

3.2 Omadacycline

The investigational product, omadacycline (formerly named PTK 0796), is the first member of the aminomethylcycline class of antibiotics, which are 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. NUZYRA® (omadacycline) has been approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with CABP caused by susceptible microorganisms.

Omadacycline has demonstrated activity against the most common CABP pathogens, including isolates resistant to older antibiotics. This study is intended to evaluate the pharmacokinetics (PK) of an oral dosing regimen on Days 1 and 2 in adults with CABP.

Please refer to the current version of the Investigator's Brochure or the NUZYRA® (omadacycline) USPI for additional information on omadacycline.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is:

- To evaluate the PK of oral (po) only omadacycline in adults with CABP.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety of omadacycline in the treatment of adults with CABP.

4.3 Exploratory Objectives

- To evaluate the efficacy of oral only omadacycline in the treatment of adults with CABP.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Description

This is an open-label Phase 1b study evaluating oral omadacycline in the treatment of adults with CABP.

This study is intended to evaluate the PK of an oral dosing regimen in adults with CABP. Subjects will initiate treatment with an oral loading dose of 300 mg BID on Day 1 followed by 300 mg QD on subsequent days.

Following a screening period of up to 24 hours, eligible subjects will be assigned to receive 7 to 10 days of po treatment. Subjects with baseline bacteremia (ie, confirmed from local blood culture drawn at screening) can receive up to 14 days of treatment after consultation with the medical monitor.

Subjects may receive oral treatment in either inpatient or outpatient settings, provided that all assessments can be completed at the timepoints required by protocol.

Eligible subjects will be assigned to the following treatment groups.

Test Article	Study Day 1	Study Day 2	Study Days 3-10
Omadacycline	300 mg po BID	300 mg po QD	300 mg po QD

po = per oral, a dosing day is a 24-hour day not a calendar day
a The total duration of treatment is 7 to 10 days. Treatment duration can be extended to up to 14 days for subjects with bacteremia that, in the opinion of the investigator, requires more than 10 days of treatment.

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

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

The planned length of subject participation in the study is up to 37 days.

5.2 Rationale for Study Design

The dosing regimen of omadacycline selected for this study is based on the nonclinical and clinical experience to date, including in vitro antibacterial activity, PK characteristics,

clinical efficacy in prior studies, the overall safety and tolerability profile, and the FDA approved dosing regimen for CABP.

A regimen of 200 mg omadacycline administered by intravenous (IV) infusion OR 100 mg omadacycline administered by IV infusion every 12 hours (q12h) on Day 1 followed by 100 mg of omadacycline administered by IV infusion once daily OR 300 mg of omadacycline administered orally once daily has been approved by US FDA for the treatment of adult patients with CABP and acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible microorganisms. In addition, an oral only regimen of 450 mg for Days 1 and 2, followed by 300 mg has been approved by US FDA for ABSSSI. The total approved treatment duration is 7 to 14 days. The oral only regimen is also being studied for the treatment of uncomplicated urinary tract infection (UTIs).

The duration for the po only regimen in this study will be 7 to 10 days. The shorter regimen is supported by the efficacy observed in the previously completed CABP Phase 3 study which included Pneumonia Outcomes Research Team (PORT) Risk Classification II, III and IV subjects, PTK0796-CABP-1200 where by Day 7 of treatment, > 80% of patients in the omadacycline treatment group had symptom improvement (as defined by the Early Clinical Response endpoint) and had reached clinical stability. In the current study, PORT Risk Class I, IV, and V subjects will be excluded.

5.3 Approximate Duration of Subject Participation

Subjects will participate in the study for up to 37 days. Following a screening period of up to 24 hours, eligible subjects will be assigned to receive treatment. Eligible subjects will be assigned to receive 7 to 10 days of po treatment. Subjects with baseline bacteremia (ie, confirmed from local blood culture drawn at screening) can receive up to 14 days of treatment after consultation with the medical monitor.

5.4 Approximate Duration of Study

The study is expected to be complete in approximately 6 months.

5.5 Approximate Number of Subjects

Up to 30 subjects will be enrolled at approximately 5 sites in the US to ensure that at least 20 subjects complete all PK sample collections. The number may be adjusted as needed to meet this requirement.

6 STUDY POPULATION SELECTION

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

6.1 Study Population

Up to 30 subjects will be enrolled at approximately 5 sites in the US to ensure that at least 20 subjects complete all PK sample collections. The number may be adjusted as needed to meet this requirement.

6.2 Inclusion and Exclusion Criteria

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

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 2 (regardless of total peripheral WBC count)
6. Has disease categorized as being PORT Risk Class II or III at Screening where initiation of antibiotics with oral therapy is appropriate in the opinion of the investigator, whether inpatient or outpatient setting (see PORT Risk Class calculation in Appendix 4).

