STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants from Birth to <18 Years of Age with COVID-19
Name of Test Drug:	Remdesivir (RDV; GS-5734™)
Study Number:	GS-US-540-5823
Protocol Version (Date):	Amendment 4.0 (06 January 2022); Amendment 4.1 (10 February 2022)
Analysis Type:	Final Analysis
Analysis Plan Version:	Version 1.0
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CSR	clinical study report
CV	coefficient of variation
DMC	data monitoring committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
ET	endotracheal tube
FAS	Full Analysis Set
FiO_2	fraction of inspired oxygen
Gilead	Gilead Sciences
HIV	human immunodeficiency virus
HLT	high-level term
IAP	interim analysis plan
Ig	immunoglobulin
IL-6	Interleukin-6
INR	international normalized ratio
IV	intravenous
LPV	lopinavir
LOD	limit of detection
LOQ	limit of quantitation
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PCT	procalcitonin
PEWS	Pediatric Early Warning Score

PK	pharmacokinetic(s)
PS	Patient Safety
PT	preferred term
PT	prothrombin time
PTT	partial thromboplastin time
Q1, Q3	first quartile, third quartile
RDV	remdesivir (GS-5734™)
RT-qPCR	reverse transcriptase quantitative polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SBECD	sulfobutylether β-cyclodextrin sodium
SD	standard deviation
SE	Standard error
SOC	system organ class
SpO_2	peripheral oxygen saturation
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
US	United States

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
CL_{ss}/F	apparent oral clearance after administration of the drug: at steady state: $CL_{ss}/F = Dose/AUC_{tau}$, where "Dose" is the dose of the drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
V_z	volume of distribution of the drug after intravenous administration
V_z/F	apparent volume of distribution of the drug
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

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 final analysis clinical study report (CSR) for Study GS-US-540-5823. This SAP is based on the study protocol amendment 4.0 dated 06 January 2022, the country specific protocol amendment 4.1 dated 10 February 2022, 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.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of remdesivir (RDV; GS-5734™) in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- To evaluate the pharmacokinetics (PK) of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years

The secondary objectives of this study are as follows:

- To evaluate the efficacy of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- To determine the antiviral activity of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- To evaluate the change from baseline in oxygenation use
- To evaluate the change from baseline in the use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
- To evaluate clinical improvement using the Pediatric Early Warning Score (PEWS) scale in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- To determine sulfobutylether β-cyclodextrin sodium (SBECD) exposures (where possible)
- To provide data on use of medications other than RDV for treatment of COVID-19

The exploratory objectives of this study are as follows:

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1.2. Study Design

This is a Phase 2/3 single-arm, open-label study of the safety, tolerability, PK, and efficacy of RDV in pediatric participants from birth to < 18 years of age with laboratory-confirmed infection with COVID-19 (refer to the protocol for complete inclusion and exclusion criteria).

At least 52 participants aged 0 days to < 18 years will be enrolled as described in the table below.

Table 1-1. Study Design

Cohort	Description	Dose	Number of participants
Pediatric participants ≥ 28 days to < 18 years old			
1	≥ 12 years to < 18 years and weight ≥ 40 kg	IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily up to 10 days	12
2	≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg	IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily up to 10 days	12
3	≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg		12
4	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg		12
Term neonatal participants 0 days to < 28 days old			
5	≥14 days to < 28 days of age, gestational age > 37 weeks and weight at screening ≥ 2.5 kg	IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily up to 10 days	≥ 4
6	0 days to < 14 days of age, gestational age > 37 weeks and birth weight ≥ 2.5 kg	IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily up to 10 days	All available
Preterm neonates and infants 0 days to < 56 days old			
7	0 days to < 56 days of age, gestational age ≤ 37 weeks and birth weight ≥ 1.5 kg	IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily up to 10 days	All available

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RDV = remdesivir (GS-5734™)

Participants must:

- Have COVID-19 confirmed by polymerase chain reaction (PCR) via a validated assay at a local laboratory
- Be hospitalized and requiring medical care for COVID-19

Participants in Cohorts 1-8 who meet eligibility criteria will be enrolled on Day 1 into a single arm of RDV using an interactive web response system, and assigned a subject number. Randomization and treatment codes are not applicable in this study. Blinding of treatment assignments or data is not applicable in this study.

Participants in Cohorts 1-5 will be enrolled in parallel. Participants in Cohorts 6 and 7 will only be enrolled once RDV exposures have been evaluated from Cohort 5 and a dose has been determined. There is no minimum number of participants to be enrolled in Cohorts 6 and 7 due to the rarity of such participants. CCI [redacted]

Participants will be treated for up to 10 days. Those participants who have demonstrated clinical improvement may be considered for a shorter treatment period.

Screening is to be completed within 2 days prior to the Day 1 visit.

At the screening visit and all subsequent study visits (or until hospital discharge - whichever comes first) laboratory analyses (hematology, chemistry, inflammatory markers, urinalysis, and routine coagulation test), vital signs (heart rate, temperature, blood pressure [mean arterial pressure if available, systolic and diastolic], respiratory rate [if not on a ventilator], oxygen saturation), complete or symptom-directed physical examinations will be performed. Nasopharyngeal and oropharyngeal samples (combined) OR nasal and oropharyngeal samples (combined), and rectal or fecal swab will be collected on Days 1, 3, 5, 7, and 10 (if feasible) for SARS-CoV-2 reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) viral load testing and possible viral resistance testing. Endotracheal tube aspirates will also be collected if the participant is intubated. If the participant is discharged prior to Day 10, the samples for SARS-CoV-2 RTqPCR viral load testing and possible viral resistance testing can be collected by assigned study staff at the participant's home or as an outpatient on the assigned days noted above, if feasible. Serum for SARS-CoV-2 IgG, IgM, and IgA serology will be collected at Screening, Day 5, Day 10 (if feasible), and the Day 30 Follow-up visit (for participants weighing $\geq$ 12 kg).

Clinical scoring using PEWS and the Ordinal Scale will occur at Screening and daily through the duration of dosing.

Day 30 Follow-up visit, as outpatient or inpatient depending on clinical status, will include vital signs, complete or symptom-directed physical examination and chemistry laboratory evaluation.

Adverse events and concomitant medications will be assessed from Screening through the Day 30 Follow-up visit.

As many of the specified sparse PK assessments should be obtained from each participant as is feasible.

1.3. Sample Size and Power

The total sample size will be at least 52 participants.

Twelve (12) participants for each cohort (Cohorts 1-4) will be enrolled in this study. Pharmacokinetic data from these participants will provide >99% power for each cohort to conclude exposure equivalence of RDV AUC_{tau} in adolescents and children vs. 25 healthy adult participants in GS-US-399-5505 study (see Table 1-2) using two one-sided tests with each performed at an alpha level of 0.05. In this power analysis, it is assumed that the expected geometric mean ratio of AUC_{tau} between the adolescents and children group vs. the adult group is equal to 1, the inter-participant standard deviation (SD) (natural log scale) of AUC_{tau} is 0.18, and the equivalency boundary is 70% to 143%.

