Paratek Pharmaceuticals, Inc.

PTK0796-PEDPK-20110

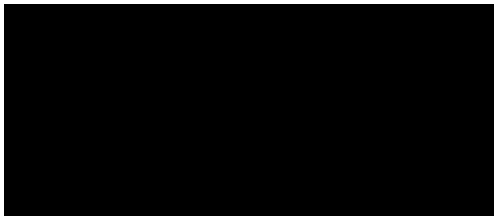
A Phase 1, Open-Label, Multi-Center Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Intravenous and Oral Doses of Omadacycline in Pediatric Subjects with Suspected or Confirmed Bacterial Infections

09/01/2023

Final Statistical Analysis Plan

Version 1.0

Prepared by:



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List of Abbreviations

Abbreviation	Definition
λ_z	apparent terminal elimination rate constant
AE	adverse event
AUC	area under the plasma concentration versus time curve
AUC_{0-48}	area under the plasma concentration versus time curve (AUC) from time 0 to 48 hours after dosing
AUC_{last}	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
AUC_{0-inf}	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
BMI	body mass index
BLQ	below the limit of quantification
CL	systemic clearance
C_{max}	maximum observed plasma concentration
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
HR	heart rate
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
n	number of observations
PK	pharmacokinetic
PT	preferred term
rsq	R squared
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
$T_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum observed plasma concentration
V_z	Apparent volume of distribution during the terminal phase

1. 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.

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting of the clinical data for Paratek Pharma Protocol PTK0796-PEDPK-20110 (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).

This SAP is written based on protocol PTK0796-PEDPK-20110, version 4.0, dated 02May2022.

2. Objectives

2.1. 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.

2.2. Secondary Objective

The secondary objective is to evaluate the safety and tolerability of single intravenous and oral doses of omadacycline in children 8 to < 18 years of age with suspected or confirmed bacterial infections.

3. Investigational Plan

3.1. 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

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 (eg, 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 aluminium- or calcium-containing products (eg, vitamins, supplements) for 4 hours after dosing.

A total of 7 blood samples for PK analysis of 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 phone call to 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.

3.2. Study Endpoints

3.2.1. Primary Endpoints

3.2.1.1. Pharmacokinetic Endpoints

Pharmacokinetic endpoints for the study are:

- 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 ($AUC_{0\text{-}inf}$)
- 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

3.2.2. Secondary Endpoints

3.2.2.1. Safety Endpoints

The safety endpoints of this study will be assessed through:

- The incidence of treatment-emergent adverse events (TEAEs), relationship to the study drug, and severity
- Serious adverse events (SAE) and adverse events (AE) leading to discontinuation of study drug
- Clinical laboratory test results (hematology and serum chemistry)
- Vital sign measurements (systolic blood pressure, diastolic blood pressure, heart rate [HR], and oral body temperature)
- Physical examination findings

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Descriptive statistics for continuous variables will be summarized using descriptive statistics (number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum). For categorical variables, frequencies and percentages will be presented.

During the analysis and reporting process, any deviations from the statistical analysis plan designed for this protocol will be described and justified in the final clinical study report (CSR).

Unless specified otherwise, baseline will be defined as the last non-missing assessment (including repeated and unscheduled assessments) prior to the study drug administration for each treatment period.

For summary of safety assessments, if there are repeated measurements at a time point, the first non-missing assessment at that time point will be used in the summary tables.

Unscheduled results will not be included in the summary tables, except for determining Baseline, but will be presented in data listings.

The methodology and data handling specifications for PK data are detailed in Section 8.

4.1 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 coort).

4.2 Analysis Populations

Pharmacokinetic (PK) Evaluable Population: The PK evaluable population (PK population) will include subjects who received study drug and have at least 1 evaluable PK parameter. Where subjects experience issues which may affect exposure to study drug (eg, emesis, dosing errors, etc), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the PK population on a case-by-case basis.

All subjects excluded from the PK population will be documented in the data listings.

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

5. Subject Disposition

5.1 Disposition

The following will be summarized for the enrolled population by treatment and total within each cohort, for all the enrolled subjects:

The number of subjects who completed the study

- The number of subjects who did not complete the study (both overall and according to reasons for discontinuation from the study)
- The number of subjects in each analysis population
- Reason for discontinuation

Subject disposition data will be summarized in a table and presented in a data listing.

5.2 Protocol Deviations

Investigators will agree to apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the CSR.

Significant protocol deviation will be defined as a subset of protocol deviations that will lead to a subject being discontinued from the study, or significantly will affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data.

Significant protocol deviations will be summarized by treatment and total within each cohort for the Safety population. All protocol deviations will be presented in a data listing.

5.3 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations will be presented in a data listing.