7. Radiographically-confirmed pneumonia, ie, new or progressive pulmonary infiltrate(s) on chest X-ray (CXR) or chest computed tomography (CT) scan consistent with acute bacterial pneumonia within 48 hours prior to the first dose of test article.
8. Ability to swallow up to 3 tablets in succession.
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, oral contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal, or vasectomized partner) from Screening through PTE. Males must agree to use an acceptable method of birth control with female partner(s) and must not donate sperm from Screening through PTE.

Main Criteria for Exclusion:

1. Has received more than 24 hours (ie, a single dose of a daily therapy or the recommended daily frequency of a short acting therapy) 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*, *S. aureus, Legionella pneumophila*).
2. Is known or suspected to have CABP caused by a pathogen that may be resistant to test article (eg, *Pseudomonas aeruginosa*, *Proteus* spp., *Morganella morganii*, *Providencia* spp., *Pneumocystis jiroveci*, obligate anaerobes, mycobacteria, fungal pathogens).
3. Suspected or confirmed empyema (a parapneumonic pleural effusion is not an exclusion criterion) or lung abscess.
4. Subjects who reside in a long-term care or subacute/intermediate healthcare facility (eg, nursing home) or a subject diagnosed with pneumonia following a recent hospitalization (overnight admission within 90 days prior to current admission).
5. Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia) within the 3 months prior to Screening or presents with a tachyarrhythmia (excluding sinus tachycardia).
6. Has any of the following at Screening:
   - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 3 \times$ Upper Limit of Normal (ULN)
   - total bilirubin $> 1.5 \times$ ULN
   - suspected or confirmed clinical evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy)
7. Requires any form of dialysis (eg, hemodialysis, peritoneal dialysis), has a history or evidence of severe renal disease, or has a calculated creatinine clearance (CrCl) of < 30 mL/minute, using the Cockcroft-Gault equation (see calculation in Appendix 2).
8. Significant immunological compromise 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 Appendix 2) Exception: Systemic corticosteroids administered within 24 hours of treatment group assignment or any time after treatment group assignment as adjunctive therapy for the current episode of CABP (at any dosage) is allowed.

9. PORT Risk Class I, IV, or V patients.
10. Known or suspected primary or metastatic neoplastic lung disease, aspiration pneumonia, active tuberculosis, cystic fibrosis, bronchiectasis, bronchial obstruction (eg, post-obstructive pneumonia), chronic neurological disorder preventing clearance of pulmonary secretions, or severe chronic obstructive pulmonary disease (COPD) (severe COPD is defined as known forced expiratory volume in 1 second [FEV_1] < 50% of predicted in a patient with FEV_1/forced vital capacity [FVC] < 70%; note that spirometry or pulmonary function testing is not required during Screening).
11. Has a life expectancy of less than or equal to 3 months.
12. Pregnant or nursing (breastfeeding) women.
13. Has any contraindication to receiving a tetracycline, including:
    - History of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline).
    - History of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
    - History of systemic lupus erythematosus or lupus-like syndrome.
    - Current clinical suspicion or diagnosis of pancreatitis.
14. Use of other investigational drugs 30 days prior to Screening.
15. Has previously been treated with omadacycline within 30 days of screening or previously enrolled in this study.
16. Any planned medical intervention that might interfere with the ability to comply with the study requirements.
17. Has any concomitant condition that, in the opinion of the investigator, is likely to interfere with evaluation of the response of the infection under study, determination of AEs, or completion of the expected course of treatment.

6.3 Screen Failures

Subjects who sign the ICF but withdraw or are withdrawn from the study before 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 interactive voice/web response system (IxRS), if used, for screen failures. Screen failure subjects may be re-screened at the discretion of the investigator and in consultation with the medical monitor as needed. Any subject who discontinues participation or is withdrawn before receiving a treatment assignment, and who is re-screened at a later time will be assigned a new subject number and recorded as re-screened.

7 STUDY TREATMENT(S)

7.1 Treatments Administered

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

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

Following a Screening period of up to 24 hours, eligible subjects will be assigned a dosing regimen of omadacycline

7.2 Identity of the Investigational Product: Omadacycline

Oral Formulation (Omadacycline)

Name	Omadacycline Tablet, 150 mg
Excipients	Lactose monohydrate, microcrystalline cellulose, sodium stearyl fumarate, crospovidone, colloidal silicone dioxide, sodium bisulfite, polyvinyl alcohol, titanium dioxide, talc, glycerol monocaprylocaprate, sodium lauryl sulfate, iron oxide yellow
How supplied	4-count wallet
Storage	Store at 25˚C (77˚F). Excursions permitted to 15°C-30°C (59˚F -86˚F) (Per Pharmacy Manual)
Preparation and handling	No special requirements
Administration	Please reference Section 7.5

7.3 Dose Selection Rationale

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

A regimen of 200 mg omadacycline administered by IV infusion OR 100 mg omadacycline administered by IV infusion q12h on Day 1 followed by 100 mg of omadacycline administered by IV infusion once daily OR 300 mg of omadacycline administered orally once daily has been approved by US FDA for the treatment of adult patients with CABP and ABSSSI caused by susceptible microorganisms. In addition, an oral only regimen of 450 mg for Days 1 and 2, followed by 300 mg has been approved by US FDA for ABSSSI. The total approved treatment duration is 7 to 14 days. The oral only regimen is also being studied for the treatment of uncomplicated UTIs.

