Clinical Trial Protocol: PTK0796-PEDPK-20110

Study Title:	A Phase 1, Open-Label, Multi-Center Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Intravenous and Oral Doses of Omadacycline in Pediatric Subjects with Suspected or Confirmed Bacterial Infections
Study Number:	PTK0796-PEDPK-20110
Study Phase:	1
Product Name:	Omadacycline (PTK 0796)
IND Number:	75,928 73,431
Indication:	Bacterial Infection
Investigators:	Multi-center
Sponsor:	Paratek Pharmaceuticals, Inc. 75 Arlington Street Suite 500 Boston, MA 02116 1000 First Ave Suite 200 King of Prussia, PA 19406
Sponsor Contact:	Tel: +1 617-275-0040
Global Medical Monitor:	[redacted] MD

Protocol Version 5.0: 14-Sep-2023

Confidentiality Statement

SYNOPSIS

Sponsor:

Paratek Pharmaceuticals, Inc.

Name of Finished Product:

Intravenous Omadacycline 100 mg (in 100 mL normal saline solutions) infused over 30 minutes
Oral Omadacycline tablet, 300 mg (150 mg tablet x 2)

Name of Active Ingredient:

Omadacycline

Study Title:

A Phase 1, Open-Label, Multi-Center Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Intravenous and Oral Doses of Omadacycline in Pediatric Subjects with Suspected or Confirmed Bacterial Infections

Study Number:

PTK0796-PEDPK-20110

Study Phase: 1

Study Rationale:

As omadacycline is active against the causative organisms in disease indications such as acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP), it is reasonable to assume that pediatric exposures comparable to adults will result in similar efficacy outcomes. As a class, tetracycline antibiotics do not substantially differ in pharmacokinetics (PK) between adults and children/adolescents.

This study is being conducted in children and adolescents already hospitalized and already receiving antibacterial treatment. As such, exposure to a single dose of omadacycline is a reasonable added therapy. Study related blood draws can be performed through indwelling catheters already in place. The study assessments following a single dose of omadacycline will be sufficient to characterize the PK of omadacycline and model exposure with multiple doses.

Primary Objective:

To characterize the PK of single intravenous (iv) and oral doses of omadacycline in children and adolescents 8 to < 18 years of age with suspected or confirmed bacterial infections.

Secondary Objective:

To evaluate the safety and tolerability of single iv and oral doses of omadacycline in children and adolescents 8 to < 18 years of age with suspected or confirmed bacterial infections.

Study Design:

This is a Phase 1, open-label, multi-center study in children and adolescent subjects (males and females, 8 to < 18 years of age) with suspected or confirmed bacterial infections who are receiving concomitant systemic antibacterial therapy. This study will consist of 2 age cohorts:

- Cohort 1 (adolescents): 12 to < 18 years of age
- Cohort 2 (children): 8 to < 12 years of age

The study will consist of a Screening period of up to 48 hours prior to dosing, a single dose of study drug on Day 1, and a Study Completion Visit between Days 4-7.

Subjects will undergo screening evaluations to determine eligibility within 48 hours prior to dosing. Approximately 40 subjects (20 per age cohort) will be enrolled to obtain at least 24 PK evaluable subjects (with a minimum of 6 subjects per treatment, per age cohort).

On Day 1, based on Principal Investigator (PI) discretion, subjects will receive either a single dose of 100 mg iv omadacycline (in 100 mL normal saline solution) infused over 30 minutes at room temperature, or they will receive a single dose of 300 mg oral omadacycline tablet (150 mg tablet x 2). Oral study drug will be administered in the morning with no food or drink except for water at least 6 hours prior to dosing. Subjects will have no food or drink except water for at least 2 hours after dosing and no dairy products, antacids, or other aluminum- or calcium-containing products (e.g., vitamins, supplements) for 4 hours after dosing.

A total of 7 blood samples for PK analysis for oral omadacycline and 8 blood samples for iv omadacycline will be collected at specified time points from prior to the time of dosing to 48 hours following dosing. Safety assessments will include monitoring of adverse events (AEs), clinical laboratory test results, vital sign measurements, and physical examination findings.

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 and modeling, clinical efficacy in prior studies, the overall safety and tolerability profile, and the Food and Drug Administration (FDA) approved dosing regimen for CABP and ABSSSI. Based on interim PK and safety analyses, the dose could be modified during the study.

This study will involve a single dose of either 100 mg iv or 300 mg oral omadacycline in a pediatric population in order to establish pediatric dosing as compared to adult subjects.

Approximate Number of Subjects/Sites:

Up to 40 subjects (20 per age cohort) will be enrolled at approximately 15 sites in the United States (US) to obtain at least 24 PK evaluable subjects (with a minimum of 6 per treatment, per age cohort).

Approximate Duration of the Study:

The clinical phase of the study is expected to be complete in approximately 12 months. The total duration of subject participation in the study, including screening, is approximately 9 days.