6. Subject Demographics/ Other Baseline Characteristics

6.1 Subject Demographics

Descriptive statistics will be calculated for the following continuous demographic characteristics:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)

Frequency counts and percentages will be tabulated for the categorical variables:

- Sex
- Ethnicity
- Race

The summaries will be presented by treatment and total within each cohort for the safety population.

Demographic information collected at screening will be presented in a data listing.

6.2 Medical History

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version to be delineated in the clinical study report [CSR]) and presented in a data listing.

7. Therapy

7.1 Prior and Concomitant Therapies

Prior and concomitant therapies will be coded using the latest version of the WHO Drug Dictionary. 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.

Medication Therapy that stop prior to the first dose of study drug will be classified as prior therapy. Therapy that start on or after the first dose of study drug will be classified as concomitant. If a therapy starts before the first dose of study drug and stops on or after the first dose of study drug, then the therapy will be classified as both prior and concomitant.

All prior and concomitant therapy will be summarized by treatment within each cohort and total within each cohort for the safety population and presented in a data listing.

7.2 Medical or Surgical Treatment Procedures

Medical or surgical treatment procedures will be presented in a data listing.

7.3 Study Treatment

The study drug administration data as collected on eCRF will be presented in a data listing.

8. Pharmacokinetic Analysis

All PK listings and individual concentration-time profiles will be presented using the safety population. PK tables and mean figures will be presented using the PK population.

8.1 Data Handling

Data rounding specifications for PK data are documented in the PK TLF shells. 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 and excluded from the summary statistics. Mean BLQ concentrations will be presented as BLQ, and the standard deviation (SD) and coefficient of variation (CV) will be reported as not applicable for descriptive statistics, if all individual values are BLQ. Missing concentrations will be treated as missing.

8.2 Plasma Concentrations

Serial blood samples will be collected from all subjects at the following time points for PK assessment of omadacycline:

<u>Oral Treatment</u>

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

Intravenous (IV) Treatment

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

The permitted windows for PK sample collection are as follows:

Pharmacokinetic time points	**Window**
Pre-dose	at least 15 minutes before study drug administration
10 minutes to 3 hours	± 5 minutes
8 to 48 hours	± 1 hour (60 minutes)

PK collections that have an actual sampling time that deviates from the predefined collection time windows will be flagged in the data listings and excluded from the calculation of concentration summary statistics.

Individual plasma concentrations of omadacycline and time deviation data will be presented in data listings. Plasma concentration data will be summarized by scheduled time point for each treatment and age cohort using descriptive statistics (number of observations (n), arithmetic mean (mean), standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum).

Individual plasma concentrations of omadacycline will be plotted by treatment, age cohort, and actual time (relative to the start of infusion for the IV Treatment) on both linear and semi-logarithmic scales. Mean plasma concentrations will be plotted by nominal time (relative to the start of infusion for the IV Treatment) on both linear and semi-logarithmic scales with both treatments and age cohort overlaid on the same plots.

8.3 Plasma Pharmacokinetic Parameters

Plasma concentration-time data will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ). The following PK parameters will be calculated for omadacycline, where data permit:

C_{max}	Maximum observed plasma concentration.
T_{max}	Time to reach maximum observed plasma concentration.
AUC_{0-48}	AUC from time 0 to 48 hours postdose, calculated using the linear trapezoidal rule.
AUC_{last}	AUC from time 0 to the last quantifiable concentration (C_{last}), calculated using the linear trapezoidal rule.
AUC_{0-inf}	AUC from time 0 extrapolated to infinity, calculated as [AUC_{last} + (C_{last} / λ_z)].
$T_{1/2}$	Elimination half-life associated with the terminal slope of the semilogarithmic concentration-time curve, calculated as: ln (2) / λ_z.
CL	Systemic clearance, calculated as: Dose / AUC_{0-inf} (after iv administration only)

V_z	Apparent volume of distribution during the terminal phase, calculated as: Dose / [λ_z * $AUC_{0\text{-}inf}$] (after iv administration only).

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed to document the selection of data points used to estimate $t_{1/2}$ using non-compartmental procedures:

λ_z	Apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase.
Number of points	Number of data points used to estimate λ_z; a minimum of 3 data points must be used, and C_{max} must not be included.
λ_z lower	Lower bound used for the estimation of λ_z.
λ_z upper	Upper bound used for the estimation of λ_z.
Rsq	Regression coefficient of determination (goodness of fit statistic); λ_z and all associated parameters will only be reported where Rsq $\geq$ 0.80.
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ due to extrapolation. $AUC_{0\text{-}inf}$, CL and V_z values will be flagged and excluded from summary statistics where $\%AUC_{ext}$ > 20%.

Actual sampling times (relative to the end of infusion for the IV Treatment) will be used for the estimation of all plasma PK parameters, and all concentrations will be included in the analysis (including concentrations collected outside predefined collection windows).