The duration for the po only regimen in this study will be 7 to 10 days. The shorter regimen is supported by the efficacy observed in the previously completed CABP Phase 3 study which included PORT Risk Classification II, III and IV subjects, PTK0796-CABP-1200 where by Day 7 of treatment, > 80% of patients in the omadacycline treatment group had symptom improvement (as defined by the Early Clinical Response endpoint) and had reached clinical stability. In the current study, PORT Risk Class I, IV, and V subjects will be excluded.

7.4 Description of Treatments

Subjects will be assigned to the following treatment group:

Test Article	Study Day 1	Study Day 2	Study Days 3-10
Omadacycline	300 mg po BID	300 mg po QD	300 mg po QD

po = per oral, a dosing day is a 24-hour day not a calendar day
a The total duration of treatment is 7 to 10 days. Treatment duration can be extended to up to 14 days for subjects with bacteremia that, in the opinion of the investigator, requires more than 10 days of treatment.

7.5 Test Article Administration

7.5.1 Oral Treatment

Subjects should receive their first dose of test article on the morning following enrollment.

All doses of oral test article should be taken with water.

All oral doses should be taken in a fasted state. Fasting is defined as no food, antacids, or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) or drink except water for at least 6 hours before dosing. After dosing, no food is permitted for 2 hours as well as no dairy products, antacids, or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours.

7.5.1.1 Management While on Oral Test Article

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

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

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

7.6 Dose Adjustments and Interruptions of Test Article

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

7.6.1 Subject Numbering

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

7.7 Dispensing Test Article

Each study site will be supplied by the sponsor with the investigational product. The po test article will be supplied to the sites in wallets that contain active omadacycline tablets.

7.8 Prior and Concomitant Therapy

Treatments that have been administered within the 7 days prior to the date of informed consent, or during the Screening phase, will be recorded in the eCRF. The investigator is to instruct the subject to notify the study site about any new medications he/she takes after the start of the test article. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with test article must be listed in the eCRF (see Section 9). In addition, for antibacterial agents and anti-emetics administered 30 days prior to screening and concomitantly, the dose, unit, frequency and route must be entered in the eCRF.

7.9 Prohibited Therapy

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

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

- More than 24 hours (ie, a single dose of a daily therapy or the recommended daily frequency of a short acting therapy) of a potentially effective systemic antibacterial treatment within the 72 hours prior to the first dose of test article.
- Antacids and multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 6 hours before and within 4 hours after oral doses.

7.10 Permitted Treatments

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

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

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

7.11 Treatment Compliance

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

7.12 Packaging and Labeling

The investigational test article, omadacycline will be packaged by the sponsor and supplied to the investigator.

7.13 Storage and Accountability

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

The designated study personnel must maintain an accurate record of the shipment and dispensing of test articles in the study specific medication accountability ledger.

7.14 Investigational Product Retention at Study Site

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

8 STUDY PROCEDURES

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

8.1 Informed Consent

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

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

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

8.2 Subject Demographics/Other Baseline Characteristics

Subject demographic and Baseline characteristic data to be collected on all subjects include: date of birth, gender, and race/ethnicity.

8.3 Medical History

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

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

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

8.4 Physical Examination

At Screening, a full physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological systems.

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

8.5 Vital Signs

Vital signs include blood pressure (BP), heart rate, pulse oximetry, RR, and body temperature.

- Blood pressure and heart rate should be measured within 30 min before, and approximately (± 15 minutes) 1 hour after the completion of the first dose.

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

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

A pulse oximeter should be used to capture oxygen saturation.

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

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

8.6 Height and Weight

Height and body weight will be collected.

8.7 Assessment of CABP Symptom Severity

The investigator will specifically assess the presence and severity level of the subject's symptoms of cough, sputum production, pleuritic chest pain, and dyspnea on a 4-point scale (absent, mild, moderate, or severe) based upon the Community Acquired Bacterial Pneumonia Subject Symptom Severity Guidance Framework for Investigator Assessment (see Appendix 3) and enter the symptom severity level into the eCRF. Subjects must have at least 3 of these 4 symptoms of CABP to be eligible for randomization in the study.

8.8 Radiologic Evaluation of Pneumonia

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

8.9 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 4). All subjects must have disease characterized as PORT Risk Class of II or III at randomization.

8.10 Clinical Laboratory Tests

All laboratory testing will be performed by the local laboratory at each site. The relevant local laboratory results from Screening will be used to assess eligibility as per the inclusion/exclusion criteria.

8.10.1 Hematology and Serum Chemistry

Blood testing will include the hematology and serum chemistry parameters as shown in Table 1 and Table 2, respectively. These results for the study timepoints indicated in Appendix 1 will be recorded in the eCRF.

