STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment
Name of Test Drug:	Remdesivir (RDV; GS-5734™)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
DAIDS	Division of AIDS
ECMO	extracorporeal membrane oxygenation
eCRF	Electronic case report form
GLPS	Global Patient Safety
HLGT	high-level group term
HLT	high-level term
ID	identification/identifier
LLN	lower limit of normal
LLT	lowest level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PCR	polymerase chain reaction
PK	pharmacokinetic
PT	preferred term
Q1, Q3	first quartile, third quartile
PaO2	partial pressure of oxygen, arterial
RDV	remdesivir
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SMQ	standardized MedDRA queries
SOC	Standard of care
SpO_2	oxygen saturation
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This Phase 3 study is conducted in two parts. In Part A, approximately 600 participants who met all eligibility criteria were randomized in 1:1:1 ratio into one of the three treatment groups (2 remdesivir [RDV] regimens and 1 standard of care [SOC]). Part B starts after Part A is completed and includes up to approximately 1000 participants.

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the analysis of Part B of Study GS-US-540-5774.

This SAP is based on the study protocol Amendment 2.0 dated 29 April 2020 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The purpose of this study is to provide remdesivir (RDV) to participants with moderate COVID-19.

The primary objective of this study is as follows:

- To evaluate the efficacy of 2 RDV regimens compared to standard of care (SOC), with respect to clinical status assessed by a 7-point ordinal scale on Day 11

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of RDV compared to SOC.

1.2. Study Design

This is a Phase 3 randomized, open-label, multicenter study of RDV therapy in participants with moderate COVID-19.

Treatment Groups

For Part A, approximately 600 participants who met all eligibility criteria were randomized in a 1:1:1 ratio into one of the following treatment groups:

- **Treatment Group 1:** continued SOC therapy together with intravenous (IV) RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5
- **Treatment Group 2:** continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10
- **Treatment Group 3:** continued SOC therapy

Part B will be enrolled after enrollment to Part A is complete. In Part B, an additional approximately 1000 new participants who meet all of the eligibility criteria will be enrolled to receive:

Extension Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10.

Key Eligibility Criteria

Participants with COVID-19 confirmed by polymerase chain reaction (PCR) who meet the following criteria:

- Willing and able to provide written informed consent (age ≥18) or assent (age ≥12 to <18, where locally and nationally approved) prior to performing study procedures
- Hospitalized and requiring medical care for COVID-19
- Oxygen saturation (SpO_2) > 94% on room air at screening
- Radiographic evidence of pulmonary infiltrates

Schedule of Assessments

The date of randomization or enrollment is considered Day 1 and it is expected that all randomized or enrolled participants receive their initial dose of RDV on Day 1.

On Days 1 through 14 or until discharge, whichever is earlier, vital signs including respiratory status will be measured and adverse events (AEs) and concomitant medications will be documented. Laboratory testing will be performed according to SOC practice with results for white blood cell (WBC) count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and any SARS-CoV-2 testing being reported to the Sponsor. Clinical status will be recorded on the 7-point ordinal scale for each day.

In addition, even if not performed as standard of care, WBC count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, and AST will be performed at Days 1, 3, 5, 8, 10, and 14 or until discharge, whichever is earlier.

Additional SARS-CoV-2 testing may be conducted at selected sites. At participating sites, nasopharyngeal swab samples will be collected at Days 1, 3, 5, 8, 10, and 14, sent to a central laboratory, and assayed using quantitative reverse transcriptase PCR to quantify SARS-CoV-2

viral load. Pretreatment and posttreatment samples with detectable SARS CoV-2 may be sequenced for resistance monitoring of the viral polymerase gene.

Randomization

For Part A, participants who met eligibility criteria were randomized in a 1:1:1 ratio to 1 of 3 treatment groups on Day 1 using an IWRS, and assigned a subject number. Randomization is not stratified. Part B is not randomized.

Sites

Up to approximately 160 centers globally.

Duration of Treatment

Participants in Part A received study treatment with RDV for 5 days (Treatment Group 1), 10 days (Treatment Group 2) or no RDV (Treatment Group 3). In Part B, Participants will receive 10 days (Extension Treatment Group) of RDV. If the participant is discharged, RDV treatment will end at that time.