Main Criteria for Inclusion:

Subjects must meet all of the following criteria at Screening and/or Pre-dose to be eligible to participate in the study:

1. Written and signed parental/legal authorized representative (LAR) informed consent must be obtained before any protocol specific assessment is performed. Pediatric assent should be obtained in accordance with local hospital and IRB policies.
2. Male and female subjects between 8 and < 18 years of age, inclusive at time of consent/assent.
3. Hospitalized, in stable condition, likely to survive the current illness, and receiving or planned to receive standard of care systemic antibacterial therapy, other than omadacycline, for a suspected or confirmed bacterial infection.
4. Expected to remain hospitalized for at least 2 days following administration of the study drug.
5. Sufficient intravascular access (peripheral or central) for study drug administration (iv treatment only) and blood draws.
6. For subjects who will receive oral study drug only, ability to swallow oral study drug 2 tablets).
7. Weight within the 5^{th} and 95^{th} percentile for age and sex.
8. Females of reproductive potential (post-menarche or has reached Tanner Stage 3 breast development) must have a negative urine or serum pregnancy test and agree to use a highly effective form of birth control (e.g., abstinence, oral contraceptive, intrauterine device, or barrier contraception [e.g., condom]) from Screening through the study completion visit. Males (if sexually active) must agree to use a highly effective method of birth control with female partner(s).
9. Subject and parent/caregiver is willing and able to adhere with the requirements and restrictions of the study.

Main Criteria for Exclusion:

Subjects meeting any of the following criteria at Screening and/or Pre-dose will be excluded from participation in the study:

1. Use of other investigational drugs within 5 half-lives or 30 days prior to Pre-dose, whichever is longer.
2. Evidence or history of a clinically significant medical condition or planned medical intervention that may, in the opinion of the investigator, pose a significant safety risk, impair study participation, or impact the subject's ability to undergo the required study procedures. (Note: Subjects must, in the opinion of the investigator, be physically and mentally competent to participate.)
3. Inability to tolerate oral medication (e.g., nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of oral medication – oral treatment only).
4. Inability to fast for 6 hours prior to dosing and/or 2 hours after dosing (oral treatment only).
5. Pregnant or nursing (breastfeeding) in post-menarche females.
6. History of hypersensitivity or allergic reaction (e.g., anaphylaxis, urticaria, other significant reaction) to any tetracycline (e.g., minocycline, doxycycline, or tigecycline).
7. Any surgical or medical condition that, in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism, or excretion of drugs.
8. Family members of the Investigator or a study center employee.

Test Article, Dose, and Mode of Administration:

- 100 mg iv omadacycline (in 100 mL normal saline solution) infused over 30 minutes OR
- 300 mg oral omadacycline tablet (150 mg tablet x 2)

Duration of Treatment:

Subjects will receive a single dose of either iv or oral omadacycline.

Pharmacokinetic Assessments

Blood samples for PK assessments of omadacycline will be collected from all subjects at the following time points:

Oral Treatment

- At least 15 minutes prior to administration of oral omadacycline 300 mg and at 1 hour (±5 min), 2 hours (±5 min), 3 hours (±5 min), 8 hours (±1 hr.), 24 hours (±1 hr.) and 48 hours (±1 hr.) after dosing

Intravenous Treatment

- At least 15 minutes prior to infusion of IV omadacycline 100 mg, at 10 minutes (±5 minutes), 0.5-hour (±5 minutes), 1-hour (±5 minutes), 2 hours (±5 minutes), 8 hours (±1 hr.), 24 hours and 48 hours (±1 hr.) after the end of the IV infusion

The following plasma PK parameters will be determined:

- Area under the plasma concentration versus time curve (AUC) from time 0 to 48hours after dosing (AUC_{0-48})
- AUC from time 0 to the last quantifiable concentration (AUC_{last})
- AUC from time 0 extrapolated to infinity (AUC_{0-inf})
- 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 ($T_{1/2}$)
- Apparent volume of distribution (V_d) after iv administration only
- Systemic clearance (CL) after iv administration only

Additional exploratory PK calculations may be performed and will be described in the statistical analysis plan.

Safety Assessments:
Safety and tolerability will be assessed by monitoring the following:

- AEs and serious adverse events (SAEs);
- Physical examinations;
- Vital signs (body weight, body temperature, blood pressure, heart rate);
- Clinical laboratory tests (hematology, serum chemistry)

Statistical Methods:

Sample Size Determination:

The sample size selected is based on an estimation approach rather than a formal hypothesis testing approach. An estimation approach with 20 subjects in each age cohort (10 subjects per treatment, per age cohort) will be enrolled. A total of 40 subjects will be enrolled so that at least 24 subjects are evaluable for PK parameter estimation (with a minimum of 6 subjects per treatment, per age cohort).

Analysis Populations:

Safety Population: The safety population will consist of all assigned subjects who received any study drug.

PK Evaluable Population: The PK population will include subjects who receive study drug and have at least 1 evaluable PK parameter. If any subject has an emesis within 2.5x median T_{max} after dosing, the subject may be excluded from PK population.

Pharmacokinetics Analysis:

Concentration and time deviation data will be presented in data listings. Plasma concentration data will be summarized by scheduled time point for each treatment 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.

Noncompartmental PK parameters will be determined from plasma concentration and actual time data using Phoenix® WinNonlin® (Certara, Princeton, New Jersey) Version 8.0 or higher or a WinNonlin validated Statistical Analysis System (SAS) program.

For the PK analysis, below the limit of quantification (BLQ) values before the first quantifiable concentration will be treated as zero. Below the limit of quantification values after the first quantifiable concentration will be set as missing. Missing concentrations will be treated as missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

For concentration summary statistics, BLQ values before the first quantifiable concentration will be treated as zero. Below the limit of quantification values after the first quantifiable concentration will be set as missing. Missing concentrations will be treated as missing.

The individual PK parameters of omadacycline will be presented in data listings. Descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum) will be calculated for the PK parameter estimates for each period (e.g., AUC_{0-48}, AUC_{last}, AUC_{0-inf}, C_{max}, T_{max}, CL (iv arm only), Vd (iv arm only) and $T_{1/2}$, from plasma concentrations). Geometric means will be included for AUC_{0-48}, AUC_{0-inf}, and C_{max}.