Table 1 Hematology

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

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Table 2 Serum Chemistry

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

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

8.10.2 Pregnancy Assessment

All female subjects will have a local laboratory urine or serum pregnancy test at Screening. Results are required for eligibility and will be retained in source documents but will not be entered in the eCRF. If a positive urine or serum pregnancy test result is obtained during Screening, the subject is not to be enrolled.

Should a positive pregnancy test be reported after a subject is enrolled, test article administration should be discontinued (see Section 8.18.6).

8.10.3 Urinalysis

A urine dipstick test will be performed at the local laboratory at Screening, which will include (at minimum) the parameters shown in Table 3. Results are intended to assist in the eligibility assessment (e.g., assessment of potential renal disease), and will be retained in source documents but will not be entered in the eCRF.

Table 3 Urine Dipstick

pH
Glucose
Ketones
Bilirubin
Blood
WBC/Leukocyte Esterase.

8.11 Pharmacokinetic Assessments

Instructions will be provided to sites with detailed information on sample collection, handling, and shipment requirements. All samples will be given a unique identifier. The exact clock time of dosing, date and time of last food intake, as well as actual sample collection date and time will be entered on the eCRF. The total volume of blood collected for pharmacokinetic assessments from each subject will be approximately 108 mL (7 tablespoons) over the course of the study.

8.11.1 PK Blood Collection and Processing

Blood Collection (plasma):

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

- Day 1: within an hour prior to Dose 1, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 hours (12 hour taken immediately before Dose 2);
  Dose 2 administered (times relative to Dose 1); 13, 13.5, 14, 14.5, 15, 16, 24 hours post dose
- Day 2: within an hour prior to dose, 1, 1.5, 2, 2.5, 3, 4, 6 hours
- Day 3: prior to the Day 3 dose
- EOT: anytime during the visit

8.11.2 Storing and Shipping of PK Samples

After all PK samples from a single subject have been collected and frozen at - 20°C or colder, the primary samples from each time point can be batched together and carefully packaged and shipped frozen at - 20°C or colder to the central laboratory designated by the sponsor. Samples are to be shipped with sufficient dry ice to remain frozen during overnight transit. For each subject and time point, the remaining stored aliquots will be retained on site at - 20°C or colder until released or requested by the sponsor.

8.12 Efficacy Assessments

8.12.1 Investigator's Assessment of Clinical Response

8.12.1.1 Investigator's Assessment of Clinical Response 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.
- Other specified reason.

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.

8.12.1.2 Investigator's Assessment of Clinical Response at PTE

The PTE assessment is to be performed 5 to 10 days after the subject's last day of therapy. The investigator will determine 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.
- Other specified reason.

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.

8.12.2 Clinical Stability

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

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

- temperature ≤37.8°C (100°F);
- heart rate ≤100 beats/minute;
- RR ≤24 breaths/minute;
- systolic blood pressure ≥ 90 mmHg; and
- arterial oxygen saturation ≥ 90% or PaO2 ≥ 60 mmHg on room air.

8.13 Adverse Events

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

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

8.14 Serious Adverse Events

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

- Results in death
- Is life-threatening (see below)
- Requires hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or birth defect
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical

judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent any one (1) of the outcomes listed above in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

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

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

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

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

8.15 Other Reportable Information

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

- Pregnancy exposure to a test article: If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.

- Lactation exposure to a test article with or without an AE.
- Overdose of a test article as specified in this protocol with or without an AE.
- Inadvertent or accidental exposure to a test article with or without an AE.

8.16 Overdose

Any administration of omadacycline of greater than 1350 mg within a 24-hour period will be an overdose, regardless of whether the overdose is intentional or accidental, it is a reportable event and the sponsor must be notified within 1 business day. 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.

8.17 Medication Errors

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

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

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

All AEs and SAEs must be handled as specified in this protocol whether or not they are associated with a medication error. A medication error associated with an SAE (including overdose, inadvertent exposure, and/or accidental exposure) will be reported with the SAE on the SAE Report Form. All other medication errors will be reported by e-mailing the Clinical Test Article Error Incident Report Form as indicated in the Emergency Contacts (see Section 2).

8.18 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.

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

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

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

8.18.1 Serious Adverse Event Reporting

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

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

8.18.2 Assessment of Relatedness

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

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

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

8.18.3 Assessment of Severity

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

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

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

8.18.4 Laboratory Findings

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

8.18.5 Worsening or Progression of Disease Under Study

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

8.18.6 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.

8.19 Concomitant Medication Assessments

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

All prescription medications, over-the-counter drugs, and recreational drugs taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant Medications/Non-Drug Therapies page of the eCRF. Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation dates, and the reason for therapy.

8.20 Subject Discontinuation or Withdrawal

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

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

Site personnel should also contact the IxRS, if used 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.

8.20.1 Replacements

Any subject who is withdrawn or discontinued from the study may be replaced at the discretion of the sponsor to meet the target of at least 20 subjects with complete PK sampling.