Discontinuation Criteria

Study drug dosing in an individual participant will be placed on hold and may be discontinued, following a review of all available clinical data by the medical monitor and discussion with the investigator, if any of the following occurs:

- Any serious adverse event (SAE) or ≥ Grade 3 AE suspected to be related to RDV.
- Any elevations in ALT > 5 × ULN; or ALT > 3 × ULN and total bilirubin > 2 × ULN, confirmed by immediate repeat testing
- Creatinine clearance < 30 mL/min

End of Study

The end of the study will be the last participant's last observation (or visit).

1.3. Sample Size and Power

In Part A, a total of approximately 600 participants were randomized in a 1:1:1 ratio to 3 treatment groups (200 participants per group).

The sample size computation was based on an assumed distribution of the 7-point ordinal scale on Day 11 for the Part A SOC treatment group. The odds ratio represents the odds of improvement in the 7-point ordinal scale for an RDV treatment group relative to the SOC treatment group. The sample size needed to detect a given odds ratio for a 1:1 randomization using a 2-tailed test at level α is given by:

$$12\ (z_{\alpha/2} + z_{\beta})^2\ /\ \theta^2(1 - \sum_{i=1}^{7} \rho_i^3)$$

Where θ is the log odds ratio, ρ_i is the overall probability (combined over SOC and either RDV treatment groups) of being in the *i*th category of the ordinal outcome, and $z_{\alpha/2}$ and z_{β} are the 1- α /2 and β quantiles of the standard normal distribution {Whitehead 1993}.

A sample size of 600 participants (200 in each group) achieves > 85% power to detect an odds ratio of 1.8 using a two-sided significance level of 0.05 for comparing each RDV treatment group (Treatment Group 1 and 2, n 200) to SOC treatment group (Treatment Group 3, n 200). In this sample size calculation, it is assumed that the probability distribution of the ordinal scale at Day 11 for Treatment Group 3 is as follows:

1. Death, 0.5%
2. Hospitalized, on invasive mechanical ventilation or ECMO, 2.5%
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices, 7%
4. Hospitalized, requiring low flow supplemental oxygen, 8%
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 15%
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration), 27%
7. Not hospitalized, 40%

The sample size calculation was performed using software PASS (Version 14.0).

The sample size for Part B is based on the anticipated need for RDV and current trends in the COVID-19 epidemic.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Data Monitoring Committee Analysis

The data monitoring committee reviewed the results from the primary analysis.

2.1.2. Primary Analysis

The primary analysis was performed after data were available from participants in Part A of the study who completed 11 days or prematurely terminated from Part A of the study on or prior to Day 11. This analysis was described in the Part A Primary Analysis SAP dated 25 May 2020. This is considered as the primary analysis of the study, but most of the analyses were repeated in the Part A Final Analysis.

2.1.3. Part A Final Analysis

The final analysis for participants randomized in Part A was performed after all these participants completed Part A of the study or prematurely terminated from Part A of the study.

2.2. Final Analysis

The final analysis for this study will be performed after all participants have completed Part B of the study or prematurely terminated from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. This SAP describes the statistical analysis methods and data presentations to be used for the analysis of Part B.

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, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all participants in the All Enrolled Analysis Set unless otherwise specified, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within a participant.

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. The analysis set will be 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.

3.1.1. All Enrolled Analysis Set

The **All Enrolled Analysis Set** will include all participants who are enrolled into Part B of the study. This is the primary analysis set for by-subject listings.

3.1.2. Expanded RDV Analysis Set

The primary analysis set for efficacy and safety analysis is defined as the **Expanded RDV-Treated Analysis Set**, which will include all participants who (1) are enrolled into Part B of the study and (2) have received at least 1 dose of RDV.

3.2. Subject Grouping

All participants enrolled into Part B of the study are in the Extension Treatment Group.

3.3. Strata and Covariates

No formal statistical testing will be performed in the analysis of Part B of the study; therefore, no covariates are planned.

3.4. Examination of Subject Subgroups

3.4.1. Subject Subgroups for Efficacy Analyses

Selected efficacy endpoints will be analyzed for the following participant subgroups:

- Age (years): (a) < 65 and (b) ≥ 65
- Sex at birth: (a) male and (b) female
- Baseline oxygen support status (based on the 7-point ordinal scale): (a) low flow oxygen, and (b) room air (See Appendix 2)
- Race: (a) Asian, (b) Black, (c) White and (d) Other. Other includes all races (including Not Permitted) other than Asian, Black and White
- Region: (a) North America, (b) Europe, and (c) Asia.