Safety Assessments:

The safety data will be summarized by treatment where applicable. The incidence of treatment-emergent AEs will be presented by treatment, system organ class, and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), relationship to the study drug, and severity. Any SAEs and AEs leading to discontinuation of study drug will also be presented in a data listing.

Clinical laboratory test results, vital sign measurements, and physical examination findings will be presented in data listings. Actual results and changes from Baseline for vital sign measurements and clinical laboratory test results will be summarized by treatment and time point.

Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary and will be presented in a data listing.

Handling of Missing Data:

Concentrations that are BLQ before the first quantifiable concentration will be treated as zero for descriptive statistics. Below the limit of quantification values after the first quantifiable concentration will be set as missing and excluded for summary statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable, if all individual values are BLQ.

Interim Analysis:
Interim PK and safety analyses will be conducted as data become available to allow for dosing modifications and/or sample size adaptation.

Review of Safety Data:
Due to the open-label design, safety review and analysis of PK samples will be performed on an ongoing basis by the sponsor. The sponsor study team, including physician and pharmacokineticist, will be part of the review. Safety review will occur at the completion of each subject individually and collectively (all subjects) to identify trends, quality concerns and any safety issues. Reviews will include PK analyses, treatment-emergent adverse events, SAEs, clinical laboratory results, vital sign measurements and Physical Examination findings. PK data will also be reviewed at periodic intervals and compared to the established PK profile in adults.

Based on the reviews, the study may continue as planned, the protocol may be amended to include additional safety evaluations or to adjust the dosing, or the study may be paused or stopped.

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LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABSSSI	acute bacterial skin and skin structure infections
AE	Adverse Event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{0-48}	AUC from time 0 to 48 hours after dosing
AUC_{0-inf}	AUC from time 0 extrapolated to infinity
AUC_{last}	AUC from time 0 to the last quantifiable concentration
BLQ	below the limit of quantification
BP	blood pressure
CABP	community-acquired bacterial pneumonia
CFR	Code of Federal Regulations
CL	clearance (Pharmacokinetics)
C_{max}	maximum observed plasma concentration
CRF	case report form
CSA	clinical study agreement
CSR	Clinical Study Report
CV	coefficient of variation
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug

IRB	Institutional Review Board
iv	Intravenous
LAR	legal authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PK	Pharmacokinetics
po	per oral
REB	Research Ethics Board
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	statistical analysis system
SD	standard deviation
T_{max}	time to reach maximum observed plasma concentration
$T_{1/2}$	terminal-phase elimination half-life
US	United States
V_d	volume of distribution
WBC	white blood cell (Count)

1 DISCLOSURE STATEMENT

Restricted Distribution of Documents

This document contains information that is confidential and proprietary to the sponsor. This information is being provided to you solely for the purpose of evaluating and/or conducting a clinical study for the sponsor. You may disclose the contents of this document only to study personnel under your supervision, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs)/Research Ethics Boards (REBs), or duly authorized representatives of regulatory agencies for this purpose under the condition that they maintain confidentiality. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity, and/or published without the prior written permission of the sponsor. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to the sponsor of any such disclosure. All other nonpublic information provided by the sponsor and any information that may be added to this document also is confidential and proprietary to the sponsor and must be kept in confidence in the same manner as the contents of this document.

2 CONTACTS

2.1 Emergency Contacts

Name/Title:	[redacted], MD Global Medical Monitor
Phone (during business hours):	[redacted]
Phone (after business hours):	
E-mail (not for emergencies):	

2.2 Additional Contacts

SAE contact information:	
E-Mail:	[redacted]

3 INTRODUCTION

Omadacycline is an aminomethylcycline, a tetracycline class antibiotic, for intravenous (iv) or oral (po) administration. Intravenous NUZYRA® (omadacycline) and oral NUZYRA® tablets have been approved by the United States (US) Food and Drug Administration (FDA) for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible microorganisms.

As omadacycline is active against the causative organisms in potential disease indications such as ABSSSI and CABP, it is reasonable to assume that pediatric exposures comparable to adults will result in similar efficacy outcomes. Therefore, it is necessary to determine the doses required to achieve these exposures. As a class, tetracycline antibiotics do not substantially differ in pharmacokinetics (PK) between adults and children/adolescents.

This study is intended to evaluate the safety, tolerability, and characterize the PK of an intravenous and oral formulation of omadacycline in order to establish pediatric dosing as compared to adult subjects.

Please refer to the current version of the Investigator's Brochure[1] or the NUZYRA® (omadacycline) US Package Insert for additional information on omadacycline.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is:

- To characterize the PK of single intravenous and oral doses of omadacycline in children and adolescents 8 to < 18 years of age with suspected or confirmed bacterial infections.

4.2 Secondary Objective

The secondary objective of this study is:

- To evaluate the safety and tolerability of single intravenous and oral doses of omadacycline in children and adolescents 8 to < 18 years of age with suspected or confirmed bacterial infections.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Description

This is a Phase 1, open-label, multi-center study in children and adolescent subjects (males and females, 8 to < 18 years of age) with suspected or confirmed bacterial infections who are receiving concomitant systemic antibacterial therapy. This study will consist of 2 age cohorts:

- Cohort 1 (adolescents): 12 to < 18 years of age
- Cohort 2 (children): 8 to < 12 years of age

The study will consist of a Screening period of up to 48 hours prior to dosing, a single dose of study drug on Day 1 and a Study Completion Visit between Days 4 to 7.