Plasma PK parameters of omadacycline will be presented in data listings and summarized separately by treatment and age cohort using descriptive statistics (number of observations (n), arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum). T_{max} will be summarized using number of observations, median, minimum, and maximum only.

9. Safety Analysis

The purpose of this section is to define the safety parameters for the study. All summaries of safety data will be conducted using the Safety population. Safety assessments will include monitoring of adverse events (AEs), clinical laboratory test results, vital sign measurements, and physical examination findings.

All safety summaries and analyses will be conducted for the Safety Analysis Set. All safety data will be presented in listings.

9.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

The incidence of treatment-emergent AEs will be presented by treatment and total, within each cohort, system organ class, and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), relationship to the study drug, and severity. Any serious adverse event (SAEs) and AEs leading to discontinuation of study drug will also be presented in a data listing.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

A serious adverse event (SAE) is defined as any AE that results in any of the following outcomes:

- Death
- Life-threatening
- 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.

The AE's relationship to study treatment will be evaluated by the investigator. The following relationships will be collected on electronic Case Report Form (eCRF): related and not related.

The severity of AEs will be classified as mild, moderate and severe.

Adverse Events will be coded by system organ class (SOC) and preferred term (PT) according to MedDRA, version to be delineated in the CSR.

An overview of AEs will be presented by treatment and total, including number and percentage of subjects with any:

- Any TEAE
- Any treatment-related TEAE
- Any moderate TEAE
- Any treatment-related moderate TEAE
- Any severe TEAE

- Any treatment-related severe TEAE
- Any SAE
- Any treatment-related SAE
- Any TEAE leading to early discontinuation
- Any death

The TEAE summary tables will include all TEAEs, TEAEs considered related to study drug, TEAEs by severity, serious TEAEs, and TEAEs leading to premature discontinuation from the study intervention by treatment within each cohort and overall, within each cohort. The TEAE summary tables will be sorted by SOC and PT. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC. A subject with 2 or more events within the same level of summarization will be counted only once in that level using the most severe incident or most related incident. Percentages will be based on the number of subjects in the safety population.

All AEs will be presented in a data listing. Separate data listings will be generated for treatment-related AEs, SAEs, and AEs leading to study discontinuation.

9.2 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.

The following laboratory tests will be performed:

Hematology	Hematocrit, Hemoglobin, Mean cell volume, WBC count, Platelet count, White blood cell differential, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
Serum Chemistry	Blood glucose, Urea, Creatinine, Sodium, Potassium, Chloride, Bicarbonate, ALT, AST, AP, Total bilirubin, Total protein, Albumin, CK, Calcium, Phosphate, Cholesterol, Uric Acid, GGT, Amylase, Lipase

SARS-CoV-2 Sample	Molecular testing for SARS-CoV-2 will be performed at the local laboratory using an upper respiratory sample (e.g. nasopharyngeal swab or saliva) collected either at Screening or upon current hospital admission. Test results from this sample are not required before a subject is enrolled
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.

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

The hematology, Serum Chemistry, SARS-CoV-2 sample, and pregnancy assessment tests will be performed at the timepoints indicated in the schedule of events (SOE). The schedule of events can be found in Section 11.

Clinical laboratory test results will be presented in data listings. Actual results and changes from Baseline in clinical hematology and serum chemistry will be summarized by treatment within each cohort ,and time point. Shift from baseline in terms of low/normal/high for hematology and serum chemistry tests, and in terms of normal/abnormal will be summarized by treatment within each cohort and time point.for the safety population.

All laboratory data will be presented in data listings.

9.3 Vital Sign Measurements

Vital sign measurements will be obtained at the time points indicated in the Schedule of Events.

Vital sign measurements will include body weight, body temperature, blood pressure, heart rate. Vital signs will be measured at the time points indicated in the schedule of events (Section 11).

Actual results and changes from baseline for vital sign measurements will be summarized by treatment within each cohort and time point for the safety population.

All vital sign data will be presented in a data listing.

9.4 Physical Examination

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.

A standard physical examination will be performed at the time points indicated in the schedule of events (Section 11). 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.

Physical examination results will be presented in a data listing.

9.5 Covid-19 Screening

Additional COVID-19 case details listing will be produced.

10. Interim Analysis

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

11 Schedule of Events

Appendix 1 Schedule of Assessments - – Intravenous Treatment Arm

	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.**	**Predose[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		
SARS-CoV-2 sample collection for local molecular testing	X										
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 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 eligibility and do not need to be collected again at Screening.
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 1 Schedule of Assessments - – Oral Treatment Period

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.	Predose[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		
SARS-CoV-2 sample collection for local molecular testing	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 ---------- >									

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 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 eligibility and do not need to be collected again at Screening.
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.