STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2/3 Single-Arm, Open-label Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Obeldesivir in Pediatric Participants With COVID-19
Name of Test Drug:	Obeldesivir (ODV; GS-5245™)
Study Number:	GS-US-611-6464
Protocol Version (Date):	Original (09 May 2023); Administrative Amendment 1 (22 June 2023); Amendment 0.1 EU (15 November 2023)
Analysis Type:	Final Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	17 June 2024
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CBC	complete blood count
CSR	clinical study report
DAIDS	Division of AIDS
DMC	data monitoring committee
DOB	date of birth
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	Full Analysis Set
GA	gestational age
HLGT	high-level group term
HLT	high-level term
ID	identifier
INR	international normalised ratio
LLOQ	lower limit of quantification
LTT	lower-level term
LOD	limit of detection
LOQ	limit of quantitation
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
ODV	obeldesivir
PK	pharmacokinetics
PopPK	population pharmacokinetics
PT	prothrombin time
Q1, Q3	first quartile, third quartile
RBC	red blood cell
RDV	remdesivir
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
RDV	remdesivir
SD	standard deviation

SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC	area under the concentration versus time curve
AUC_{0-12}	partial area under the concentration versus time curve from time "x" to time "xx"
C_{max}	maximum observed concentration of drug
C_{trough}	concentration at the end of the dosing interval

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-611-6464. This SAP is based on the study protocol original dated 09 May 2023, study protocol administrative amendment 1 dated 22 June 2023, study protocol amendment 0.1 EU dated 15 November 2023 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

This study was terminated early; hence only the analyses outlined in this SAP will be performed.

1.1. Study Objectives and Endpoints

Primary Objective(s)	Primary Endpoint(s)
• To evaluate the plasma pharmacokinetics (PK) of ODV in pediatric participants with COVID-19	• PK parameters ($AUC_{0\text{-}12}$, C_{max}, and C_{trough}) for ODV metabolite, GS-441524
• To evaluate the safety and tolerability of ODV in pediatric participants with COVID-19	• Incidence of treatment-emergent adverse events (AEs) by Day 35 • Incidence of treatment-emergent laboratory abnormalities by Day 35
Secondary Objective(s)	**Secondary Endpoint(s)**
• To assess the impact of ODV on time to sustained alleviation of targeted COVID-19 symptoms in pediatric participants with COVID-19	• Time to sustained alleviation of targeted COVID-19 symptoms by Day 35
• To evaluate the antiviral activity of ODV on SARS-CoV-2 nasal swab viral load in pediatric participants with COVID-19	• Change from baseline in SARS-CoV-2 nasal swab viral load at Day 5
• To assess the impact of ODV on the requirement for supplemental oxygen in pediatric participants with COVID 19	• Proportion of participants who require supplemental oxygen support (low flow oxygen, high flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation) by Day 35
• To evaluate palatability and acceptability of ODV in pediatric participants with COVID-19	• Assessment of palatability and acceptability scores of each formulation at Day 5

• To provide data on the use of medications other than remdesivir (RDV) and ODV for treatment of COVID-19 in pediatric participants with COVID-19	• Proportion of participants with concomitant use of medications other than RDV and ODV for treatment of COVID-19 by Day 35
• To assess the impact of ODV on COVID-19-related hospitalizations or all-cause death in pediatric participants with COVID-19	• Proportion of participants with COVID-19-related hospitalization or all-cause death by Day 35

1.2. Study Design

This is a Phase 2/3, single-arm, multi-cohort, open-label study to evaluate the safety, PK, and efficacy of ODV in pediatric participants with COVID-19 who are at risk of progression to severe disease.

At least 52 participants aged 0 days to < 18 years were planned to be enrolled as described in Table 1-1. Participants were enrolled in a staggered manner and received treatment with ODV. Cohorts were opened for enrollment based upon availability of a suitable pediatric formulation and availability of preliminary safety and PK data.