Meanwhile, twelve (12) participants from each cohort (Cohorts 1-4) will also provide >99% power to conclude exposure equivalence of RDV C_{max} in adolescents and children, compared to 26 healthy adult participants in GS-US-399-5505 study (see Table 1-2), assuming the expected geometric mean ratio of C_{max} between the adolescents and children group and the adult group is equal to 1, the inter-participant SD (natural log scale) of C_{max} is 0.19, and the equivalency boundary is 70% to 143%.

Sample size and power calculations were made using the software package nQuery Advisor(R) Version 8.5.

Table 1-2. Remdesivir, Nucleoside Metabolite GS-441524, and GS-704277 Plasma PK Parameters by Dose Following 30-Minute IV Infusion(s) of Remdesivir in Healthy Adult Participants in GS-US-399-5505

Study	**GS-US-399-5505**		
PK Parameter[a]	Multiple RDV Dose (100mg) Day 5 and 10 **N = 26[b]**		
Plasma RDV	Remdesivir	GS-441524 Metabolite	GS-704277 Metabolite
C_{max} (ng/mL)	2228.8 (19.2)	145.0 (19.3)	245.5 (33.9)
C_{tau} (ng/mL)	--	69.2 (18.2)	--
C_{last} (ng/mL)	8.1 (46.9)	12.2 (50.0)	3.9 (27.5)
T_{max} (h)	0.68 (0.25, 0.75)	1.51 (1.50, 2.00)	0.75 (0.75, 0.78)
T_{last} (h)	4.00 (4.00, 4.02)	96.00 (96.00, 96.00)	8.00 (8.00, 8.00)
$t_{1/2}$ (h)[d]	0.96 (0.86, 1.08)	27.36 (25.29, 30.32)	1.23 (1.15, 1.38)
AUC_{last} (h·ng/mL)	1562.8 (17.0)	4189.3 (17.7)	454.4 (31.8)
AUC_{tau} (h·ng/mL)	1585.3 (16.6)	2229.2 (18.4)	461.5 (31.4)
CL_{ss} (mL/h)	65068.7 (19.8)	--	--
V_z (mL)	92557.2 (29.5)	--	--

% CV = percentage coefficient of variation; IV = intravenous; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir (GS-5734™)
Certain parameters are missing since Lambda_z is not reliably estimable.
a Data are presented as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3).
b N = 25 for AUC_{tau}, $t_{1/2}$, CLss, and Vz
c N = 25 for C_{tau} and N = 20 for $t_{1/2}$
Source: GS-US-399-5505 Final CSR Table 15.10.1.1.6.1, 15.10.1.1.6.3, 15.10.1.1.6.2, 15.10.1.1.6.4.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

Prior to the final analysis, an interim analysis was conducted to support the submission of applications to extend the indication for RDV to include pediatric participants 28 days of age and older weighing at least 3kg. The interim analysis was performed after (i) all participants in Cohorts 1-4 had been enrolled and had completed the study or prematurely discontinued from the study, (ii) participants in Cohort 8 as of the last date of enrolment into Cohorts 1-4 had completed the study or prematurely discontinued from the study, (iii) outstanding data queries had been resolved or adjudicated as unresolvable, and (iv) the data had been cleaned and finalized.

The Interim Analysis Plan (IAP) describes the analysis plan for the Cohorts 1-4 and 8 interim analysis.

2.1.1. DMC Analysis

An external multidisciplinary Data Monitoring Committee (DMC) reviewed safety, PK, and efficacy data after the first 27 enrolled participants in Cohorts 1-4 had completed the study or prematurely discontinued from the study.

The DMC reviewed the safety, PK, and efficacy data and determined that the study could continue according to the protocol without modification. More details are documented in the DMC charter.

2.2. Final Analysis

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, SD or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented. For PK analyses, the geometric mean, 95% confidence interval (CI) of the geometric mean, and the mean and SD of the natural log-transformed values will also be provided, if appropriate.

By-participant listings will be presented for all participants in the All Enrolled Analysis Set and sorted by subject identifier (ID) number, visit date, and time (if applicable). Data collected on log forms, such as adverse events (AEs), will be presented in chronological order within the participant. The cohort group to which participants were initially assigned 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. Participants included in each analysis set will be determined before database finalization for final analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

A summary of the number and percentage of participants in each analysis set will be provided by cohort and overall total.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all participants who are enrolled into the study. This is the primary analysis set for by-participant listings.

3.1.2. Full Analysis Set

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

3.1.4. Pharmacokinetic Analysis Set

The RDV PK analysis set includes all enrolled participants who received at least 1 dose of RDV and for whom PK concentrations of RDV are available.

The Metabolites (GS-441524 and GS-704277) PK analysis set includes all enrolled participants who received at least 1 dose of RDV and for whom PK concentrations of metabolite(s) (analytes) are available.

The SBECD PK analysis set includes all enrolled participants who received at least 1 dose of RDV and for whom PK concentrations of SBECD are available.

3.2. Subject Grouping

Participants will be analyzed based on the cohort group to which they were initially assigned as well as overall.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling participants.
No covariates will be included in efficacy and safety analyses.

3.4. Examination of Subject Subgroups

There are no prespecified subject 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.

Missing pre-treatment laboratory results will be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary. 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 7.4.

3.6.2. Outliers

Outliers 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, unless specified otherwise.

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 (in years) 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 (e.g., 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.

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

- A value that is 1 unit less than the lower LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, 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 LOQ but have a positive signal will be reported as "< LOQ SARS-CoV-2 detected" and those negative results will be reported as "No SARS-CoV-2 detected". The data will be imputed as follows:

- A value of half of the LOQ will be used to calculate descriptive statistics if the datum is reported as "< LOQ SARS-CoV-2 detected".

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

Refer to Table 13-3 for more details on the viral load samples LOQ and LOD. Participants with negative viral load at baseline are not included in the viral load analysis.

Any SARS-CoV-2 viral load samples collected on or after the participants are receiving additional COVID-19 treatments (see Table 13-1) will be excluded from the viral load analysis.

For participants who had received IV RDV prior to the enrollment of this study, their viral loads will be excluded from the analysis.

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

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/ First Dose Date is the day of first dose of study drug administration, as recorded on the Study Drug Administration eCRF.

Last Dose Date is defined as the maximum, nonmissing, nonzero dose end date of treatment recorded on the Study Drug Administration eCRF form with "Study Drug Permanently Withdrawn" box checked for participants who prematurely discontinued or completed study drug according to the Study Drug Completion eCRF. Refer to Section 12 for missing date imputation, if necessary.

Last Study Date is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for participants who prematurely discontinued study according to the Study Completion eCRF.

Baseline value is defined as the last nonmissing value obtained on or prior to the first dose date (and time, if available) unless otherwise specified.

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 vital signs, respiratory, hematology and chemistry laboratory parameters are presented in Table 3-1 and Table 3-2.