9 STUDY ACTIVITIES

The full assessment schedule is presented in the Schedule of Events (see Appendix 1). Subjects should be seen for all visits on the designated day.

9.1 Screening Phase

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

9.2 Treatment Phase

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

9.3 EOT Visit Procedures

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

9.4 Follow-up Phase

9.4.1 Post-Treatment Evaluation Visit Procedures

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

9.4.2 Final Follow-up

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

10 STUDY SUSPENSION, TERMINATION, AND COMPLETION

10.1 Study Completion and Post-Study Test Article

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

No long-term follow-up of subjects is planned, with the exception of pregnancies, as described in Section 8.18.6, and SAEs described in Section 8.18.1.

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

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

10.2 Study Suspension or Termination

The sponsor may suspend or terminate the study at any time for any reason. Should this be necessary, subjects should be seen as soon as possible and treated as described in Sections 8.20 and 9.3 for prematurely withdrawn subjects. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs and/or Ethics Committees (ECs) of the early termination of the study.

If the investigator suspends or prematurely terminates their participation in the study, the investigator will promptly inform the sponsor and the IRB/IEC/REB and provide them with a detailed written explanation. Subjects should be seen as soon as possible and treated as described in Sections 8.20 and 9.3 for prematurely withdrawn subjects. The investigator will also return all test articles, containers, and other study materials to the sponsor.

11 QUALITY CONTROL AND ASSURANCE

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

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan (SAP). After finalization of the SAP, any additional analyses or changes to analyses that may be required will be fully disclosed in the Clinical Study Report (CSR.).

Analyses will be performed after the database lock at which all eCRFs are completed, entered and source data verified; all safety laboratory results have been reported; all AEs fully characterized (e.g., relationship to test article determined) and coded; characterization of protocol deviations as major/minor completed, and all queries have been resolved.

Exploratory analyses may also be performed. Listings of individual subject's data will be produced.

12.2 Determination of Sample Size

This study is designed to evaluate the PK profile of an oral dosing regimen, 300mg BID on Day 1 and QD on Day 2, in adults with CABP. The sample size determination is based on consideration of the precision of the estimate, GMR of $AUC_{(0-48)}$ for 300mg po to 100mg IV, derived from model-based simulations of omadacycline concentration data (Phase I studies).

With 20 evaluable subjects, there will be 90% probability that the 90% CIs of the GMR for $AUC_{(0-48)}$ will be within 80% and 125%. Up to 30 subjects will be enrolled so that at least 20 subjects are evaluable for bioavailability estimation.

The number may be adjusted as needed to meet this requirement.

12.3 Analysis Populations

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

- The PK population will consist of all assigned subjects who receive test article and have PK samples collected.
- The Safety population will consist of all assigned subjects who receive at least one dose of test article.
- The intent-to-treat (ITT) population will consist of all assigned subjects.

Additional populations may be defined in the SAP as appropriate.

12.4 Demographics and Baseline Characteristics

Demographics (including age, ethnicity and race) and baseline characteristics will be summarized. Descriptive statistics of the duration of test article treatment will be provided. The number and percentage of subjects who prematurely discontinued test article and the reason for discontinuation and the number and percentage of subjects prematurely discontinuing the study and the primary reason for discontinuation will be presented.

12.5 Primary Endpoint(s)

12.5.1 Pharmacokinetic Endpoint

The following plasma PK parameters will be determined:

- Area under the plasma concentration time curve (AUC) from time 0 to 48 hours after dosing (AUC_{0-48})
- Area under the plasma concentration time curve (AUC) from time 0 to 24 hours after dosing (AUC_{0-24})
- AUC from time 0 to the last quantifiable concentration (AUC_{last})
- Maximum observed plasma concentration (C_{max})
- Time to reach maximum observed plasma concentration (T_{max})
- Elimination half-life associated with the terminal slope of the semilogarithmic concentration-time curve ($T_{1/2}$)

The observed omadacycline concentration-time data after an oral dosing regimen, BID on Day 1 and QD on Day 2, in CABP patients will be evaluated. 300mg administered orally is the dose that provided equivalent total exposure as measured by AUC relative to the 100mg IV dose (CPTK796-A2104). The oral bioavailability of omadacycline is 34%.

Using the superposition principle, the AUC of a single 100mg IV dose on Day 1 for n=63 healthy subjects were totaled to evaluate the $AUC_{(0-48)}$ of the established omadacycline IV dosing regimen (q12h on Day 1 followed by q24h on Day 2). $AUC_{(0-48)}$ values are then summarized and serve as the comparator for this current study. Safety and efficacy in CABP patients were demonstrated with this dosing regimen (PTK796-CABP-1200), but only sparse PK sampling was conducted. The final population PK model for omadacycline, which includes CABP patients from the PTK0796-CABP-1200 study, generated similar $AUC_{(0-48)}$ values for the 100mg IV dosing regimen.