Table 1-1. Study Design

Cohort	Description	Dose	Number of participants
Pediatric participants ≥ 28 days to < 18 years old			
1	≥ 6 years to < 18 years and weight ≥ 40 kg	ODV CCI administered orally BID for 5 days	12
2	≥ 6 years to < 18 years and weight ≥ 20 kg to < 40 kg	ODV CCI administered orally BID for 5 days	12
3	≥ 2 years to < 18 years and weight ≥ 12 kg to < 20 kg	TBC	12
4	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg	TBC	12
Term neonatal participants 0 days to < 28 days old			
5	≥ 14 days to < 28 days of age, GA ≥ 37 weeks and weight ≥ 2.5 kg	TBC	≥ 4
6	0 days to < 14 days of age, GA ≥ 37 weeks and birth weight ≥ 2.5 kg	TBC	All available
Preterm neonates and infants 0 days to < 56 days old			
7	0 days to < 56 days of age, GA < 37 weeks and birth weight ≥ 1.5 kg	TBC	All available

GA = gestational age; TBC = To be confirmed.

Participants had to have:

- SARS-CoV-2 infection confirmed by polymerase chain reaction or an alternative molecular diagnostic assay
- Initial onset of COVID-19 signs/symptoms ≤ 5 days before screening with ≥ 1 sign/symptom
- Presence of ≥ 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness due to COVID-19

Randomization and treatment codes were not applicable in this study. Blinding of treatment assignments or data was not applicable in this study.

The study treatment period was 5 days with a posttreatment follow-up period of 30 days after the last dose of study drug.

The schedule of study procedures is presented in Appendix 1.

1.3. Sample Size and Power

The total sample size was planned to be at least 52 participants.

A minimum of 12 evaluable participants from each cohort (Cohorts 1-4) provides > 90% power to reject the null hypothesis that there is at least a 30% difference in GS-441524 AUC_{0-12} and C_{max}, respectively, between pediatric and adult participants, using 2 one-sided tests with each performed at an alpha level of 0.05. This power analysis assumes that the expected geometric mean ratio between the pediatric participants versus the adult group is 1, the equivalency boundary is 70% to 143%, and the interparticipant standard deviation (SD) of AUC_{0-12} and C_{max} are 0.19 h•ng/mL and 0.18 ng/mL respectively (natural log scale, preliminary results from Study GS-US-611-6248).

The sample size calculation was performed using SAS® Software Version 9.4.

This study was terminated early; hence the number of participants originally planned to be enrolled as outlined above was not achieved.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

As the study has been terminated early, interim analyses are no longer required.

2.1.1. Dose Selection Analysis

As the study has been terminated early, dose selection analyses for additional cohorts are no longer required.

2.1.2. Data Monitoring Committee Analyses

As the study has been terminated early, data monitoring committee (DMC) analyses are no longer required.

2.2. Final Analysis

The final analysis will be performed after all participants enrolled at the time of study termination have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

2.3. Changes from Protocol-Specified Analyses

This study was terminated early; hence only the analyses outlined in the subsequent sections will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Due to the low number of participant in the study at the time of early termination, no tables or figures will be provided for this study.

By-participant listings will be presented for all participants in the All Enrolled Analysis Set and sorted by cohort, participant identitifier (ID) number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within the participant. The cohort to which participants were enrolled will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each TFL.

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all participants who received a study participant ID number in the study after screening.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled participants who took at least 1 dose of study drug. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all participants who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.4. Pharmacokinetic Analysis Set

The PK Analysis Set will include all enrolled participants who took at least 1 dose of study drug and have at least 1 nonmissing concentration value reported by the PK laboratory for GS-441524. This is the primary analysis set for all PK analyses. Within the PK Analysis Set, those participants with PK exposure data successfully derived from the population PK (PopPK) modeling will be included in the analyses related to PK exposure.

3.1.5. Virology Analysis Set

The Virology Analysis Set will include all enrolled participants who took at least 1 dose of study drug and have a baseline SARS-CoV-2 viral load $\geq$ lower limit of quantification (LLOQ). Refer to Section 3.7 for the definition of LLOQ.

3.2. Participant Grouping

For analyses, participants will be grouped according to the cohort to which participants were enrolled.

3.3. Strata and Covariates

This study is not randomized. It therefore did not use a stratified randomization schedule when enrolling participants. No covariates will be included in efficacy and safety analyses.

3.4. Examination of Participant Subgroups

There are no prespecified participant subgroupings for efficacy and safety analyses.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.3.

3.6.2. Outliers

Outliers of non-PK data will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

In general, age collected at Day 1 will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the enrollment date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (for eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation (LOQ) will be imputed as follows:

- A value that is 1 unit less than the LLOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LLOQ). For eg, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.

- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ, respectively).