Table 3-1. Analysis Windows for Vital Signs (Heart Rate, Temperature, Blood Pressure [MAP if available, Systolic and Diastolic], Respiratory Rate, and Oxygen Saturation)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline/Day 1	1		1
Day 2	2	2	2
Day 3	3	3	3
Day 4	4	4	4
Day 5	5	5	5
Day 6	6	6	6
Day 7	7	7	7
Day 8	8	8	8
Day 9	9	9	9
Day 10	10	10	10
Day 30	30	25	35

Table 3-2. Analysis Windows for Hematology, Chemistry, Urinalysis, and Routine Coagulation Tests

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline/Day 1	1		1 (pre dose)*
Day 2	2	1 (post dose)*	3
Day 5	5	4	6
Day 8	8	7	8
Day 10	10	9	11
Day 30 **	30	25	35

* For Baseline, the upper limit includes values collected at or prior to the first dose date/time. For Day 2, the lower limit includes values collected after the first dose date/time on Day 1.
** Only the comprehensive metabolic panel will be collected on Day 30

Nasopharyngeal and oropharyngeal samples (combined) OR nasal and oropharyngeal samples (combined), and rectal or fecal swab will be collected on Days 1, 3, 5, 7, and 10 (if feasible) for SARS-CoV-2 reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) viral load testing and possible viral resistance testing. Endotracheal tube aspirates will also be collected if the particpant is intubated. If the participant is discharged prior to Day 10, the samples for SARS-CoV-2 RTqPCR viral load testing and possible viral resistance testing can be collected by assigned study staff at the participant's home or as an outpatient on the assigned days noted above, if feasible.

Serum for SARS-CoV-2 IgG, IgM, and IgA serology will be collected at Screening, Day 5, Day 10 (if feasible), and the Day 30 Follow-up visit for participants with weight ≥ 12 kg.

The analysis windows for SARS-CoV-2 RT-qPCR viral load and serology for SARS-CoV-2 are presented in Table 3-3 and Table 3-4.

Table 3-3. Analysis Windows for SARS-CoV-2 RT-qPCR Viral Load Testing

Visit ID	Testing	Nominal Day	Lower Limit	Upper Limit
Baseline/Day 1	SARS-CoV-2 RT-qPCR viral load	1		1 (pre dose)
Day 3	SARS-CoV-2 RT-qPCR viral load	3	2	3
Day 5	SARS-CoV-2 RT-qPCR viral load	5	4	5
Day 7	SARS-CoV-2 RT-qPCR viral load	7	6	8
Day 10	SARS-CoV-2 RT-qPCR viral load	10	9	11
Discharge*	SARS-CoV-2 RT-qPCR viral load	Day of discharge		

* If the participant is discharged prior to Day 10, the SARS-CoV-2 samples/swabs will be collected on the day of discharge. Thereafter, these samples can be collected by assigned study staff at the participant's home or as an outpatient on the assigned days noted above.

Table 3-4. Analysis Windows for Serology for SARS-CoV-2 (IgG, IgM, and IgA)

Visit ID	Testing	Nominal Day	Lower Limit	Upper Limit
Baseline/Day 1#	Serology for SARS-CoV-2 (IgG, IgM, and IgA)	1		1 (pre-dose)
Day 5	Serology for SARS-CoV-2 (IgG, IgM, and IgA)	5	4	6
Day 10	Serology for SARS-CoV-2 (IgG, IgM, and IgA)	10	9	11
Discharge*	Serology for SARS-CoV-2 (IgG, IgM, and IgA)	Day of discharge		
Day 30	Serology for SARS-CoV-2 (IgG, IgM, and IgA)	30	25	35

Includes the serum for SARS-CoV-2 IgG, IgM, and IgA serology collected at Screening.
* If the participant is discharged prior to Day 10, the serology for SARS-CoV-2 will be collected on the day of discharge. Thereafter, these samples can be collected by assigned study staff at the participant's home or as an outpatient on the assigned days noted above.

Clinical scoring using the PEWS (0 to 3 on each of 3 categories) will be recorded at Screening and daily through the duration of dosing. Results will be summarized for each Study Day without windows.

The 7-point Ordinal Scale is an assessment of the clinical status of a given Study day. Each day, the worst (ie, lowest ordinal) score from the previous day will be recorded (ie, on Day 3, the

lowest ordinal score from Day 2 is obtained and recorded for Day 2). Results will be summarized for each Study Day without windows.

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 Study Day or analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis does not require 1 value per Study Day or analysis window.

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

- For baseline, the last nonmissing value on or prior to the first dosing date (and time, if available) of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity for categorical data.

- For postbaseline values (other than PCR negative confirmation):

  — The record collected on the day closest to the nominal day will be selected.

  — If there are 2 days equidistant from the nominal day, the later day will be selected.

  — If there is more than 1 record on the selected day, values will be selected for analysis as follows:

    ■ For PCR, if there is more than 1 record on the selected day, the latest value will be selected. 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 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.

- For postbaseline values of PCR negative confirmation:

  — Use all available data to derive negative confirmation except if there are multiple records on the same day in which case the worst value will be used for negative confirmation for that day.

  — The record closest to the nominal day for that visit will be selected.

  — If there are 2 records that are equidistant from the nominal day, the later record will be selected.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

Key study dates (i.e., first participant screened, first paticipant enrolled, last participant enrolled, and last participant last visit for the CSR) will be provided.

A summary of participant enrollment will be provided by cohort for each country, investigator and overall total. The summary will present the number and percentage of participants enrolled. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

A summary of participant disposition will be provided by cohort and overall total for all screened participants. This summary will present the number of participants screened, the number of participants who met all eligibility criteria but were not enrolled along with the reasons the participants were not enrolled, the number of participants enrolled, the number of participants enrolled but never treated, the number of participants in the Safety Analysis Set, and the number of participants in the FAS.

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

The following by-participant listings will be provided by subject ID number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order)

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by summarizing the number of doses received by cohort and overall total for the Safety Analysis Set.

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

4.3. Protocol Deviations

A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion, or took prohibited medications from Screening to the Day 30 Follow-up visit, including:

- Investigational agents for COVID-19 with direct antiviral effect including approved HIV protease inhibitors such as lopinavir (LPV)/ ritonavir (RTV), chloroquine, interferon, etc.
- Strong inducers of P-glycoprotein (e.g. rifampin, rifabutin, carbamazepine, phenytoin or herbal medications)

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations, and the total number of important protocol deviations by deviation category (e.g., eligibility criteria, informed consent) will be summarized by cohort and overall total for the Safety Analysis Set. A by-participant listing will be provided for those participants with important protocol deviations.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (i.e., age, sex, race, and ethnicity) and baseline characteristics (i.e., body weight [in kg], body weight-for-age z-scores, height [in cm], height-for-age z-scores, body mass index [BMI; in kg/m2], BMI-for-age percentiles, BMI-for-age z-scores) will be summarized by cohort and overall total using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set. No formal statistical testing is planned.

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

5.2. Other Baseline Characteristics

The following other baseline characteristics will be summarized by cohort and overall total using descriptive statistics for continuous variables and number and percentage of participants for categorical variables.