3.4.2. Subject Subgroups for Safety Analyses

Incidence of all treatment-emergent AEs (TEAEs) will be summarized for the following participant subgroups:

- Age (years): (a) < 65 and (b) ≥ 65
- Sex at birth: (a) male and (b) female
- Baseline oxygen support status based on the 7-point ordinal scale: (a) low flow oxygen, and (b) room air (See Appendix 2)
- Race: (a) Asian, (b) Black, (c) White and (d) Other. Other includes all races (including Not Permitted) other than Asian, Black and White
- Region: (a) North America, (b) Europe, and (c) Asia.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in the analysis of Part B of the study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

Missing data can have an impact upon the interpretation of trial data. In general, values for missing data will not be imputed, unless methods for handling missing data are specified.

In this study, a missing pre-treatment laboratory result 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 7.2.5.2, and for prior and concomitant medications in Section 7.5.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes, unless specified otherwise. All data will be included in the analyses.

3.7. Data Handling Conventions and Transformations

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 first dose 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.

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

- The 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 LOQ).

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study Day 1 is defined as the first dosing date of study drug.

Study Days are calculated relative to Study Day 1 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 form.

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 Appendix 2 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, the laboratory visit dates including the 28-day follow-up visit date, and the death date (if applicable, only for participants who prematurely discontinued study according to the Study Completion eCRF).

Baseline value is defined as the last value obtained on or prior to the first dose date (and time, if available) 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 purposes of analysis, observations will be assigned to analysis windows. The study day as defined in Section 3.8.1 will be used when data are summarized by visit.

Vital signs were to be collected daily; therefore, windows are not assigned and results will be summarized for each Study Day, except for Study Day 28. For Study Day 28, the nominal day is Study Day 28, the lower limit is Study Day 15 and there is no upper limit.

Ordinal scale results were to be recorded prior to dosing on Study Day 1. The worst result for each day from Day 1 (after first dose) through the earliest of discharge date or Day 14 was to be recorded. For participants who were discharged after Day 14, changes in score category were to be recorded each day from Day 15 to the earliest of discharge date or Day 28. For the ordinal scale, baseline is defined as the value recorded prior to dosing, or the last value obtained prior to the first dose date if the predose value was not recorded on the day of dosing. Results will be summarized for each Study Day without windows. If more than one result was reported on the same day, the worst result will be selected.

The analysis windows for hematology and chemistry laboratory parameters are presented in Table 3-1.

Table 3-1. Analysis Windows for Hematology and Chemistry Laboratory Tests (hemoglobin, hematocrit, platelet count, WBC, ALT, AST, total bilirubin, glucose, serum creatinine, and creatinine clearance)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline/Day 1	1		1 (predose)*
Day 3	3	1 (postdose)*	3
Day 5	5	4	6
Day 8	8	7	8
Day 10	10	9	11
Day 14	14	12	15
Post Day 14**	28	16	

* For Baseline, the upper limit includes values collected at or prior to the first dose date/time. For Day 3, the lower limit includes values collected after the first dose date/time on Day 1.
** Post Day 14 laboratory values will be considered for treatment emergent laboratory presentations only.

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

Depending on the statistical analysis method, single values may be required for each Study Day/ 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:

  For windows spanning multiple days, the record(s) 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.

  - For laboratory values and SpO2 and partial pressure of oxygen, arterial (PaO2), if there is more than 1 record on the selected day, the worst value will be selected. See Appendix 2 for definition of worst value.
  - 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. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

The number and percentage of participants enrolled at each investigator site will be summarized using the Expanded RDV-Treated Analysis Set. The denominator for this calculation will be the number of participants in the Expanded RDV-Treated Analysis Set.

The summary of subject disposition will be provided for all screened participants. This summary will include the number of participants screened, screen failure participants who were not enrolled, participants who met all eligibility criteria and were not enrolled, participants enrolled, participants enrolled but never treated, and participants in the Expanded RDV-Treated Analysis Set.

In addition, the number and percentage of the participants in the following categories will be summarized:

- Completed 10-day treatment on study drug as recorded on the Study Drug Completion form
- Prematurely discontinuing study drug prior to completion of 10 days of dosing with summary of reasons for discontinuing study drug as recorded on the Study Drug Completion form
- Completed study
- Prematurely discontinuing from study with summary of reasons for discontinuing study as recorded on the Study Completion form.