SARS-CoV-2 viral load results that are below LLOQ but have a positive signal will be reported as "< 2228 cp/mL SARS-CoV-2 detected" and those that are below the lower limit of detection (LOD) and negative will be reported as "No SARS-CoV-2 detected". The data will be imputed as follows:

- A value of 1114 copies/mL (half of the LOQ 2228 copies/mL) will be used to calculate descriptive statistics if the datum is reported as "< 2228cp/mL SARS-CoV-2 detected".

- A value of 746.5 copies/mL (half of the LOD 1493 copies/mL) will be used to calculate descriptive statistics if the datum is reported as "No SARS-CoV-2 detected".

Base 10 logarithm transformation will be used for analyzing SARS-CoV-2 viral load.

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, Study Day 1 is the day of first dose of study drug administration.

Last Dose Date is defined as the maximum, nonmissing, nonzero dose end date of treatment recorded on the Study Drug Administration eCRF with "Check box if study drug was permanently withdrawn" checked for participants who prematurely discontinued or completed study drug according to the Study Drug Completion eCRF. Refer to Section 4.2 for missing date imputation, if necessary.

Last Study Date is the latest of the study drug start dates and end dates, the in-person or virtual visit dates, the vital sign collection dates, the participant and/or caregiver COVID-19 symptom assessment questionnaire dates, the laboratory collection dates, and the death date (if applicable, for participants who died during the study, the death date will be the Last Study Date. For participants who died after completing the study or after prematurely discontinuing the study, the death date will not be considered for the Last Study Date).

Baseline value is defined as the last value obtained on or prior to the first dose of study drug administration date unless otherwise specified (see Section 3.8.3).

3.8.2. Analysis Visit Windows

Participant visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows for chemistry laboratory tests, hematology laboratory tests, and vital signs are provided in Table 3-1.

Table 3-1. Analysis Visit Windows for Chemistry Laboratory Tests, Hematology Laboratory Tests, and Vital Signs

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 3	3	2	4
Day 5	5	5	20
Day 35	35	21	≥ 35

Hematology laboratory tests include complete blood count (CBC) with differential.
Chemistry laboratory tests include albumin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen, creatinine, estimated glomerular filtration rate (eGFR) using bedside Schwartz formula, ionized calcium, carbon dioxide, chloride, total serum protein, potassium, and sodium.
Vitals signs include heart rate, temperature, blood pressure (mean arterial pressure [MAP] if available, systolic and diastolic), respiratory rate, and oxygen saturation.

The analysis windows for coagulation laboratory tests are provided in Table 3-2.

Table 3-2. Analysis Visit Windows for Coagulation Laboratory Tests

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 5	5	2	≥ 5

Coagulation laboratory tests include prothrombin time (PT), activated partial thromboplastin time (aPTT) with calculated international normalised ratio (INR).

The analysis windows for urinalysis laboratory tests are provided in Table 3-3.

Table 3-3. Analysis Visit Windows for Urinalysis Laboratory Tests

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1

Urinalysis laboratory tests include bilirubin, glucose, erythrocytes, and leukocytes.

The analysis windows for SARS-CoV-2 midturbinate nasal swab and microbiology laboratory tests are provided in Table 3-4.

Table 3-4. Analysis Visit Windows for SARS-CoV-2 Midturbinate Nasal Swab and Microbiology Laboratory Tests

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 3	3	2	4
Day 5	5	5	6
Day 8	8	7	11
Day 14	14	12	25
Day 35	35	26	≥ 35

Microbiology laboratory tests include Influenza A Virus, Influenza B Virus, Respiratory Syncytial Virus (RSV), and SARS-CoV-2.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline data, the last nonmissing value on or prior to the first dose of study drug administration date will be selected, unless specified differently. If there are multiple records on the same day, the baseline value will be selected as follows:
  - For continuous data:
    - For SARS-CoV-2 viral load data, the geometric mean (copies/mL) will be taken.
    - For other continuous data, the average of the measurements will be taken.
  - For categorical data:
    - For SARS-CoV-2 infection status, the highest severity (ie, a positive PCR result) will be selected.
    - For other categorical data, the lowest severity will be selected.

- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected with the exception of SARS-CoV-2 viral load data in which the latest record will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, values will be selected as follows:
    - For SARS-CoV-2 viral load, if there are multiple records with the same time or no time recorded on the same day, the geometric mean value (copies/mL) will be taken.
    - For red blood cell (RBC) Morphology result, if there is more than 1 record on the selected day, all results will be selected.
    - For other parameters, if there is more than 1 record on the selected day, the average will be taken for continuous data and the worst severity will be taken for categorical data, unless otherwise specified.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

By-participant listings sorted by participant ID number (in ascending order) will be provided for the following:

- Enrollment
- Participant disposition, including cohort, date of enrollment, first dose date, last dose date, end of study date, study drug discontinuation, study discontinuation, and reasons for study drug or study discontinuation

4.2. Extent of Study Drug Exposure and Adherence

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in days. If the last study drug dosing date is missing, the last dosing date is imputed as the earliest date from the following:

- Day 5 if the participant took 2 tablets on Day 1
- Day 6 if the participant took 1 tablet on Day 1
- Last study visit date

Study day for the imputed last dosing date will not exceed Study Day 6.

A by-participant listing of study drug administration will be provided separately by participant ID number (in ascending order).

4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry but enrolled in the study, will be summarized regardless of whether they were exempted by the sponsor or not. A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. A by-participant listing will be provided for those participants with protocol deviations, included a column specifying whether the protocol deviation is important.

4.4. Assessment of Disaster or Public Health Emergency Impact

The study is in participants with COVID-19 thus no additional assessment of COVID-19 impact will be included.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics include:

- Age [in years]
- Age group (< 28 days; 28 days to < 2 years; 2 to < 12 years; 12 to < 18 years)
- Sex at birth (Male; Female)
- Race (American Indian or Alaska Native; Asian; Black; Native Hawaiian or Pacific Islander; White; Not Permitted; Other)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino; Not Permitted)
- Baseline body weight [in kg]
- Baseline body mass index (BMI) [in kg/m^2]
- BMI-for-age Z-scores
- BMI-for-age percentile category (< 5th Percentile; 5th to < 85th Percentile; 85th to < 95th Percentile; ≥ 95th Percentile)
  - Details on BMI-for-age percentiles are available in Appendix 2.

A by-participant demographic listing, including the informed consent date, will be provided by participant ID number (in ascending order). Note: If information on Apgar score for participants < 24 hours, head circumference (in cm) for participants < 28 days, birth weight (in kg) for participants < 56 days of age and/or gestational age (in weeks) for participants < 1 year has been collected this information will be listed.

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- Duration of COVID-19 symptoms prior to first dosing date (days)
  - Defined as: First Dosing Date – Onset Date of First/Earliest COVID-19 Symptom
- Duration from first positive SARS-CoV-2 diagnostic test to first dosing date (days)
  - Defined as: First Dosing Date – Date of COVID-19 Diagnosis
- Risk factors linked to medical history:
  - CCI [redacted]

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
  - CCI

- Total number of risk factors
- Baseline COVID-19 vaccination status: (a) Yes; (b) No
- Baseline respiratory viral coinfections: (a) None; (b) Yes subdivided into: (i) Influenza A; (ii) Influenza B; (iii) RSV
- Baseline SARS-CoV-2 viral load (as a continuous variable, and a categorical variable: (a) < 6 $\log_{10}$ copies/mL: (b) ≥ 6 $\log_{10}$ copies/mL)
- Baseline eGFR using the bedside Schwartz formula (mL/min/1.73 m^2)
- Baseline ALT (U/L)

A by-participant listing of other baseline characteristics will be provided by participant ID number (in ascending order).

5.3. Medical History

Medical history will be collected at screening for general conditions (ie, conditions not specific to the disease being studied). Medical history will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

General medical history data will be collected at screening and listed only.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

There is no primary efficacy endpoint in this study.

6.2. Secondary Efficacy Endpoints

By-participant listings sorted by participant ID number (in ascending order) will be provided for the following:

- COVID-19 symptoms assessed by the participant and/or caregiver COVID-19 symptom assessment questionnaire data
- SARS-CoV-2 nasal swab viral load
- Oxygen supplementation
- Hospitalization

CCI [redacted]

6.4. Changes From Protocol-Specified Efficacy Analyses

The definition of the Virology Analysis Set was modified so that participants with a baseline SARS-CoV-2 viral load < LLOQ will not be included in the Virology Analysis Set.

This study was terminated early; hence the protocol-specified efficacy analyses will not be provided. Only by-participant listings will be presented.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of MedDRA. System organ class, high-level group term (HLGT), high-level term (HLT), preferred term, and lowest-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For each episode, the highest grade attained should be reported as defined in the grading scale. The DAIDS scale is available at the following location:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 (fatal) according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE eCRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

7.1.6.1. Summaries of AE incidence in Combined Severity Grade Subsets

By-participant listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All Deaths

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed using both quantitative and qualitative methods. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, serum chemistry, and coagulation separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher will be flagged in the data listings, as appropriate.