- Oxygen support status at baseline based on the 7-point ordinal scale: (a) invasive mechanical ventilation, (b) non-invasive ventilation or high flow oxygen, (c) low flow oxygen, and (d) room air
- Clinical status (7-point ordinal scale)
- COVID-19 symptoms (respiratory, gastrointestinal, neurological, circulatory, systemic inflammatory response)
- Duration of hospitalization prior to first dose of RDV (days)
- Duration of symptoms prior to first dose of RDV (days)
- SARS-Cov-2 viral load (log10 copies)
- Aspartate aminotransferase (AST) (U/L)
- Alanine aminotransferase (ALT) (U/L)
- Electrocardiogram (ECG) (normal, abnormal [not clinically significant, clinically significant])

- Creatinine (mg/dL)
- Estimated glomerular filtration rate (eGFR) using the Bedside IDMS-traceable Schwartz formula (mL/min/1.73 m^2)

The summary of these baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

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

5.3. Medical History

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

A summary table will present the number and percentage of participants reporting each medical history preferred term, sorted first in alphabetical order by system organ class (SOC) and then by preferred term (PT) in descending order of total frequency within SOC for each cohort and overall total for the Safety Analysis Set. No formal statistical testing is planned.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

There is no primary efficacy endpoint in this study.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Clinical improvement based on scoring using the 7-point Ordinal Scale

Clinical improvement improvement based on scoring using the 7-point Ordinal Scale will be derived as follows:

- If a participant dies while hospitalized (as recorded on the Death Report eCRF and Hospitalization Information eCRF), the endpoint on the day of death and all subsequent days through Day 10 will be set to Death (=1).
- If the participant is discharged alive, the endpoint on the day of discharge alive and all subsequent days through Day 10 will be set to Not hospitalized (=7).
- If the participant is discharged alive and dies on the same day or a later day (as recorded on the Death Report eCRF and Hospitalization Information eCRF), the endpoint on the day of discharge alive and all subsequent days until the day of death will be set to Not hospitalized (=7). On the day of death and all subsequent days through Day 10, the endpoint will be set to Death (=1).

Every effort will be made to obtain clinical status data for all participants prior to discharge alive. The last known clinical status will be used for days with missing clinical status (eg, where the reason for Hospital Discharge is not “Discharged Alive” and the participant has not died). All postbaseline days with missing ordinal scale score, from Day 2 to Day 10, will use the previous last known clinical status.

Clinical improvement is investigated in two settings:

- $\geq$ 1 point improvement from baseline clinical status or discharged alive
- $\geq$ 2-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale

Recovery is defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7.

Clinical improvement based on scoring using the PEWS Improvement Scale

Clinical improvement is investigated in two settings:

- ≥ 1 point improvement from baseline clinical status or discharged alive
- ≥ 2-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale

Recovery is defined as an improvement from a baseline score of 1-3 to a score of 0, or being discharged alive, whichever comes first.

Time (days) to discharge from hospital

- Duration of hospitalization from Day 1 = number of days from first dose to date discharged alive.
- Total duration of hospitalization = number of days from hospital admission to date discharged alive.

Oxygen usage and ventilation modality and settings

Oxygen support status is defined based on the 7-point ordinal scale.

Days to the first confirmed negative PCR result

- Confirmed negative PCR result is defined as 2 consecutive negative PCR results or a negative PCR result at the last available sample for participants who completed or discontinued from this study.

6.2.2. Analysis of Secondary Endpoints

The FAS will be the primary analysis set for secondary efficacy endpoints. No formal statistical testing is planned.

Clinical improvement based on scoring using the 7-point Ordinal Scale

For each cohort and overall total, clinical status and change from Baseline in clinical status by Study Day as well as last available assessment will be summarized by the number and percentage of participants for each category. It should be noted that the main timepoint of interest for this endpoint is Day 10. In addition, a stacked bar chart will also be provided for each cohort and overall total depicting the percentage of participants for each category by Study Day. Furthermore, descriptive statistics for change from Baseline in clinical status by Study Day and last available assessment will also be provided for each cohort and overall total.

Time to clinical improvement (days) will be modelled using a competing risk analysis. The competing event is death. Participants not achieving clinical improvement at the last assessment will be censored on the day of the last clinical assessment. In addition, the cumulative incidence from the competing risk analysis will also be graphically presented. The number and percentage of participants with clinical improvement will also be summarized by cohort and overall total.

Time to ≥ 1-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale will be modelled using a competing risk analysis. The competing event is death. Participants not achieving ≥ 1-point improvement at the last assessment will be censored on the day of the last clinical assessment. In addition, the cumulative incidence from the competing risk analysis will also be graphically presented. Furthermore, the number and percentage of participants with a ≥ 1-point improvement or discharged alive based on the 7-point ordinal scale on Day 2 through Day 10 as well as last available assessment will be summarized by cohort and overall total.

Time to recovery based on the 7-point ordinal scale will be modelled using a competing risk analysis. The competing event is death. Participants not achieving recovery at the last assessment will be censored on the day of the last clinical assessment. In addition, the cumulative incidence from the competing risk analysis will also be graphically presented. Furthermore, the number and percentage of participants with recovery based on the 7-point ordinal scale on Day 2 through Day 10 as well as last available assessment will be summarized by cohort and overall total.

Clinical improvement based on scoring using the PEWS Improvement Scale

For each cohort and overall total, clinical status and change from Baseline in clinical status by Study day will be summarized for the number and percentage of participants for each PEWS improvement scale category (behavior, cardiovascular, respiratory) as well as total score. It should be noted that the main timepoint of interest for this endpoint is Day 10. A stacked bar chart will also be provided for each cohort and overall total for each PEWS improvement scale category (behavior, cardiovascular, respiratory) depicting the percentage of participants for each category by Study Day.

Time to ≥ 2-point improvement or discharged alive will be modelled using a competing risk analysis for each PEWS improvement scale category (behavior, cardiovascular, respiratory). The competing event is death. Participants not achieving ≥ 2-point improvement at the last assessment will be censored on the day of the last clinical assessment. In addition, the cumulative incidence from the competing risk analysis for each PEWS improvement scale category (behavior, cardiovascular, respiratory) will also be graphically presented. The number and percentage of participants with a ≥ 2-point improvement or discharged alive on Day 2 through Day 10 or discharged alive for each PEWS improvement scale category (behavior, cardiovascular, respiratory) will also be summarized by cohort and overall total.

Time to ≥ 1-point improvement or discharged alive will be modelled using a competing risk analysis for each PEWS improvement scale category (behavior, cardiovascular, respiratory). The competing event is death. Participants not achieving ≥ 1-point improvement at the last assessment will be censored on the day of the last clinical assessment. In addition, the

cumulative incidence from the competing risk analysis for each PEWS improvement scale category (behavior, cardiovascular, respiratory) will also be graphically presented. Furthermore, the number and percentage of participants with a ≥ 1-point improvement or discharged alive on Day 2 through Day 10 or discharged alive for each PEWS improvement scale category (behavior, cardiovascular, respiratory) will be summarized by cohort and overall total.