Subjects will undergo screening evaluations to determine eligibility within 48 hours prior to dosing. Approximately 40 subjects (20 per age cohort) will be enrolled.

On Day 1, per Principal Investigator (PI) discretion, subjects will receive a single dose of either intravenous or oral omadacycline. For those receiving intravenous omadacycline, a 100 mg IV dose (in 100 mL normal saline solution) infused over 30 minutes at room temperature will be administered. For those receiving oral omadacycline, a single dose of 300 mg oral omadacycline tablet (150 mg tablet x 2) will be administered.

Oral study drug will be administered in the morning in a fasted state with no food or drink except for water at least 6 hours prior to dosing. Fasting is defined as no food, antacids, or multivitamins containing multivalent cations (e.g., aluminum, magnesium, calcium, bismuth, iron, or zinc) or drink except water for at least 6 hours before dosing. Subjects will have no food or drink except water for at least 2 hours after dosing and no dairy products, antacids, or other aluminum- or calcium-containing products (e.g., vitamins, supplements) for 4 hours after dosing.

A total of 7 blood samples for PK analysis for oral omadacycline and 8 blood samples for iv omadacycline will be collected at specified time points prior to dosing and through 48 hours after dosing. Safety assessments will include monitoring of adverse events (AEs), clinical laboratory test results, vital sign measurements, and physical examination findings.

Subjects will complete a Study Completion visit 4 to 7 days after dose completion. This visit may be performed via telehealth with subject's parent/legal authorized representative (LAR) to review ongoing medications and adverse events if the subject has already been discharged from the hospital before Day 4.

Refer to the Schedule of Events (Appendix 1) for the summary of subject visits and assessments through study completion.

The planned length of subject participation in the study is up to 9 days.

5.2 Rationale for Study Design

As omadacycline is active against the causative organisms in disease indications such as ABSSSI and CABP, it is reasonable to assume that pediatric exposures comparable to adults will result in similar efficacy outcomes. As a class, tetracycline antibiotics do not substantially differ in PK between adults and children/adolescents.

This study is being conducted in children already hospitalized and already receiving antibacterial treatment. As such, exposure to a single dose of omadacycline is a reasonable added therapy. Study related blood draws can be performed through indwelling catheters already in place. The study assessments following a single dose of omadacycline will be sufficient to characterize the PK of omadacycline and model exposure with multiple doses.

5.3 Approximate Duration of Subject Participation

Subjects will participate in the study for up to 9 days.

5.4 Approximate Duration of Study

The study is expected to be complete in approximately 12 months.

5.5 Approximate Number of Subjects

Up to 40 subjects will be enrolled at approximately 15 sites in the US to obtain at least 24 PK evaluable subjects with a minimum of 6 subjects per treatment, per age cohort.

6 STUDY POPULATION SELECTION

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

6.1 Study Population

Hospitalized children and adolescents between the ages of 8 and < 18 with suspected or confirmed bacterial infections who are receiving concomitant systemic antibacterial therapy will participate in this study. Up to 40 subjects will be enrolled at approximately 15 sites in the US to obtain at least 24 PK evaluable subjects with a minimum of 6 subjects per treatment, per age cohort.

6.2 Inclusion and Exclusion Criteria

Each subject must meet all of the following criteria at Screening and/or Pre-dose to be eligible to participate in the study:

Main Criteria for Inclusion:

1. Written and signed parental/LAR informed consent must be obtained before any protocol specific assessment is performed. Pediatric assent should be obtained in accordance with local hospital and IRB policies.
2. Male and female subjects between 8 and < 18 years of age, inclusive at time of consent/assent.
3. Hospitalized, in stable condition, likely to survive the current illness, and receiving or planned to receive standard of care systemic antibacterial therapy, other than omadacycline, for a suspected or confirmed bacterial infection.
4. Expected to remain hospitalized for at least 2 days following administration of the study drug.
5. Sufficient intravascular access (peripheral or central) for study drug administration (iv treatment only) and blood draws.
6. For subjects who will receive oral study drug only, ability to swallow oral study drug (2 tablets).
7. Weight within the 5^{th} and 95^{th} percentile for age and sex.
8. Females of reproductive potential (post-menarche or has reached Tanner Stage 3 breast development) must have a negative urine or serum pregnancy test and agree to use a highly effective form of birth control (e.g., abstinence, oral contraceptive, intrauterine device, or barrier contraception [e.g., condom]) from Screening through the study completion visit. Males (if sexually active) must agree to use a highly effective method of birth control with female partner(s).
9. Subject and parent/caregiver is willing and able to adhere with the requirements and restrictions of the study.

Main Criteria for Exclusion:

Subjects meeting any of the following criteria at Screening and/or Pre-dose will be excluded from participation in the study:

1. Use of other investigational drugs within 5 half-lives or 30 days prior to Pre-dose, whichever is longer.
2. Evidence or history of a clinically significant medical condition or planned medical intervention that may, in the opinion of the investigator, pose a significant safety risk, impair study participation, or impact the subject's ability to undergo the required study procedures. (Note: Subjects must, in the opinion of the investigator, be physically and mentally competent to participate.)
3. Inability to tolerate oral medication (e.g., nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of oral medication – oral treatment only).
4. Inability to fast for 6 hours prior to dosing and/or 2 hours after dosing (oral treatment only).
5. Pregnant or nursing (breastfeeding) in post-menarche females.
6. History of hypersensitivity or allergic reaction (e.g., anaphylaxis, urticaria, other significant reaction) to any tetracycline (e.g., minocycline, doxycycline, or tigecycline).
7. Any surgical or medical condition that, in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism, or excretion of drugs.
8. Family members of the Investigator or a study center employee.