The comparative bioavailability assessment between the test, 300mg po in CABP patients, and the reference, 100mg IV in healthy subjects, will be based on 90% confidence intervals (CIs) for the geometric mean ratios (GMR) of $AUC_{(0-48)}$ for the two dosing regimens being within 80% and 125%.

Plasma concentration data and PK parameters will be summarized by time point using descriptive statistics (number of subjects, mean, standard deviation (SD), coefficient of

variation (CV), median, minimum, and maximum). Mean and individual plasma concentration versus time profiles will be presented in figures on both linear and semilogarithmic scales. Geometric means will be included for area under the concentration-time curve (AUC) and maximum observed plasma concentration (C_{max}).

Individual plasma concentration, time deviation and PK parameters will be presented in data listings.

Any additional exploratory PK calculations will be further described in the SAP.

12.6 Secondary Endpoint(s)

12.6.1 Safety Endpoint(s)

All safety analyses will utilize the Safety population. 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. Adverse events 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 by system organ class (SOC) and preferred term (PT), by SOC, PT and severity, and by SOC, PT and relationship to test article. Additional tabulations will provide summaries by SOC and PT of subjects experiencing SAEs and TEAEs leading to discontinuation of test article.
Treatment-emergent adverse events leading to dose interruption of test article, and TEAEs of special interest.

The following variables will be analyzed descriptively in the Safety population:

- Vital signs (systolic and diastolic BP, pulse/heart rate, body temperature, pulse oximetry, RR), including change from Baseline by time point measured
- Clinically notable vital signs (meeting predefined criteria as specified in the SAP) by time point measured
- Laboratory parameters, including change from Baseline by visit and overall worst post-baseline
- Clinically notable laboratory parameters (meeting predefined criteria as specified in the SAP) by visit and overall worst post-baseline

12.6.2 Exploratory Endpoint(s)

The efficacy outcome is defined as the Investigator's Assessment of Clinical Response with outcomes of Clinical Success, Clinical Failure or Indeterminate (see Section 8.12.1) in the ITT 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.

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

- Assessment of signs and symptoms of CABP by the investigator
- Clinical Stability

12.6.3 Resource Utilization Endpoint(s)

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

- Hospital admission
- Emergency Department and Physician visits

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

12.7 Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified. Detailed data imputation rules will be described in the SAP.

If available, pharmacokinetic parameters from the concentration-time profile data of patients who drop out or are withdrawn will be calculated but will be excluded from the final statistical analysis.

12.8 Multiple Comparisons and Multiplicity

No formal comparisons are planned.

12.9 General Data Summaries

For continuous variables, descriptive statistics (number [n], mean, SD, median, minimum, and maximum) will be provided.

For categorical variables, patient counts, and percentages will be provided. Categories for missing data will be presented if necessary.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

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

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

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

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

13.2 Institutional Review Board or Independent Ethics Committee Approval

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

13.3 Ethical Conduct of the Study

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

13.4 Patient Information and Consent

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

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

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

13.5 Direct Access, Data Handling, and Record Keeping

13.5.1 Investigator

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

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

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

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

13.5.2 Sponsor

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

13.6 Protocol Adherence

13.6.1 Violations/Deviations

Investigators will agree to apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its agents to request approval of a prospective protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC/REB, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

13.6.2 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for subject safety may be implemented

prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

13.7 Subject Injury

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

13.8 Pre-Study Documentation

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

- Completed and signed form 1572 or equivalent
- All applicable country-specific regulatory forms
- Current signed and dated curricula vitae for the investigator, sub-investigators, and other individuals having significant investigator responsibility who are listed on the form 1572 or equivalent, or the clinical study information form
- Copy of the IRB/IEC/REB approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the subject must be approved by the IRB/IEC/REB. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC/REB must also be provided to the sponsor.
- Copy of the IRB/IEC/REB-approved informed consent document to be used
- Where applicable, a list of the IRB/IEC/REB members and their qualifications, and a description of the committee's working procedure
- Copy of the protocol sign-off page signed by the investigator
- Fully executed CSA
- Where applicable, a financial disclosure form
- A written document containing the name, location, certification number, and date of certification of the laboratories to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the statement of investigator form. The sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The sponsor must be notified if normal values or units of measurement change.

13.9 Retention of Data

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

13.10 Publication and Disclosure Policy

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

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

The institution and Principal Investigator (PI) shall not publish or present data from an individual study center until the complete multi-center study has been presented in full or for 2 years after the termination of the multi-center study, whichever occurs first. Subsequent publications must refer to the multi-center findings. Thereafter, if the PI expects to participate in the publication of data generated from this site, the institution and PI shall submit reports, abstracts, manuscripts, and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 days to respond with any requested revisions, including, without limitation, the deletion of confidential information. The PI shall act in good faith upon requested revisions, except that the PI shall delete any confidential information from such proposed publication. The PI shall delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

14 REFERENCE LIST

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

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7. **Spellberg, et al.** The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America. CID. 2008;46:155-164.