The denominator for the percentages of participants in each category will be the number of participants in the Expanded RDV-Treated Analysis Set.

A data listing of reasons for study drug/study discontinuation will be provided.

4.2. Extent of Study Drug Exposure

4.2.1. Exposure to Study Drug

Number of doses received will be summarized for participants in the Expanded RDV-Treated Analysis Set.

4.3. Protocol Deviations

A listing will be provided for all enrolled participants who violated at least 1 inclusion or exclusion criterion. The listing will include the criteria not met.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations by deviation reason and the total number of important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized for the Expanded RDV-Treated Analysis Set. A by-subject listing will be provided for those participants with important protocol deviations.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic data (eg, sex, race/ethnicity, and age) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of participants for categorical data. The summaries of demographic data and baseline participant characteristics will be provided for the Expanded RDV-Treated Analysis Set.

Age group (< 65 and ≥ 65) will be summarized.

A by-subject demographic listing will be provided.

5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized using descriptive statistics:

- Clinical status (7-point ordinal scale)
- Duration of hospitalization prior to first dose of RDV
- Duration of symptoms prior to first dose of RDV
- AST
- ALT
- Oxygen support status based on the 7-point ordinal scale (low-flow oxygen, room air)
- Region (North America, Europe, Asia)

5.3. Medical History

Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is considered to be preexisting and should be documented as medical history. General medical history data will be collected at screening and coded using MedDRA. A summary table will present the percentages of participants reporting each medical history preferred term, sorted first in alphabetical order by system organ class and then by preferred term (PT) in descending order of total frequency within system organ class. Preferred terms with the same total frequency will be sorted in alphabetical order.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

The primary efficacy endpoint was analyzed for Part A of the study and is not described in this SAP.

6.2. Efficacy Endpoints of Interest

Efficacy endpoints of interest include endpoints based on clinical status assessed by a 7-point ordinal scale. The endpoint will be derived by combining the available death, hospital discharge alive and ordinal scale assessment reported by the site, where death supersedes discharge alive and discharge alive supersedes the ordinal scale score reported by the site. The proportion of participants for each ordinal scale category is expressed as percentages for presentation purpose.

Sites were instructed to report the worst ordinal scale category for each day. Therefore, the ordinal scale result on the day the participant was discharged alive does not necessarily reflect Not hospitalized (7). The definition of clinical status based on the 7-point ordinal scale is defined as follows:

- If a participant dies while hospitalized (as recorded on the Death eCRF and Hospitalization eCRF), the endpoint on the day of death and all subsequent days through Day 28 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 28 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 eCRF and Hospitalization 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 28, 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 post-baseline days with missing ordinal scale score, from Day 2 to Day 14 and Day 28, will use the previous last known clinical status.

Efficacy endpoints of interest include

- Clinical status on Days 1 to 14, Day 28 and last available assessment
- Change in clinical status on Days 5, 7, 11, 14, 28, and last available assessment
- Time to clinical improvement (days): Clinical improvement is defined as a ≥ 2-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale using the definition specified above.

- Percentage of participants with a ≥ 2-point improvement or discharged alive based on the 7-point ordinal scale using the definition specified above on Day 5, Day 7, Day 11, Day 14, Day 28, and last available assessment

- Time to ≥ 1-point improvement (days) from baseline clinical status on the 7-point ordinal scale using the definition specified above.

- Percentage of participants with a ≥ 1-point improvement based on the 7-point ordinal scale using the definition specified above on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment

- Time to recovery based on the 7-point ordinal scale using the definition above, where 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

- Percentage of participants with recovery based on the 7-point ordinal scale using the definition specified above on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment

- Number of days of oxygen support while hospitalized through discharge alive, death or Day 14 based on the 7-point ordinal scale reported values (See Appendix 2). This summary will present results separately for participants who died on or prior to Day 14 and those who were discharged alive on or prior to Day 14 and will include:

    Days on invasive mechanical ventilation

    Days on high-flow oxygen devices

    Days requiring low-flow supplemental oxygen

Because oxygen support status was collected only while the participant was in the hospital, if a participant was discharged alive and died afterwards, the participant will be included only in the summary for participants discharged alive. Oxygen support status is defined based on the 7-point ordinal scale (See Appendix 2)

- Shift in oxygen support status from baseline to Days 5, 7, 11, 14, 28 and last available assessment

- Duration of hospitalization (days) (duration from hospital admission and duration from Day 1). Duration of hospitalization is calculated through Days 11 and 28 for participants who were discharged alive prior to Days 11 and 28, respectively. If participants were rehospitalized for COVID-19 related reasons, the hospitalization discharge information is entered in the eCRF database using the latest hospitalization admission.