Time to recovery based on the PEWS scale on Day 2 through Day 10, and last available assessment will be modelled using a competing risk analysis for each PEWS improvement scale category (behavior, cardiovascular, respiratory). The competing event is death. Participants not achieving a score of 0 at the last assessment will be censored on the day of the last clinical assessment. In addition, the cumulative incidence from the competing risk analysis for each PEWS improvement scale category (behavior, cardiovascular, respiratory) will also be graphically presented. Furthermore, the number and percentage of paricipants with recovery based on the PEWS scale on Day 2 through Day 10, and last available assessment for each PEWS improvement scale category (behavior, cardiovascular, respiratory) will be summarized by cohort and overall total.

Time (days) to discharge from hospital

Time to discharge from hospital will be modelled using a competing risk analysis. The competing event is death. Participants not discharged from hospital will be censored on the day of the last clinical assessment. In addition, the cumulative incidence from the competing risk analysis will also be graphically presented.

Descriptive statistics for duration of hospitalization from Day 1 and total duration of hospitalization will also be provided for each cohort and overall total. In addition, information on hospitalization status will be summarized for each cohort and overall total. Only participants who are discharged alive on or prior to Day 30 will be included in the duration of hospitalization through Day 30 follow-up visit analysis.

Oxygen usage and ventilation modality and settings

Descriptive statistics will be provided by cohort and overall total for the number of days of oxygen support through discharge alive, death or Day 10 based on the 7-point ordinal scale reported values, including:

- Days on invasive mechanical ventilation
- Days on high flow oxygen devices
- Days requiring low flow supplemental oxygen

As oxygen support status will be collected only while the participant is in the hospital, if a participant is discharged alive and dies afterwards, the participant will be included only in the summary for participants discharged alive.

The shift in oxygen support status from baseline to Days 2 - 10, and last available assessment will also be provided for each cohort and overall total.

Change from baseline in SARS-CoV-2 viral load up to Day 10 or up to the first confirmed negative PCR result (whichever comes first)

Descriptive statistics for viral load and change from baseline in viral load will be provided by cohort and overall total for the following:

- Day of discharge and each study day up to Day 10 or up to the first confirmed negative PCR result (whichever comes first)
- Day of discharge and each study day up to Day 10

Separate summary tables will be provided for each sample type: (a) nasal/oropharyngeal samples, (b) nasopharyngeal/oropharyngeal samples, (c) endotracheal tube (ET) aspirates, and (d) rectal or fecal swabs.

Days to the first confirmed negative PCR result, where confirmed is defined by 2 consecutive negative PCR results

For each cohort and overall total, the number and percentage of participants with:

- At least 1 negative PCR result
- Confirmed negative PCR result

will be summarized separately for each sample type: (a) nasal/oropharyngeal samples, (b) nasopharyngeal/oropharyngeal samples, (c) ET aspirates, and (d) rectal or fecal swabs.

Time to first confirmed negative PCR result will be modelled separately for each sample type: (a) nasal/oropharyngeal samples, (b) nasopharyngeal/oropharyngeal samples, (c) ET aspirates, and (d) rectal or fecal swabs, using a competing risk analysis. The competing event is death. Participants not not achieving a confirmed negative PCR at the last assessment will be censored on the day of the last clinical assessment.

6.3. Exploratory Efficacy Endpoints

6.3.1. Analysis of Exploratory Endpoints

CCI [redacted]

CCI [redacted]

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), PT, and lower-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 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 AEs (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 Patient Safety (PS) Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent AEs (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

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1. Summaries of AE incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number and percentage of participants who experienced at least 1 treatment-emergent AE (TEAE) in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

One of the primary endpoints of the study is the proportion of participants with TEAEs. Therefore, the number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, HLT (if applicable), PT, and cohort:

- TEAEs

For the AE categories described below, summaries will be provided by SOC, PT, and cohort:

- TEAEs with Grade 3 or higher

- TE treatment-related AEs

- TE treatment-related AEs with Grade 3 or higher

- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug
- TE AEs leading to death (i.e., outcome of death)

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetical order of SOC (and HLT within each SOC if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs, TE SAEs, TE treatment-related AEs, and TE treatment-related SAEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All TE treatment-related AEs
- All AEs with severity of Grade 3 or higher
- All SAEs
- All TE treatment-related SAEs
- All Deaths
- All AEs leading to premature discontinuation of study drug

7.1.6.2. Summaries of AE Incidence by Severity

A brief, high-level summary of the number of percentage of participants who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, HLT (if applicable), PT, and treatment group.

For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs by maximum severity

- TE treatment-related AEs by maximum severity

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC (and HLT within each SOC if applicable) and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given participant during the study.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for participants who have permanently discontinued study drug. 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 subject ID number and visit in chronological order for hematology, coagulation, inflammatory markers, serum chemistry, and urinalysis separately. It should be noted that the routine coagulation test will only be done for cohorts 5-7 at Screening and Day 10 or Discharge). Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the DAIDS grading scale will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by cohort for each of the following laboratory categories and tests

- Hematology (Hemoglobin [g/dL]; Hematocrit [%]; Platelet Count [x10^9/L]; WBC [x10^9/L])

- Chemistry (ALT [U/L]; AST [U/L]; Glucose [mg/dL]; Serum Creatinine [mg/dL]; eGFR, Bedside Schwartz [mL/min/1.73m^2])

- Coagulation (Prothrombin Time [PT] [sec]; Activated Partial Thromboplastin Time [aPTT] [sec]; Prothrombin International Normalized Ratio [INR])

as follows:

- Baseline values

- Values at each postbaseline time point

- Change from baseline at each postbaseline time point

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.2.

One of the secondary endpoints is descriptive statistics of bilirubin concentrations in < 14 days old participants. If there are sufficient participants who are < 14 days old in the Safety Analysis Set then descriptive statistics for bilirubin will be repeated for the subset of participants who are < 14 days old when enrolled into their respective cohorts. In addition descriptive statistics for bilirubin will also be provided for the subset of participants who are ≥ 14 days old when enrolled into their respective cohorts. A by-participant listing of bilirubin concentrations will be provided by subject ID number and visit in chronological order for the subset of participants who are < 14 days old as well the subset of participants who are ≥ 14 days old when enrolled into their respective cohorts.

In addition, line plots showing the median (Q1, Q3) change from baseline at each postbaseline time point will also be provided for the following laboratory parameters:

- ALT (U/L)
- AST (U/L)
- Serum creatinine (mg/dL)
- eGFR, using the Bedside IDMS-traceable Schwartz formula (mL/min/1.73 m^2)
- Total bilirubin (mg/dL)

  Note: This will be produced only for participants who are ≥ 14 days old.

7.2.2. 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. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately. The DAIDS scale is available at the following location:

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

7.2.2.1. 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 for 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.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline time point.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values up to 30 days after last dosing date.

A by-participant listing of laboratory abnormalities will be provided by subject 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 displayed.

Abnormalities in coagulation parameters will be graded for INR, PT, and aPTT.