Appendix 1 Schedule of Events

Study Phase	Screening[a]	Treatment Phase				Follow-up Phase	
Study Day[b]		Day 1	Day 2	Day 3	Day 7-10/ EOT[c]	PTE[d]	Final Follow-up[e]
Signed Informed Consent[f]	X						
Medical History, current medical conditions, demography	X						
Assessment of CABP symptom severity[g]	X		X	X	X	X	
Chest X-ray or CT scan[h]	X						
PORT Risk Class, ABG (or pulse oximetry) [i]	X						
Blood samples for local lab hematology/chemistry//pregnancy test[j]	X				X	X	
Urine samples for local lab urine tests/pregnancy test[j]	X						
Review of Inclusion and Exclusion criteria/Treatment Group Assignment (if Eligible)	X						
Test Article Administration and Accountability[l]		X	X	X	X		
Physical examination[m]	X		X	X	X	X	
Vital signs[n]							
Height and weight	X						
Body temperature	X	X	X	X	X	X	
Blood Pressure	X	X[o]	X	X	X	X	
Pulse Oximetry	X	X	X	X	X	X	
Pulse/Heart Rate	X	X[o]	X	X	X	X	
Respiratory Rate	X	X	X	X	X	X	

Study Phase	Screening[a]	Treatment Phase				Follow-up Phase	
Plasma samples (in heparin) for PK analyses		X[p]	X[q]	X[r]	X[s]		
Assessment for need for continued therapy[t]		X ---------- X					
Investigator's Assessment of Clinical Response					X	X	
Adverse Events[u]	X ---------- X						
Prior/Concomitant Medications and Procedures[k]	X ---------- X						
Assessment of Resource Utilization	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, 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, RR = respiratory rate, SAE = serious adverse event.

[a] Following the signing of an ICF, all Screening evaluations, with the exception of the radiographic confirmation of pneumonia, should be completed within the 24 hours prior to treatment group assignment. The radiographic confirmation of pneumonia should be completed within the 48 hours prior to the first dose of test article.

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

[c] 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.

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

[e] To be conducted 30 to 37 days after the start of the first dose of test article. The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be Clinical 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.

[f] Written and signed ICF must be obtained before any assessment is performed.

[g] The investigator should assess the severity of the subject's CABP symptoms of cough, sputum production, pleuritic chest pain, and dyspnea based upon the Community Acquired Bacterial Pneumonia Subject Symptom Severity Guidance Framework for Investigator Assessment (Appendix 3).

[h] Subjects must have a confirming CXR or CT scan consistent with acute bacterial pneumonia within the 48 hours prior to the first dose of test article.

[i] Only subjects with a PORT Risk Class of II or III for whom oral only treatment for CABP is appropriate are eligible for enrollment.

[j] Hematology and serum chemistry evaluations will be performed at each of the timepoints indicated. A serum or urine pregnancy test (for women only) and urine dipstick will be performed only at Screening. The relevant local laboratory results from Screening will be used to assess eligibility as per the inclusion/exclusion criteria.

[k] 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. Additional information, including start and stop time, will be collected for any prior or concomitant antibiotic.

[l] All oral doses should be taken in a fasted state (no food, antacids, or multivitamins containing multivalent cations [eg, aluminum, magnesium, calcium, bismuth, iron, or zinc] or drink except water for at least 6 hours before dosing). Subjects discharged with po test article will be asked to return all unused test article and packaging at each visit and site staff will perform accountability. The total duration of test article therapy for all subjects will be 7 to 10, up to 14 for bacteremia.

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

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

[o] BP and heart rate should be measured within 30 min before, and approximately (± 15 minutes) 1-hour after the completion of the doses on Day 1.

[p] PK sample collection on Day 1:within an hour prior to Dose 1, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 hours (12 hour taken immediately before Dose 2); Dose 2 administered (times relative to Dose 1); 13, 13.5, 14, 14.5, 15, 16, 24 hours post dose

[q] PK sample collection on Day 2:within an hour prior to dose, 1, 1.5, 2, 2.5, 3, 4, 6 hours [r] PK sample collection on Day 3: prior to the Day 3 dose

[s] PK sample collection on EOT is anytime during the visit after the final dose.

Study Phase	Screening[a]	Treatment Phase	Follow-up Phase

[t] The total duration of test article therapy for all subjects will be 7 to 10 days, up to 14 days for bacteremia.
[u] A subject's AEs and SAEs will be recorded and reported from signing of the ICF to the Final Follow-up assessment.

Appendix 2 Equations and Conversion Factors

1. Cockcroft-Gault equation to calculate creatinine clearance (CrCl) (See Sections 6.2):

(140-age [years]) * weight (kg) * (Z)	Z = 1.0, if Male
Cr (mg/dL) * 72	Z = 0.85, if Female

2. Corticosteroid conversions (Sections 6.2):

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.