- All-cause mortality

6.2.1. Analysis of Efficacy Endpoints of Interest

The number and percentage of participants in each clinical status category for each day from Baseline through Day 14 and at Day 28 and using the last available assessment will be summarized. These results will be summarized using (1) the clinical status definition in Section 6.2 and (2) with the definition specified in Section 6.2 but excluding days with missing ordinal scale score not due to death or discharge alive. In addition, stacked bar charts by study day (Baseline through Day 14 and at Day 28) will be produced using the definition specified in Section 6.2.

The number and percentage of participants in each clinical status category for each day from Baseline through Day 14 and at Day 28 and last available assessment will be summarized within each subgroup defined in Section 3.4.1.

The change from baseline in clinical status category on Days 5, 7, 11, 14, 28 and last available assessment will be summarized by group using descriptive statistics.

Number of days of oxygen support status modes (invasive mechanical ventilation, high flow oxygen, low flow oxygen) will be calculated as the number of days oxygen support was reported on the 7-point ordinal scale eCRF through death, discharge alive, or Day 14 and presented using descriptive statistics.

A shift table of baseline oxygen support status (death, invasive mechanical ventilation, high flow oxygen, low flow oxygen, room air, discharge alive) to Days 5, 7, 11, 14, 28 and the last available status will be included.

Duration of hospitalization will be calculated only for participants who are discharged alive on or prior to Days 11 and 28 and will be summarized using descriptive statistics.

All-cause mortality will be estimated using the Kaplan-Meier product limit method with all available data. Participants who did not die will be censored at the last study day.

Days to clinical improvement and days to recovery will be estimated using a competing risk analysis approach, with death as the competing risk. Participants without the endpoint being analyzed will be censored on the day of the last non-missing ordinal scale assessment.

Forest plots by subgroup will be presented for cumulative incidence of recovery on Day 28.

The number and percent of participants with ≥ 1-point improvement, ≥ 2-point improvement, and recovery will be presented with 95% confidence intervals on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment.

Analyses will be performed using the Expanded RDV-Treated Analysis Set.

6.3. Changes from Protocol-Specified Efficacy Analyses

There are no changes from the protocol-specified efficacy analysis.

7. SAFETY ANALYSES

Safety data will be summarized for the participants in the Expanded RDV-Treated Analysis Set. All safety data collected on or after the date that study drug was first dispensed through 30 days after last dose will be summarized for the Expanded RDV-Treated Analysis Set, unless specified otherwise. All safety data will be included in data listings.

7.1. Endpoint of Interest

The proportion of participants with any treatment emergent adverse events in the Extension Treatment Group, an endpoint of interest, will be summarized.

7.2. Adverse Events and Deaths

7.2.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using MedDRA. System organ class, high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.2.2. 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 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening) or Grade 5 (fatal) according to toxicity criteria specified in the document above. The severity grade of events for which the investigator did not record severity will be left as “missing” for data listings.

7.2.3. 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.” Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.2.4. Serious Adverse Events

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

7.2.5. Treatment-Emergent Adverse Events

7.2.5.1. 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.

7.2.5.2. 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 month and year (or year) of 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 month and year (or year) of the AE onset 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 marked as ongoing or on or after 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.

7.2.6. Summaries of Adverse Events and Deaths

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by system organ class, HLT, and PT. For other AEs described below, summaries will be provided by system organ class and PT using the Expanded RDV-Treated Analysis Set:

- Grade 3 or higher treatment-emergent AEs
- All treatment-emergent study drug-related AEs
- Grade 3 or higher treatment-emergent study drug-related AEs
- All treatment-emergent SAEs
- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs that caused premature discontinuation from study drug
- Treatment-emergent deaths

A brief, high-level summary of AEs described above will be provided by the number and percentage of participants who experienced the above AEs. Treatment-emergent deaths observed in the study will also be included in this summary.

Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of system organ class and HLT within each system organ class (if applicable), and then by PT in descending order of total frequency within each system organ class. 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 treatment-emergent AEs, treatment-emergent AEs with Grade 3 or higher, treatment-emergent study drug-related AEs, treatment-emergent study drug-related AEs with Grade 3 or higher, and treatment-emergent SAEs will be summarized by PT only, in descending order of total frequency. Preferred terms with the same total frequency will be sorted in alphabetical order. Treatment-emergent AEs and study-drug related treatment-emergent AEs will also be summarized by highest grade.

Data listings will be provided for the following:

- All AEs
- Study-Drug-Related AEs
- AEs with severity of Grade 3 or higher
- SAEs
- Study-Drug-Related SAEs
- Deaths
- AEs leading to premature discontinuation of study drug

7.2.7. Additional Analysis of Adverse Events

7.2.7.1. Renal Events

Preferred terms for renal events are from the acute renal failure Standardised MedDRA Query (SMQ). The selected PT listing was provided by GLPS and reviewed by Gilead medical monitors (see details in Appendix 3).

Treatment-emergent renal AEs will be summarized by PT only, in descending order of total frequency. In addition, treatment-emergent renal AEs will be listed.

7.2.7.2. Hepatic Events

Liver function test increased events include ALT increased, AST increased, hepatic enzyme increased, hypertransaminasaemia, liver function test increased, and transaminaseses increased. Preferred terms for hepatic events are from the search term list 'Acute and non-infectious liver events.' The selected PT listing was provided by GLPS and reviewed by Gilead medical monitors (see details in Appendix 4).

Treatment-emergent liver function test increased AEs and hepatic events will be summarized by PT only, in descending order of total frequency. An overall summary of treatment-emergent hepatic AEs will be provided. In addition, treatment-emergent hepatic AEs will be listed.

7.3. 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 Expanded RDV-Treated Analysis Set and will include data collected up to the last dose of study drug plus 30 days. 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-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and PCR separately. Values falling outside of the 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.

7.3.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided for each laboratory test as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window

A baseline laboratory value will be defined as the last nonmissing value obtained on or prior to the date (and time, if applicable) of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits indicated in Appendix 2.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.3.2. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 (July 2017) will be used for assigning 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.

7.3.2.1. 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. 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.

7.3.2.2. Summaries of Laboratory Abnormalities

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

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 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-subject listing of laboratory abnormalities and Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order.

7.4. Body Weight, and Vital Signs

Descriptive statistics will be provided for body weight, and vital signs (including heart rate, respiratory rate, blood pressure) as follows:

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

In the case of multiple values on one Study Day, data will be selected for analysis as described in Section 3.8.3.

Temperature will not be summarized due to different methods of measuring temperature. SpO_2 and PaO_2 will not be summarized due to multiple measures through varying oxygen supplementation methods.

A by-subject listing of body weight, BMI, and vital signs (including heart rate, respiratory rate, temperature, and blood pressure) will be provided by subject ID number and visit in chronological order. Similarly, a by-subject listing of oxygen saturation (including oxygen delivery mode, oxygen concentration, oxygen flow, SpO_2, and PaO_2) will be provided.

7.5. Prior and Concomitant Medications

Concomitant use of traditional herbal treatments including herb sho-saiko-to (or Xiao-Shai-Hu-Tang) or investigational agents with putative antiviral activity for COVID-19 including approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, interferon, etc is prohibited in participants receiving RDV.

Concomitant use of investigational agents such as approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, interferon, etc while receiving RDV is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.

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. 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 name 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 year missing from start date (but with day and/or month) will be considered concomitant unless the stop date is prior to the first dosing date. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

Summaries of concomitant medications will be provided for the Expanded RDV-Treated Analysis Set. Participants with any concomitant medications will be listed.

7.6. Other Safety Measures

A data listing will be provided for participants experiencing pregnancy during the study.

7.7. Subject Subgroup for Safety Endpoints

Incidence of all treatment-emergent AEs will be repeated within each subgroup defined in Section 3.4.2 using the Expanded RDV-Treated Analysis Set.

7.8. Changes from Protocol-Specified Safety Analyses

There are no changes from the protocol-specified safety analysis

8. REFERENCES

Whitehead J. Sample size calculations for ordered categorical data. Stat Med 1993;12 (24):2257-71.

9. SOFTWARE

SAS® Version 9.4 (SAS Institute Inc., Cary, NC.) is to be used for all programming of tables, listings, and figures.