For the INR of prothrombin time 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.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of particpants who were reported to have the following laboratory test values for postbaseline measurements:

- AST > 3 x upper limit of reference range (ULN)
- ALT > 3 x ULN
- AST or ALT > 3 x ULN
- Total bilirubin > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, particpants will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, particpants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of particpants in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of particpants who met at least 1 of the above criteria will be provided.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for body weight and vital signs as follows:

- Baseline value
- Values at each postbaseline analysis visit
- Change from baseline at each postbaseline analysis visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and vital signs measured at unscheduled visits will be included for the baseline value selection. It should be noted that temperature will not be summarized due to different methods of measuring temperature. Oxygen saturation (SpO_2 and PaO_2) will also not be summarized due to collection under different oxygen support statuses.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.2. No formal statistical testing is planned.

A by-participant listing of vital signs will be provided by subject ID number and analysis 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.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a participant took the first dose of study drug.

A summary of prior medications will not be provided.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a participant took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of participants for each cohort. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-participant listing sorted by subject ID number and administration date in chronological order.

7.4.3. COVID-19 Medications Other Than the Study Drug

COVID-19 medications from the first day of first dose of study drug administration until the end of the study will be categorized into the following categories:

- Experimental antiviral
- Immune modulator
- Anti-inflammatory
- Antiviral antibody therapy
- Other medication

Refer to Table 13-1 for the list of COVID-19 medications and the associated categories. It should be noted that a COVID-19 medication may belong to more than one category.

One of the secondary endpoints is the proportion of participants with concomitant use of medications other than RDV for treatment of COVID-19. Therefore, a summary table will present the number and percentages of participants with concomitant use of COVID-19 medications by cohort and overall for the Safety Analysis Set, sorted first by categories and then by PT in descending order of total frequency.

7.5. Electrocardiogram Results

A by-participant listing of ECG results will be provided by subject ID number (in ascending order).

7.6. Other Safety Measures

A by-participant listing will be provided for those participants experiencing pregnancy during the study.

A by-participant listing of chest imaging reslts will also be provided by subject ID number (in ascending order).

7.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

Sparse PK assessments will be conducted in all participants at participating sites. A single PK blood sample is planned to be collected at the following times and visits:

- Cohorts 1-4 and Cohort 8:
  - Day 2: end of infusion (± 15 minutes) and 4 hours (±30 minutes) post end of infusion
  - Day 3: pre-infusion (≤ 60 minutes) and 2 hours (± 15 minutes) post end of infusion
  - CCI
- Cohorts 5, 6 and 7, Day 2 OR Day 3:
  - Day 2: end of infusion (± 15 minutes) and 4 hours (±30 minutes) post end of infusion
  - Day 3: pre-infusion (≤ 60 minutes) and 2 hours (± 15 minutes) post end of infusion

As many of the specified PK time points should be obtained from each participant as is feasible.

8.2. PK Analyses

Concentrations of RDV, the metabolites (GS-441524 and GS-704277), and SBECD in plasma will be determined using validated bioanalytical assays.

The analytes and parameters presented in Table 8-1 will be used to evaluate the PK objectives of the study.

Table 8-1. PK Parameters for Each Analyte

Analytes	Sample Matrix	Parameters
RDV	Plasma	AUC_{0-24} loading dose (h*ng/mL), C_{max} loading dose (ng/mL), AUC_{tau} steady state (h*ng/mL), C_{max} steady state (ng/mL), $t_{1/2}$ steady state (h), CL_{ss} (L/h), V_{ss} (L)
GS-441524	Plasma	AUC_{0-24} loading dose (h*ng/mL), C_{max} loading dose (ng/mL), AUC_{tau} steady state (h*ng/mL), C_{max} steady state (ng/mL), C_{tau} steady state (ng/mL), $t_{1/2}$ steady state (h)
GS-704277	Plasma	AUC_{0-24} loading dose (h*ng/mL), C_{max} loading dose (ng/mL), AUC_{tau} steady state (h*ng/mL), C_{max} steady state (ng/mL), $t_{1/2}$ steady state (h)

8.2.1. Statistical Analysis Methods

Individual participant concentration data for RDV, the metabolites (GS-441524 and GS-704277), and SBECD will be listed and summarized using descriptive statistics. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented by time point. In addition, the geometric mean, 95% CI of the geometric mean, and the mean and SD of the natural log-transformed values will be presented for individual participant PK parameter data.

Individual concentration data listings and summaries will include all participants with concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration below the limit of quantitation (BLQ) will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower LOQ for postdose time points.

The following tables will be provided for each analyte by cohort and overall total:

- Individual participant concentration data and summary statistics
- Individual participant PK parameters and summary statistics

The following figures will be provided for each analyte by cohort and overall total:

- Boxplots of selected PK parameters
  - RDV: AUC_{tau} steady state (h*ng/mL), C_{max} steady state (ng/mL), $t_{1/2}$ steady state (h), CL_{ss} (L/h), V_{ss} (L)
  - GS-441524: AUC_{tau} steady state (h*ng/mL), C_{max} steady state (ng/mL), C_{tau} steady state (ng/mL), $t_{1/2}$ steady state (h)
  - GS-704277: AUC_{tau} steady state (h*ng/mL), C_{max} steady state (ng/mL), $t_{1/2}$ steady state (h)
- PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age will be provided in listings.

9. REFERENCES

GS-US-399-5505 Final Clinical Study Report. A Phase 1, Blinded, Randomized, Placebo-Controlled, Multiple-Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Intravenous Remdesivir in Healthy Volunteers. 09 April 2020. Page 63 – 69.

GS-US-540-5823 Data Monitoring Committee (DMC) Charter. A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Remdesivir (GS 5734™) in Participants from Birth to < 18 Years of Age with COVID-19. 22 June 2020. Page 1 – 35.

GS-US-540-5823 Interim Study Report. A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Remdesivir (GS 5734™) in Participants from Birth to < 18 Years of Age with COVID-19. 04 October 2021.

10. SOFTWARE

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

nQuery Advisor(R) Version 8.5. Statistical Solutions, Cork, Ireland.

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Study Procedures Table

		Administration Period[b]										Follow-up Period
	Screening	Baseline/ Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 30 (± 5 days)
Assent/Parent or Legal Guardian consent	X											
Inclusion/Exclusion criteria	X											
Focused medical history	X											
Documentation of SARS-CoV-2 confirmation by PCR	X											
ECG	X											
Complete or symptom-directed physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[c]	X	X	X	X	X	X	X	X	X	X	X	X
Height/Length	X											X[d]
Head circumference and last recorded Apgar score if < 24 hours of age	X											X[d]
Birth weight and gestational age if < 56 days	X											
Vital signs (heart rate, temperature, blood pressure [MAP if available, systolic and diastolic], respiratory rate, oxygen saturation)	X	X	X	X	X	X	X	X	X	X	X	X
Documented respiratory status	X	X	X	X	X	X	X	X	X	X	X	X

		Administration Period[b]										Follow-up Period
	Screening	Baseline/ Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 30 (± 5 days)
If available, record chest radiographic impression (or other imaging) but not mandatory to perform otherwise	X	X	X	X	X	X	X	X	X	X	X	
Tanner Stage assessment if ≥ 6 years of age		X										
Hematology, chemistry, urinalysis	X		X			X			X		X	X[e]
Routine coagulation test (Days 5 and 10 only for Cohorts 5-6 and Day 10 only for Cohort 7)	X		X			X			X		X	
Inflammatory Markers (D-dimer, Ferritin, qCRP, Procalcitonin, and IL-6)	X		X			X			X		X	
ESR If ≥4 kg (Cohorts 1-4 only)	X		X			X			X		X	
Neonatal bilirubin panel for all neonates < 14 days, and any neonate presenting with jaundice	X										X	
Serology for SARS-CoV-2 if ≥ 12 kg (IgG, IgM, and IgA)[f]	X					X					X	X
Pregnancy test (urine/blood)	X											