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) for screen failures. Screen failure subjects may be re-screened at the discretion of the investigator and in consultation with the medical monitor as needed. Any subject who discontinues participation or is withdrawn before receiving a treatment assignment, and who is re-screened at a later time will be assigned a new subject number and recorded as re-screened.

7 STUDY TREATMENT(S)

7.1 Treatments Administered

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

The test articles should be administered only to subjects who have provided pediatric assent (as appropriate per local regulations) and informed consent signed by his/her parent/LAR 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 48 hours, eligible subjects will be assigned a dosing regimen of omadacycline per PI discretion.

7.2 Identity of the Investigational Product: Omadacycline

Oral Formulation (Omadacycline)

[redacted]

Administration Please reference Section 7.5

Intravenous Formulation (Omadacycline)

[redacted]

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 and modeling, clinical efficacy in prior studies, the overall safety and tolerability profile, and the FDA approved dosing regimen for CABP and ABSSSI. Based on interim PK and safety analyses, the dose could be modified during the study.

This study will involve a single dose of either 100 mg IV or 300 mg oral omadacycline in a pediatric population in order to establish pediatric dosing as compared to adult subjects.

7.4 Description of Treatments

Subjects will be assigned to a single dose of either 100 mg intravenous omadacycline (in 100 mL normal saline solution) infused over 30 minutes or 300 mg oral omadacycline (150 mg tablet x 2).

Eligible subjects will fall into one of the following treatment groups:

Test Article Administration	Adolescents 12 to < 18 years of age	Children 8 to < 12 years of age
IV Omadacycline	10 pts	10 pts
Oral Omadacycline	10 pts	10 pts

7.5 Test Article Administration

7.5.1 Administration of Oral and IV Treatment

Subjects will receive a single dose of either IV or oral test article on Day 1.

Oral Omadacycline

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 (e.g., 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 and no dairy products, antacids, or multivitamins containing multivalent cations (e.g., aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours.

IV Omadacycline

Infusion of IV test article in 100 mL normal saline solution will be administered continuously over approximately 30 minutes. Infusion start and stop times are to be recorded in the source documents and on the eCRF.

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 and pediatric assent, the subject will be assigned a unique subject number. Subjects who have been pre-screened, but who do not sign a pediatric assent/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 a pediatric assent and 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.

7.8 Prior and Concomitant Therapy

Treatments that have been administered within the 72 hours prior to the date of informed consent and pediatric assent, or during the Screening phase, will be recorded in the eCRF. The investigator is to instruct the subject and his/her parent/LAR to notify the study site about any new medications he/she takes after the administration of the test article. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject receives treatment with test article must be listed in the eCRF (see Section 8.15).

7.9 Prohibited Therapy

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

The following therapies are excluded:

- Antacids and multivitamins containing multivalent cations (e.g., 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. Treatment for infection under study is at the discretion of the investigator or the subject's health care provider and will be considered as a concomitant medication.

Subjects or caregivers 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 test article 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 by subject's parent/LAR before any study-related procedures have been performed. Pediatric assent is also required as appropriate per local regulations. Upon signing of the informed consent and pediatric assent, the subject will then be assigned a study subject number. Adverse events (AEs) must be recorded from the time the ICF/pediatric assent is signed. The investigator will maintain a subject master list to document every subject who has signed an ICF/pediatric assent. A copy of this list should be retained in the investigator's study files.

8.1 Informed Consent and Pediatric Assent

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 and pediatric assent must be reviewed by the sponsor and approved by the IRB/IEC/REB.

Before any procedures specified in the protocol are performed, a subject and his/her parent/LAR must:

- Be informed of all pertinent aspects of the study and all elements of informed consent and pediatric assent (when applicable)
- 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 and pediatric assent (when applicable)

8.2 Subject Demographics/Other Baseline Characteristics

Subject demographic and Baseline characteristic data to be collected at screening 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/assent will be recorded.

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, eyes, ears, nose, throat, lungs, heart, abdomen, lymph nodes, extremities, and brief neurological exam.

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 (blood pressure [BP], heart rate [HR], and body temperature) will be measured at the timepoints indicated in the Schedule of Events (Appendix 1).

The subject's BP and heart rate at all time points should be captured after at least 5 minutes (+ 5 minutes) of rest while in a supine position.

Systolic and diastolic BP will be measured using an automated calibrated device, with an appropriately sized cuff. Heart rate will be measured using an automated calibrated device, when available. If not available, heart rate will be measured manually.

Temperature will be obtained using an electronic (rapid reading) device whenever possible. Temperature can be measured using the method preferred by the study site (e.g., oral, rectal, tympanic membrane, axillary). Both the temperature and method of measurement will be captured in the eCRF.

8.6 Height, Weight, and BMI

Both height and body weight will be obtained with shoes off.

8.7 Clinical Laboratory Tests

All laboratory testing will be performed by the local laboratory at each site. All hematology and serum chemistry parameters and blood tests outlined in Table 1 and Table 2 are required to be collected to determine study eligibility. Laboratory tests collected as part of standard of care within 24 hours of consent/assent may be used for determining eligibility and do not need to be repeated provided that all protocol required parameters have been collected.

If any of the required parameters are not collected as part of standard of care testing, laboratory samples must be drawn and results obtained for missing parameters in order to determine subject eligibility.