7.2.1. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 (July 2017) will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1.

7.2.1.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days participants who permanently discontinued study drug, or the last available date in the database snapshot for participants who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.1.2. Summaries of Laboratory Abnormalities

A by-participant listing of treatment-emergent laboratory abnormalities will be provided by participant ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades and abnormal flags displayed.

For INR and aPTT, protocol specified toxicity grading scale depends on the upper limit of normal range (ULN). While the ULN of INR and aPTT depends on whether the participant is taking anticoagulant medication or not (ie, Not taking oral anticoagulant: 0.8 – 1.2; Taking oral anticoagulant: 2.0 – 3.0), this information is not collected by the reference laboratory. As a result, INR and aPTT will be graded by assuming participant is not taking an oral anticoagulant, which is a conservative approach that may lead to over-reporting of abnormalities for INR and aPTT.

7.2.2. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined using the participants who were reported to have the following laboratory test values for postbaseline measurements:

- AST: (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin > 2 x ULN
- ALP > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN

A listing of participants who met at least 1 of the above criteria will be provided.

7.3. Body Weight and Vital Signs

A by-participant listing of vital signs will be provided by participant ID number and visit in chronological order. Body weight, height, and BMI will be included in the vital signs listing, if space permits. If not, they will be provided separately.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the Gilead-modified World Health Organization (WHO) Drug dictionary.

Prior medications are defined as any medications with a start date prior to the first dosing date of study drug, regardless of when the stop date is. If a partial start date is entered, the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be considered as prior medications.

Concomitant medications are defined as medications taken while a participant took study drug.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order. This listing will include Anatomical Therapeutic Chemical (ATC) drug class Level 2.

7.5. Tanner Stage Assessment

Tanner Stage results at Day 1 and during the study, if available, will be listed.

7.6. Palatability and Acceptability Assessment

Palatability and acceptability assessments will be listed.

7.7. Other Safety Measures

A by-participant listing of participant pregnancies during the study will be provided by participant ID number (in ascending order).

7.8. Changes From Protocol-Specified Safety Analyses

This study was terminated early; hence the protocol-specified safety analyses will not be provided. Only by-participant listings will be presented.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

A single PK blood sample was planned to be collected at the following times and visits:

- Cohorts 1 and 2:
  - Days 3: 1 sample between CCI [redacted]
  - Day 5: predose CCI [redacted] and at CCI [redacted] CCI [redacted] postdose
  - Day 5: CCI [redacted] postdose for hospitalized participants only

As many of the above specified PK samples should have been obtained from each participant as was feasible.

8.2. PK Analyses Related to Sparse PK Sampling

The following listings will be provided:

- PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age from the PK samples as well as concentration data.

8.3. Changes From Protocol-Specified PK Analyses

This study was terminated early; hence the protocol-specified PK analyses will not be provided. Only by-participant listings will be presented.

9. REFERENCES

Centers for Disease Control and Prevention. Defining BMI categories. Available at: https://www.cdc.gov/obesity/basics/childhood-defining.html Accessed: 18 April 2024; Last Reviewed: 21 March 2023.

Centers for Disease Control and Prevention. Growth Chart Training. Available at: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm Accessed: 18 April 2024; Last Reviewed: 15 August 2023.

World Health Organization. Child growth standards. Available at: https://www.who.int/toolkits/child-growth-standards/software Accessed: 18 April 2024.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Schedule of Assessments

	Screening/ (D –1)[a]	Baseline/ D 1[a]	D 3	D 5	D 8	D 14	D 21	D 28	EOS/ D 35
	–	–	–	–	± 1 d	± 2 d	± 2 d	± 2 d	± 5 d
	In person		In person or remote[b]	In person	In person or remote[b]		Virtual[c]		In person
Participant and/or parent or legal guardian consent/assent	CCI								
Medical history[d]									
Document SARS-CoV-2 infection									
Complete physical examination[e]									
Symptom-directed physical examination[e]									
Body weight									
Height/length[f]									
Last recorded Apgar score if < 24 hours of age									
Birth weight if < 56 days of age									
Gestational age if < 1 years of age									
Vital signs[g]									
Tanner stage assessment if ≥ 6 years of age									
Hematology, chemistry									
Urinalysis									
Routine coagulation test (PT/aPTT with calculated INR)									
Neonatal bilirubin panel for all neonates < 14 days, and any neonate presenting with jaundice									
Urine pregnancy test[h]									
Midturbinate nasal swab[i]									
Review inclusion/exclusion criteria									
Participant and/or caregiver symptom assessment[j]									
PK sample[k]									
Study drug dispensation									
Study drug administration[l]									
Study drug return[m]									
Concomitant medications									
Hospitalization details[n]									
Oxygen supplementation requirement[o]									