	Screening	Administration Period[b]										Follow-up Period
		Baseline/ Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 30 (± 5 days)
Nasopharyngeal and oropharyngeal samples (combined), rectal or fecal swab, and ET aspirates (if intubated) for SARS-CoV-2 PCR testing and possible viral sequencing[f]		X		X		X		X			X	
Pediatric Early Warning Score Improvement Scale[g]	X	X	X	X	X	X	X	X	X	X	X	
Ordinal Scale	X	X	X	X	X	X	X	X	X	X	X	
Plasma PK assessments[h]			X	X		X						
IV RDV administration		X[i]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]												

CoV = coronavirus; CRP = C-reactive protein; ECG = electrocardiogram; ET = endotracheal tube; Ig = immunoglobulin; IV = intravenous; MAP = mean arterial pressure; PK =pharmacokinetic; RDV = remdesivir (GS-5734™); SARS = severe acute respiratory syndrome; TBD = to be determined

a If the Screening and Day 1 visits occur within 24 hours, only the following procedures need to be completed: Tanner Stage assessment and samples for SARS-CoV-2 PCR testing and viral sequencing
b The following evaluations are to be completed on Days 2-10 or until discharge, whichever comes earlier.
c CCI [redacted]
d Record length and head circumference if < 28 days at enrollment.
e Comprehensive metabolic panel (Chemistry 14) only.
f If the subject is discharged prior to Day 10, the Serology for SARS-CoV-2 and SARS-CoV-2 samples/swabs will be collected on the day of discharge. Thereafter, these samples can be collected by assigned study staff at the subject's home or as an outpatient on the assigned days noted above.
g If a subject is on a ventilator, a score of 3 should be given in the respiratory category.
h CCI [redacted]
i IV administration on Day 1 with either IV RDV 200 mg (Cohort 1), IV RDV 5 mg/kg (Cohorts 2-5), or RDV dose TBD (Cohorts 6-7).
j IV administration daily up to Day 10 with either IV RDV 100 mg (Cohort 1), IV RDV 2.5 mg/kg (Cohorts 2-5), or RDV dose TBD (Cohorts 6-7).

k All subjects 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.

l CCI [redacted]

Appendix 2. Pediatric Early Warning Score

	0	1	2	3
Behavior	Playing Appropriate	Sleeping	Irritable	Lethargic **and/or** Confused **and/or** Reduced response to pain
Cardiovascular	Within normal parameters for age Pink **and/or** Capillary refill 1-2 seconds	Tachycardia < 20 above normal for age **and/or** Pale **and/or** Capillary refill 3 seconds	Tachycardia 20-29 above normal for age Gray **and/or** Capillary refill 4 seconds	Tachycardia ≥ 30 above or bradycardia ≥ 10 below normal for age **or** Gray Capillary refill ≥ 5 seconds
Respiratory	Within normal parameters No retractions	Respiratory rate > 10 above normal parameters using accessory muscles **and/or** 30+ %FiO_2 or 3+ L/min	Respiratory rate > 20 above normal parameters and retractions **and/or** 40+ %FiO_2 or 6+ L/min	Respiratory rate ≥ 5 below normal parameters with retractions and grunting **and/or** 50% FiO_2 or 8+ L/min

Appendix 3. Programming Specifications

1) If the age from the Day 1 eCRF is not available, age will be calculated as follows:

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

   a) AGE (years) is calculated from the number of days between the DOB and Study Day 1,

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

   c) Divide the result in (b) by 12,
   AGE = the integer of the result in (c),
   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 non-missing screening date) and have a screening number. For summaries the same participant is counted only once.

3) Screen failure participants are the participants who 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 to.

4) Participants in the All Enrolled Analysis Set are defined as participants enrolled into the study. IXRSRAND is the source to determine whether the participants is enrolled (ie, participant with non-missing ENRDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (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 the participant took at least 1 dose of study drug and assigned as blank if the participant was never dosed.

6) In the disposition table, the reasons for premature discontinuation are displayed in the order as they appear on the eCRF.

7) Body mass index (BMI)

   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.

8) Details of additional COVID-19 medications are provided in table below.

Table 13-1. Additional COVID-19 Medications

Drug name	ATC Code	WHODRUG Preferred Term
Chloroquine	P01BA	CHLOROQUINE
Hydroxychloroquine	P01BA	HYDROXYCHLOROQUINE
Lopinavir/ritonavir	J05AR	LOPINAVIR/RITONAVIR
Ribavirin	J05AP	RIBAVIRIN
Bamlanivimab/Etesevimab	--	BAMLANIVIMAB/ETESEVIMAB
Casirivimab/Imdevimab	--	CASIRIVIMAB/IMDEVIMAB
Molnupiravir	--	MOLNUPIRAVIR

ATC = anatomical therapeutic chemical

Additional medications may be included during final review of concomitant medications prior to data finalization.

9) Grouping on COVID-19 medications other than the study drug

Table 13-2. Grouping on the COVID-19 Medications other than the Study Drug

Standardized Medication Name	Experimental antiviral	Immune modulator	Anti-inflammatory	AntiViral antibody therapy	Other medication
ANAKINRA	N	Y	Y	N	N
AZITHROMYCIN	Y	Y	Y	N	N
BETAMETHASONE	N	Y	Y	N	N
CLARITHROMYCIN	N	N	Y	N	N
CYCLOBENZAPRINE	N	N	N	N	Y
DEXAMETHASONE	N	Y	Y	N	N
DEXAMETHASONE SODIUM PHOSPHATE	N	Y	Y	N	N
DIPHENHYDRAMINE; ZINC ACETATE	N	N	N	N	Y
ENOXAPARIN	N	N	N	N	Y
ENOXAPARIN SODIUM	N	N	N	N	Y
GANCICLOVIR	Y	N	N	N	N
HYDROCORTISONE	N	Y	Y	N	N
HYDROCORTISONE SODIUM SUCCINATE	N	Y	Y	N	N

Standardized Medication Name	Experimental antiviral	Immune modulator	Anti-inflammatory	AntiViral antibody therapy	Other medication
HYDROXYCHLOROQUINE	Y	N	N	N	N
IMMUNOGLOBULIN G HUMAN	N	Y	N	N	N
IMMUNOGLOBULIN HUMAN NORMAL	N	Y	N	N	N
IMMUNOGLOBULINS NOS	N	Y	N	N	N
LEVOFLOXACIN	N	N	N	N	Y
METHYLPREDNISOLONE	N	Y	Y	N	N
ONDANSETRON	N	N	N	N	Y
PLASMA	N	N	N	Y	N
POTASSIUM PHOSPHATE DIBASIC	Y	Y	Y	N	N
POTASSIUM PHOSPHATE DIBASIC;SODIUM PHOSPHATE	Y	Y	Y	N	N
PREDNISOLONE	N	Y	Y	N	N
PREDNISOLONE SODIUM PHOSPHATE	N	Y	Y	N	N
PREDNISONE	N	Y	Y	N	N
REMDESIVIR	N	N	N	N	Y
RITUXIMAB	N	Y	N	N	N
TOCILIZUMAB	N	Y	Y	N	N
ZINC	N	N	N	N	Y

Additional medications may be included during final review of COVID-19 medications other than the study drug prior to data finalization.