The relevant local laboratory results from Screening will be used to assess eligibility as per the inclusion/exclusion criteria.

8.7.1 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

WBC = white blood cell

Table 2 Serum Chemistry

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

ALT = alanine aminotransferase, AP = alkaline phosphatase, AST = aspartate aminotransferase, CK = creatine phosphokinase, GGT = gamma-glutamyl transpeptidase

8.7.2 SARS-CoV-2 Sample

Testing for SARS-CoV-2 will be performed in accordance with site's standard of care and local policy.

8.7.3 Pregnancy Assessment

Females of reproductive potential (post-menarchal or has reached Tanner Stage 3 breast development) will have a local laboratory urine or serum pregnancy test at Screening. Results are required for eligibility, retained in source documents, and will 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.

8.8 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. A total of 7 blood samples for pharmacokinetic analysis of oral omadacycline and 8 blood samples for iv omadacycline will be collected at specified time points prior to dosing and throughout the 48 hours from time of dosing.

8.8.1 PK Blood Collection and Processing

Blood Collection (plasma):

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

Oral Treatment

- At least 15 minutes prior to administration of oral omadacycline 300 mg and at 1-hour (±5 minutes), 2 hours (±5 minutes), 3 hours (±5 minutes), 8 hours (±1 hr.), 24 hours (±1 hr.) and 48 hours (±1 hr.) after dosing

Intravenous Treatment

- At least 15 minutes prior to infusion of IV omadacycline 100 mg, at 10 minutes (±5 minutes) , 0.5-hour (±5 minutes), 1-hour (±5 minutes), 2 hours (±5 minutes), 8 hours (±1 hr.), 24 hours (±1 hr.) and 48 hours (±1 hr.) after the end of the IV infusion 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.

8.9 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 (e.g., use for nonclinical reasons) of a test article.
- An AE that has been associated with the discontinuation of the use of a test article.

8.10 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 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 (e.g., 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.

8.11 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: 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.

8.12 Overdose

Any administration of omadacycline of greater than 100 mg intravenously or 300 mg orally 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.

8.13 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 Other Reportable Events Report Form as indicated in the Emergency Contacts (see Section 2).

8.14 Recording and Reporting

A subject's AEs and SAEs will be recorded and reported from the signing of the ICF/assent to the time of the Study Completion visit. The investigator must instruct the subject and his/her parent/LAR 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.

8.14.1 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]

8.14.2 Assessment of Relatedness

The investigator will assess causality (i.e., 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, i.e., 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.

8.14.3 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.

8.14.4 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.

8.14.5 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.

8.15 Concomitant Medication Assessments

The investigator should instruct the subject and his/her parent/LAR 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.

8.16 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 e.g., 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.

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, e.g., dates of telephone calls, registered letters, etc.

8.16.1 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 24 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 assessments and visits on the designated time and day.

9.1 Screening Phase

The Screening visit should be completed within a 48-hour period prior to enrollment and dosing. The Screening procedures will be used to establish subject eligibility and Baseline characteristics for each subject. Following the signing of an ICF/pediatric assent, the site staff will collect/perform the assessments detailed in Appendix 1.

9.2 Treatment Phase

The open label treatment period is a single dose administered on one day.

9.3 Study Completion Visit Procedures

The Study Completion evaluation should be conducted 4 to 7 days after dosing. This visit may be performed via telehealth with subject's parent/LAR to review ongoing medications and adverse events if the subject is discharged from the hospital before Day 4.

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 Study Completion Visit. The study will be completed when the last subject has either discontinued or completed the Study Completion Visit.

No long-term follow-up of subjects is planned, with the exception of pregnancies, as described in Section 8.14.5, and SAEs described in Section 8.10.

Sites will be notified by the Sponsor 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 9.3 and 8.16. 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 8.16 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 eCRFs and instructions for their completion, the procedure for obtaining informed consent/assent, 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 eCRFs 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

The sample size selected is based on an estimation approach rather than a formal hypothesis testing approach. An estimation approach with 20 subjects in each age cohort (10 subjects per treatment, per age cohort) will be enrolled. A total of 40 subjects will be enrolled so that at least 24 subjects are evaluable for PK parameter estimation (with a minimum of 6 subjects per treatment, per age cohort).

12.3 Analysis Populations

Safety Population: The safety population will consist of all assigned subjects who received study drug.

PK Evaluable Population: The PK population will include subjects who receive study drug and have at least 1 evaluable PK parameter. If any subject has an emesis within 2.5x median T_{max} after dosing, the subject may be excluded from PK population.

12.4 Interim Analysis

Interim PK and safety analyses will be conducted as data become available to allow for dosing modifications and/or sample size adaptation.

12.5 Review of Safety Data

Due to the open-label design, safety review and analysis of PK samples will be performed on an ongoing basis by the sponsor. The sponsor study team, including physician and pharmacokineticist, will be part of the review. Safety review will occur at the completion of each subject individually and collectively (all subjects) to identify trends, quality concerns and any safety issues. Reviews will include PK analyses, treatment-emergent adverse events, SAEs, clinical laboratory results, vital sign measurements and Physical Examination

findings. PK data will also be reviewed at periodic intervals and compared to the established PK profile in adults.

Based on the reviews, the study may continue as planned, the protocol may be amended to include additional safety evaluations or to adjust the dosing, or the study may be paused or stopped.

12.6 Demographics and Baseline Characteristics

Demographics (including age, gender, and race/ethnicity) 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.

12.7 Primary Endpoints

12.7.1 Pharmacokinetic Endpoint

Concentration and time deviation data will be presented in data listings. Plasma concentration data will be summarized by scheduled time point for each treatment 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.