	Screening/ (D −1)[a]	Baseline/ D 1[a]	D 3	D 5	D 8	D 14	D 21	D 28	EOS/ D 35
	–	–	–	–	± 1 d	± 2 d	± 2 d	± 2 d	± 5 d
	In person		In person or remote[b]	In person	In person or remote[b]		Virtual[c]		In person
Adverse events[p]	CCI								
Acceptability/palatability assessment									

aPTT = activated partial thromboplastin time; COVID-19 = coronavirus disease 2019; D/d = day; EOS = end of study; Ig = immunoglobulin; INR = international normalized ratio; MAP = mean arterial pressure; PT = prothrombin time; PK = pharmacokinetic(s); RT-qPCR = reverse transcription-quantitative polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

a Screening window is within 48 hours of the baseline visit. Baseline visit may occur on the same day as screening. If the Day 1 and Screening visits occur within the same calendar day, do not repeat assessments common to Screening and Day 1 visits.
b An in-person visit will occur either at a medical facility or as a remote visit at home by a health care professional (where permitted).
c Virtual visit is defined as an interaction with a health care professional using telephone or online based interaction (eg, telehealth, webcast, videoconferencing).
d Medical history will include the date of first COVID-19 symptoms, overall COVID-19 symptoms, all COVID-19 vaccinations prior to screening, demographics, baseline characteristics, allergies, and all other medical history.
e A complete physical examination includes source documentation of general appearance and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; and neurological. Urogenital and reproductive examination should only be completed if clinically indicated. A physical examination will only be conducted during an in-person visit by a qualified health care professional.
f Record length and head circumference if < 28 days at enrollment.
g Vitals signs include heart rate, temperature, blood pressure (MAP if available, systolic and diastolic), respiratory rate, and oxygen saturation. Vital signs will be collected at in-person visits only.
h For female participants of childbearing potential only.
i The nasal swab sample will be used for SARS-CoV-2 RT-qPCR, potential infectious viral titer assessment, potential resistance testing, and viral coinfection.
j Participant and/or caregiver symptom assessment will be completed on stipulated days via a questionnaire (Protocol Section 6.3.7).
k Refer to Protocol Section 6.3.5 for PK samples collection timepoints. PK samples will be collected on CCI for Cohorts 1 and 2.
l Study drug administration time will be recorded by investigational site personnel or by participant/parent/caregiver via a diary. Participant to withhold their dose prior to arriving to the site on Day 5, as the dose will be administered at the site.
m Study drug bottle should be returned by the participant on Day 5, if the participant has already completed both doses of study drug. If the participant has the last dose of study drug remaining by the conclusion of the Day 5 in-person visit, the participant may return the study drug bottle if an in-person visit is conducted on any subsequent visits (including EoS visit). Alternatively, the participant may courier the study drug bottle to the site.
n To be collected for hospitalized participants. Information to be collected: hospitalization date, reason for hospitalization, discharge date, and discharge outcome.
o To be collected for hospitalized participants. Refer to Protocol Section 6.3.4 for information collection on oxygen supplementation or oxygenation.
p All participants presenting with multisystem inflammatory syndrome in children (MIS-C; https://emergency.cdc.gov/han/2020/han00432.asp) should be monitored and treated as clinically indicated.
q To be collected for hospitalization participants.

Appendix 2. Programming Specifications

1) If "Age at Day 1" on the Demographics eCRF is not available, age [in years] will be calculated as follows:

   a) Only year is provided for the date of birth (DOB). Use July 1 for the month and day.

      i) AGE [in years] is calculated from the number of days between the DOB and Study Day 1,

      ii) Use the SAS INTCK function to determine the number of "1st-of-month days" (for eg, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),

      iii) Divide the result in (ii) by 12,

AGE = the integer of the result in (iii).