10) Graded Laboratory Abnormalities Summary

— The following labels will be used for laboratory abnormalities and Grade 3 or 4 laboratory abnormalities summary tables and listings:

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Basophils	Increase	Basophils (Increased)
	Eosinophils	Increase	Eosinophils (Increased)
	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Lymphocytes	Decrease	Lymphocytes (Decreased)
	Monocytes	Increase	Monocytes (Increased)
	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)
	Calcium	Decrease	Calcium (Decreased)
	Calcium, Ionized	Decrease	Calcium, Ionized (Decreased)
	Creatine Kinase	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	Direct Bilirubin	Increase	Direct Bilirubin (Increased)
	eGFR, Bedside Schwartz	Decrease	eGFR, Bedside Schwartz (Decreased)
	GGT	Increase	GGT (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Serum Carbon Dioxide	Decrease	Serum Carbon Dioxide (Decreased)
	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)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
Coagulation	Prothrombin Time	Increase	Prothrombin Time (Increased)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	Activated Partial Thromboplastin Time	Increase	Activated Partial Thromboplastin Time (Increased)
	Prothrombin Intl. Normalized Ratio	Increase	Prothrombin Intl. Normalized Ratio (Increased)
Urinalysis	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)

11) Lab and blood pressure evaluation

Test	Evaluation
globulin	globulin in g/dL = Total Protein in g/dL – Albumin in g/dL
albumin: globulin (A:G) ratio	A:G (%) = Albumin in g/dL / (Total Protein in g/dL – Albumin in g/dL)
BUN to Creatinine ratio (%)	BUN: SCr (%) = BUN/ SCr, where BUN is Blood Urea Nitrogen (mg/dL); Cr is Creatinine (mg/dL)
eGFR (Bedside IDMS-traceable Schwartz GFR Calculator for Children)	GFR (mL/min/1.73 m²) = (0.413 × Height in cm) / Creatinine in mg/dL
mean arterial pressure (MAP)	mean arterial pressure = diastolic pressure + (1/3) × pulse pressure, where pulse pressure = systolic pressure – diastolic pressure.

12) Confidence Interval (CI) for Single Proportion

- The 95% CI for percentage estimate is calculated based on the Clopper-Pearson exact method.

```
proc freq;
 by cohort;
 tables event/ binomial alpha=0.05;
 exact binomial;
 output out=_ci95 binomial;
run;
```

13) TEAE

Events with Missing Onset Day and/or Month

An event is considered treatment emergent if 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, 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, and

c) End date is as follows:
The (complete) end date is on or after the first dose date, or
The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of study drug, or
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.

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

- Raw measurements will be reported the same as the data captured electronically or on the eCRF.

- Standard deviation and standard error will be reported to one more significant decimal place than the raw measurement.

- Mean, median, minimum, Q1, Q3, maximum, 95% CIs will be reported to the same number of decimal places of the raw measurements.

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

15) Last dose date is not expected to be missing. However, if last dose date is missing due to data issues, it will be imputed using the maximum of non-missing, non-zero dose, study drug start and stop dates.

16) Ordinal scale and oxygen support status

- The Ordinal Scale is an assessment of the clinical status of a given study day. Each day, the worst (ie, lowest ordinal) score from the previous day will be recorded (ie, on Day 3, the lowest ordinal score from Day 2 is obtained and recorded for Day 2). The original Ordinal Scale (A to G) has been converted to a 7-point scale with the associated oxygen support status defined in the following table:

Ordinal Scale		Oxygen Support Status
1	Death	Death
2	Hospitalized, on invasive mechanical ventilation or ECMO	Invasive Mechanical Ventilation
3	Hospitalized, on non-invasive ventilation or high flow oxygen devices	High Flow Oxygen
4	Hospitalized, requiring low flow supplemental oxygen	Low Flow Oxygen
5	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)	Room Air
6	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration)	Room Air
7	Not hospitalized	Discharge

17) Censoring rules for competing risk analysis

- Time to ≥ 2 point improvement and time to ≥ 1 point improvement: if a participant did not experience the event of interest and did not die, the participant was censored at the last non-missing assessment date. Participants who died were considered to have experienced a competing event.

- Time to recovery: Participants not achieving recovery at the last assessment were censored on the day of the last assessment. Participants who died were considered to have experienced a competing event.

- Time to discharge from hospital: Participants not discharge at the last assessment were censored on the day of the last clinical assessment. Participants who died were considered to have experienced a competing event.

18) Details on the LOQ and LOD for the viral load samples are provided below.

Table 13-3. Viral Load Sample Details

Sample type	Limit of quantitation (copies/mL)	Limit of detection (copies/mL)
Nasal/oropharyngeal samples Nasopharyngeal/oropharyngeal samples ET aspirates	1018	925
Rectal or fecal swabs	488	306

19) Quantitative and categorical summary on SARS-CoV2 results and change from baseline in SARS-CoV-2 viral load up to Day 10 or up to the first confirmed negative PCR result (whichever comes first)

- For quantitative summary (e.g., mean viral load, change from baseline etc.), "Inconclusive" SARS-CoV2 result is set to missing

- For categorical SARS-CoV2 summary, 3 categories will be included, i.e. Positive, Inconclusive, Negative

  — Positive = Any numeric result or "< 1018cp/mL SARS-CoV-2 detected" (for Nasal/oropharyngeal samples, Nasopharyngeal/oropharyngeal samples, or ET aspirates) or "< 488cp/mL SARS-CoV-2 detected" (for rectal or fecal swabs)

  — Negative = "No SARS-CoV2 detected"

  — Inconclusive = "Inconclusive"

20) Days to the first confirmed negative PCR result

- Categorical SARS-CoV2 and SARS-CoV2 negative summary will be separated out by sample type. There will be no combined positive or negative category using 2 or 3 sample types.

- Confirmed negative PCR result is defined as 2 consecutive negative results, or negative at last available sample for participants who completed or discontinued from study. Notice 2 negative results from the same day do not equal confirmation.

- For a negative SARS-CoV2 confirmation, "Inconclusive" SARS-CoV2 result will not be considered as missing thus a "Negative" followed by a "Inconclusive" is NOT a confirmed negative PCR result.

- All participants without a confirmed SARS-CoV2 negative result will be censored on the last day with available PCR test results.

GS-US-540-5823_SAP_v1.0_Final_Cohorts_1_to_8

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	22-May-2023 11:23:50
PPD	Global Development Lead (GDL) eSigned	22-May-2023 18:13:26
PPD	Clinical Pharmacology eSigned	24-May-2023 14:33:01