Noncompartmental PK parameters will be determined from plasma concentration and actual time data using Phoenix® WinNonlin® (Certara, Princeton, New Jersey) Version 8.0 or higher or a WinNonlin validated statistical analysis system (SAS) program.

The following plasma PK parameters will be determined:

- Area under the plasma concentration versus time curve (AUC) from time 0 to 48hours after dosing (AUC_{0-48})
- AUC from time 0 to the last quantifiable concentration (AUC_{last})
- AUC from time 0 extrapolated to infinity (AUC_{0-inf})
- 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 ($T_{1/2}$)
- Apparent volume of distribution (V_d) after iv administration only
- Systemic clearance (CL) after iv administration only

Additional exploratory PK calculations may be performed and will be described in the statistical analysis plan.

For the PK analysis, below the limit of quantification (BLQ) values before the first quantifiable concentration will be treated as zero. Below the limit of quantification values after the first quantifiable concentration will be set as missing. Missing concentrations will be treated as missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

For concentration summary statistics, BLQ values before the first quantifiable concentration will be treated as zero. Below the limit of quantification values after the first quantifiable concentration will be set as missing. Missing concentrations will be treated as missing.

The individual PK parameters of omadacycline will be presented in data listings. Descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum) will be calculated for the PK parameter estimates for each period (e.g., AUC from time 0 to 48 hours after dosing [AUC_{0-48}], AUC from time 0 to the last quantifiable concentration [AUC_{last}], AUC from time 0 extrapolated to infinity [AUC_{0-inf}], maximum observed plasma concentration [C_{max}], time to reach maximum observed plasma concentration [T_{max}], clearance [CL] (iv arm only), apparent volume of distribution [V_d] (iv arm only) and $T_{1/2}$, from plasma concentrations). Geometric means will be included for AUC_{0-48}, AUC_{0-inf}, and C_{max}.

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

12.8 Secondary Endpoints

12.8.1 Safety Endpoints

The safety data will be summarized by treatment where applicable. The incidence of treatment-emergent AEs will be presented by treatment, system organ class, and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), relationship to the study drug, and severity. Any SAEs and AEs leading to discontinuation of study drug will also be presented in a data listing.

Clinical laboratory test results, vital sign measurements, and physical examination findings will be presented in data listings. Actual results and changes from Baseline for vital sign measurements and clinical laboratory test results will be summarized by treatment and time point.

Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary and will be presented in a data listing.

12.9 Data Handling Conventions

Concentrations that are BLQ before the first quantifiable concentration will be treated as zero for descriptive statistics. Below the limit of quantification values after the first quantifiable concentration will be set as missing and excluded for summary statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable, if all individual values are BLQ. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

12.10 Multiple Comparisons and Multiplicity

No formal comparisons are planned.

12.11 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

See Section 13.5.1 for Investigator responsibilities for data handling, access and record keeping.

13.2 Institutional Review Board or Independent Ethics Committee Approval

The protocol and the proposed ICF and pediatric assent must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. A signed and dated statement that the protocol, ICF and pediatric assent 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 Harmonization (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 and pediatric assent must be reviewed by the sponsor and approved by the IRB/IEC/REB. See Section 8.1 for further detail on Patient Information and Consent requirements.

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

14 REFERENCE LIST

[1] Investigator's Brochure

Appendix 1. Schedule of Assessments

		Schedule of Assessments – Intravenous Treatment Arm										
Study Phase		**Screening[a]**		**IV Treatment Period**								**Study Completion[b]**
Study Day		**D –2 to D–1**	**D1**						**D2**	**D3**		**D4-D7**
					Post Dose Timepoint							
Study Timepoint		**–48 hrs.**	**Pre-dose[c]**	**Infusion**	**10 Min.**	**0.5 Hr.**	**1 Hr.**	**2 Hrs.**	**8 Hrs.**	**24 Hrs.**	**48 Hrs.**	
Informed consent		X[d]										
Assent (as required/permitted)		X[d]										
Inclusion/exclusion criteria		X	X									
Medical history/current medical conditions		X										
Demography		X										
Physical examination[e]		X								X		
Height & Weight		X[f]										
Serum or urine pregnancy test[g]		X										
Vital signs (BP & HR)[h]		X	X				X		X	X		
Temperature		X	X							X		
Hematology		X[i]								X		
Serum chemistry		X[i]								X		

		Schedule of Assessments – Intravenous Treatment Arm										
Study Phase		**Screening[a]**		**IV Treatment Period**								**Study Completion[b]**
Study Day		**D –2 to D–1**	**D1**						**D2**	**D3**		**D4-D7**
					Post Dose Timepoint							
Study Timepoint		**–48 hrs.**	**Pre-dose[c]**	**Infusion**	**10 Min.**	**0.5 Hr.**	**1 Hr.**	**2 Hrs.**	**8 Hrs.**	**24 Hrs.**	**48 Hrs.**	
Study drug administration[j]				X								
PK blood collection			X		X	X	X	X	X	X	X	
Adverse events[k]		< ---------- X ---------- >										
Prior/concomitant medications[l]		< ---------- X ---------- >										
		BMI = body mass index, BP = blood pressure, D = study day, HR = heart rate, ICF = informed consent form, PK = pharmacokinetic [a] Screening period of up to 48 hours is permitted. [b] Study completion visit may be performed via telehealth with subject's parent/LAR to review ongoing medications and adverse events if the subject is discharged from the hospital before Day 4. [c] Pre-dose window is defined as after consent and at least 15 minutes prior to study drug administration. [d] Written and signed ICF/assent as applicable must be obtained before any protocol-specific assessment is performed. [e] Full physical examination to be performed at Screening and 24 hours post-dose. Symptom-driven physical exams may be performed at other timepoints as necessary. [f] Both height and weight to be obtained with shoes off. [g] For post-menarchal females of childbearing potential or females who have reached Tanner Stage 3 of breast development only. [h] Blood pressure and heart rate to be performed after at least 5 minutes of rest while in supine position. [i] Blood samples for hematology and chemistry will be assessed by site's local laboratory. If standard of care laboratory assessments were performed within 24 hours prior to consent/assent, these results may be used for purposes of determining eligibility provided they meet protocol requirements for all screening labs. Refer to Section 8.7.										