Age for laboratory test reference range will be based on the age at the sample collection date.

2) All screened participants refer to all participants who are screened (ie, with nonmissing screening date) and have a screening number. For summaries the same participant is counted only once.

3) Screen failure participants are the participants who either:

   — were screened and answered "No" for any inclusion criteria or "Yes" for any exclusion criteria regardless of which version of protocol the participant was consented

   — met all inclusion and exclusion criteria but were not enrolled.

4) Participants in the All Enrolled Analysis Set are defined as participants enrolled into the study. IXRSRAND is the source to determine whether the participant is enrolled (ie, participant with nonmissing ENRDTN in the IXRSRAND dataset), and confirmed by information recorded on the ENROLL eCRF (ie, ENROLLYN = "Yes" in ENROLL dataset).

5) Enrolled treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the enrolled treatment if a participant took at least 1 dose of study drug. TRT01A is assigned as blank if the participant was never dosed.

6) Body mass index (BMI) will be calculated only at baseline as follows:

   — BMI = (weight [kg]) / (height [meters]^2)

Baseline height and weight will be used for this calculation if available.

7) BMI-for-age percentile:

   a) Participants < 24 months: BMI-for-age percentile will be computed using WHO SAS package: www.who.int/toolkits/child-growth-standards/software

   b) Participants ≥ 2 years to < 20 years will be computed based on CDC: www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

8) Risk factors defined in the inclusion criteria:

   — Information on following risk factors is collected on the Medical History eCRF:

   - CCI [redacted]
   - CCI [redacted]
   - CCI [redacted]
   - CCI [redacted]
   - CCI [redacted]
   - CCI [redacted]
   - CCI [redacted]

9) TEAE

Events with Missing Onset Day and/or Month

An event is considered TE if all of the following 3 criteria are met:

   a) The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of study drug administration, and

   b) The month and year (or year) of the onset date is the same as or before the month and year (or year) of the 30th day after the date of the last dose of study drug administration, and

   c) End date is as follows:

      i) The (complete) end date is on or after the first dose date, or

      ii) The month and year (or year) of end date is the same as or after the month and year (or year) of the first dose of study drug, or

      iii) End date is completely missing

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as TEAE if end date meets any of the 3 criteria specified above.

10) The precision in reporting numerical values should be as follows:

a) Raw measurements will be reported the same as the data captured electronically or on the eCRF for all but hematology and chemistry values.

b) SD and SE will be reported to one more significant decimal place than the raw measurement.

c) Mean, median, minimum, Q1, Q3, and maximum will be reported to the same number of decimal places of the raw measurements.

Exceptions may be considered; for eg, if more than 4 significant digits are provided for the measurement.

Precision for derived parameters as follows:

Parameters	Decimal Places
BMI	2
PK concentration	2

11) Incomplete death dates will be imputed as the maximum of the study drug start dates, study drug end dates, clinic or virtual visit dates (LSTSVDT), laboratory visit dates (LSTLBDT), COVID-19 symptom assessment questionnaire dates plus 1.

12) Graded Laboratory Abnormalities Summary

The following labels will be used for laboratory abnormalities listings:

Category	Lab Test Label Used in l-lbtox Listing	Toxicity Direction	Lab Test Label Used in t-lbtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Lymphocytes	Decrease	Lymphocytes (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	Creatinine Clearance	Decrease	Creatinine Clearance by Cockcroft-Gault, Gilead Calculated (Decreased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose	Increase	Serum Glucose (Hyperglycemia)
	Serum Glucose	Decrease	Serum Glucose (Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
Coagulation	Activated partial thromboplastin time (aPTT)	Increase	Activated Partial Thromboplastin Time (Increased)
	Prothrombin Intl. Normalized Ratio (INR)	Increase	Prothrombin Intl. Normalized Ratio (Increased)
	Prothrombin Time	Increase	Not Applicable

Refer to item 13 below for more information on glucose.

13) Glucose

Fasting is not required per protocol for collecting glucose sample. Mixed fasting glucose and nonfasting glucose results are presented in the dataset. Fasting glucose or nonfasting Glucose is graded per DAIDS grading scale. The treatment-emergent glucose abnormality will be determined per Section 7.2.1 without regard to fasting status (hyperglycemia or hypoglycemia).

GS-US-611-6464-Final-Analysis-SAP-v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	PPD
PPD	Clinical Pharmacology eSigned	
PPD	Global Development Lead (GDL) eSigned	