3. Conversion of immature neutrophils (band) forms in K/µL or K/mL to % bands (Sections 6.2):

([bands K/µL]/[total WBC K/µL]) × 100 = % bands
OR
([bands K/mL]/[total WBC K/mL]) × 100 = % bands

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 PORT Risk Class Calculation

Adapted from Fine.

Subject Characteristic	Point Assignment
Age	
Male	Age (years)
Female	Age (years) -10
Nursing home resident[a]	+10
Coexisting illnesses	
Neoplastic disease[b]	+30
Liver disease[c]	+20
Congestive heart failure[d]	+10
Cerebrovascular disease[e]	+10
Renal disease[f]	+10
Physical-examination findings	
Altered mental status[g]	+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)[f]	+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 (ineligible for study)	91-130
V (ineligible for study)	≥ 131

Crcl = creatinine clearance, CT = computed tomography, PORT = Pneumonia Outcomes Research Team

[a] 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 #4.

[b] 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 #10.

[c] 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 #7 should not be enrolled.

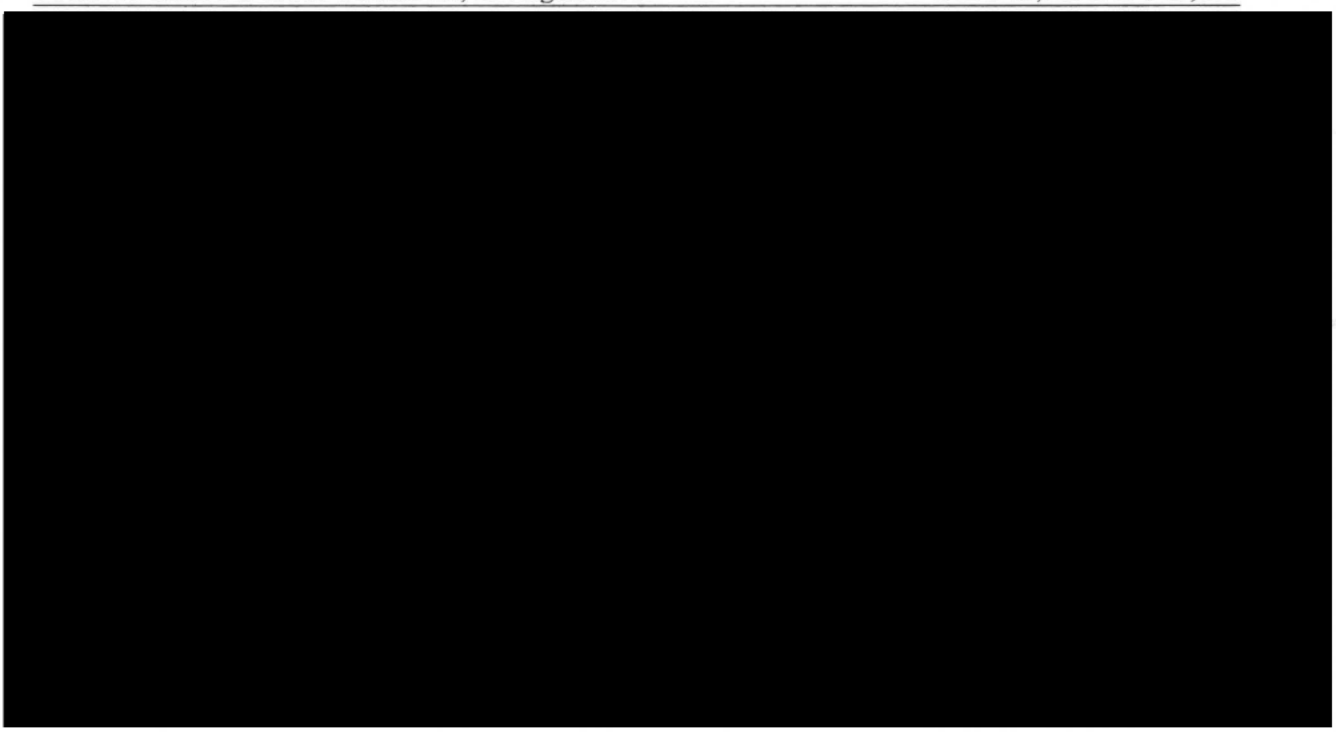
[d] Congestive heart failure is defined as systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest radiograph, echocardiogram, multiple gated acquisition scan, or left ventriculogram. Subjects with acute congestive heart failure are excluded from the study and should not be enrolled per Exclusion Criterion #5.

[e] Cerebrovascular disease is defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or CT.

Subject Characteristic	Point Assignment

[f] 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.

[g] 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 6 Investigator's Signature

Study Title:	A Phase 1 Multi-Center Study to Measure the Pharmacokinetics of Oral Omadacycline in Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP)
Study Number:	PTK0796-CABPPO-19109
Final Date:	26 August 2019

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

Signed:_____ Date:_____

Investigator Name:_____

Investigator Title:_____

Investigator Affiliation:_____

Investigator Address:_____

Investigator Phone Number:_____