		Schedule of Assessments – Intravenous Treatment Arm										
Study Phase		**Screening[a]**		**IV Treatment Period**								**Study Completion[b]**
Study Day		**D –2 to D–1**	**D1**						**D2**	**D3**		**D4-D7**
					Post Dose Timepoint							
Study Timepoint		**–48 hrs.**	**Pre-dose[c]**	**Infusion**	**10 Min.**	**0.5 Hr.**	**1 Hr.**	**2 Hrs.**	**8 Hrs.**	**24 Hrs.**	**48 Hrs.**	
		[j] IV study drug infusion should be administered at room temperature continuously over 30 minutes. [k] Adverse events will be assessed from the time of signing the consent/assent until the study completion visit. [l] All medications taken within 72 hours prior to signing of consent/assent will be collected, in addition to all medications taken during the study.										

Schedule of Assessments – Oral Treatment Arm

Study Phase	**Screening[a]**	**Oral Treatment Period**								**Study Completion[b]**
Study Day	**D –2 to D–1**	**D1**						**D2**	**D3**	**D4-D7**
			Post Dose Timepoint							
Study Hour	**–48 hrs.**	**Pre-dose[c]**	**0**	**1 Hr.**	**2 Hrs.**	**3 Hrs.**	**8 Hrs.**	**24 Hrs.**	**48 Hrs.**	
Informed consent	X[d]									
Assent (as required/permitted)	X[d]									
Inclusion/exclusion criteria	X	X								
Medical history/current medical conditions	X									
Demography	X									
Physical examination[e]	X							X		
Height & Weight	X[f]									
Serum or urine pregnancy test[g]	X									
Vital signs (BP & HR)[h]	X	X			X		X	X		
Temperature	X	X						X		
Hematology	X[i]							X		
Serum chemistry	X[i]							X		
Study drug administration[j]			X							
PK blood collection		X		X	X	X	X	X	X	
Adverse events[k]	< ----------X ---------- >									
Prior/concomitant medications[l]	< ---------- X ---------- >									

Schedule of Assessments – Oral Treatment Arm

Study Phase	Screening[a]	Oral Treatment Period								Study Completion[b]
Study Day	D –2 to D–1	D1						D2	D3	D4-D7
			Post Dose Timepoint							
Study Hour	–48 hrs.	Pre-dose[c]	0	1 Hr.	2 Hrs.	3 Hrs.	8 Hrs.	24 Hrs.	48 Hrs.	

BMI = body mass index, BP = blood pressure, D = study day, HR = heart rate, ICF = informed consent form, PK = pharmacokinetic

[a] Screening period of up to 48 hours is permitted.

[b] Study completion visit may be performed via telehealth with subject's parent/LAR to review ongoing medications and adverse events if the subject is discharged from the hospital before Day 4.

[c] Pre-dose window is defined as after consent and at least 15 minutes prior to study drug administration.

[d] Written and signed ICF/assent as applicable must be obtained before any protocol-specific assessment is performed.

[e] Full physical examination to be performed at Screening and 24 hours post-dose. Symptom-driven physical exams may be performed at other timepoints as necessary.

[f] Both height and weight to be obtained with shoes off.

[g] For post-menarchal females of childbearing potential only.

[h] Blood pressure to be performed in supine position.

[i] Blood samples for hematology and chemistry will be assessed by site's local laboratory. If standard of care laboratory assessments were performed within 24 hours prior to consent/assent, these results may be used for purposes of determining provided they meet protocol requirements for all screening labs. Refer to Section 8.7.

[j] Oral study drug will be administered to subjects in the morning with no food or drink except water for at least 6 hours prior to dosing. After oral dosing, subjects will have no food or drink except water for at least 2 hours and no dairy products, antacids, or multivitamins for 4 hours.

[k] Adverse events will be assessed from the time of signing the consent/assent until the study completion visit.

[l] All medications taken within 72 hours prior to signing of consent/assent will be collected, in addition to all medications taken during the study.

Appendix 2. Sponsor Signature

Study Title:	A Phase 1, Open-Label, Multi-Center Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Intravenous and Oral Doses of Omadacycline in Pediatric Subjects with Suspected or Confirmed Bacterial Infections
Study Number:	PTK0796-PEDPK-20110
Final Date:	14-Sep-2023

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

Signed: [redacted] Date: [redacted]

[redacted] MD
Senior Director, Medical Affairs
Paratek Pharmaceuticals, Inc.

Appendix 3. Investigator's Signature

Study Title:	A Phase 1, Open-Label, Multi-Center Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Intravenous and Oral Doses of Omadacycline in Pediatric Subjects with Suspected or Confirmed Bacterial Infections
Study Number:	PTK0796-PEDPK-20110
Final Date:	14-Sep-2023

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: _____