PASS Version 14 (NCSS, LLC, Kaysville, Utah) was used for planned sample size and power calculation.

10. SAP REVISION

Revision Date	Section	Summary of Revision	Reason for Revision

11. APPENDICES

Appendix 1. Study Procedures Table

	Screening	Baseline / Day 1[b]	Day 2	Day 3	Day 4	Day 5	Days 6 and 7	Day 8	Day 9	Day 10	Days 11, 12, and 13	Day 14	Day 28[c] Follow-up (±5 days)
Written Informed Consent	X												
Medical History	X												
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Laboratory Testing	X	X		X		X		X		X		X	
Respiratory Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Ordinal Scale		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X												
CCI													
Virologic Testing[e]		X		X		X		X		X		X	
RDV Dosing for Group 1		X	X	X	X	X							
RDV Dosing for Group 2		X	X	X	X	X	X	X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X

a Includes heart rate, respiratory rate, temperature, blood pressure, SpO_2, and body weight. Body weight collected on Screening and Day 1 and otherwise if available.
b Assessments need not be repeated if performed within 24 hours of screening procedures.
c Day 28 evaluations completed if the visit is conducted in person. Only adverse event and concomitant medications review completed if visit conducted by phone.
CCI
e Virologic (SARS CoV 2) testing for subjects/sites participating in this portion of the study on Days 1, 3, 5, 8, 10, and 14.
Data collection other than adverse events and concomitant medications should stop at Day 14 or discharge, whichever is earlier.

Appendix 2. 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 the protocol the participant was consented to.

4) Participants in the 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 non-missing ENRDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN "Yes" in ENROLL dataset).

5) Treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is as the enrolled treatment if participant took at least 1 dose of study drug and assigned as "Never Dosed" 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) Definition of worst values for laboratory and SpO_2 and PaO_2 results.

Test	Result
ALT	Highest result
AST	Highest result
Creatinine	Highest result
Glucose	Highest result if any >ULN and none <LLN Lowest result if any <LLN and none >ULN Otherwise use the average
Total bilirubin	Highest result
GFR/Creatinine Clearance	Lowest result
Hemoglobin	Lowest result
Hematocrit	Lowest result
Platelet count	Lowest result
WBC	Lowest result
SpO_2	Lowest result
PaO_2	Lowest result

If there are 2 values with the same "worst" numerical result on the same day, the later value is chosen.

9) For demographics tables, "Not Permitted", "Unknown", or missing categories will be excluded from percentage with the exception of Race Category where "Not Permitted" is included in "Other."

10) Confidence Interval for single percentage

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

```
proc freq;
by trt;
tables event/ binomial;
exact binomial;
run;
```

11) Competing risk analysis

EVENT 1 if the participant had the event; EVENT 2 if the participant died prior to having the event, and EVENT 0 if the subject did not have the event and did not die.

SAS code to obtain a cumulative incidence function plot and dataset for further processing for time to first event table:

```
proc lifetest outcif  outcif plots  cif;
strata trt;
time days*event(0) / failcode  1; *Note: this produces data for the event of interest only;
run;
```

SAS code to obtain support tables:

```
proc univariate;
 by trt event;
 var days;
 output pctlpre  P_ min  min max  max pctlpts   10, 25, 50, 75, 90;
run;
```

12) TEAE

Events with Missing Onset Day and/or Month

An event is considered treatment emergent if any of the following 3 criteria are met:

i. 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

ii. 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

iii. 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.

13) 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 for all but hematology and chemistry values.

The precision for reporting numerical values for hematology and chemistry is as follows:

Laboratory category	Laboratory parameter	Number of digits after the decimal place for mean, median, minimum, Q1, Q3, maximum
Hematology	Hemoglobin (g/dL)	1
Hematology	Hematocrit (%)	1
Hematology	Platelet count (x10^9/L)	0
Hematology	WBC (x10^9/L)	2
Chemistry	ALT (U/L)	0
Chemistry	AST (U/L)	0
Chemistry	Total bilirubin (mg/dL)	2
Chemistry	Glucose (mg/dL)	0
Chemistry	Serum creatinine (mg/dL)	2
Chemistry	Creatinine Clearance by Cockcroft-Gault (mL/min)	1

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

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 example, if more than 4 significant digits are provided for the measurement.

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

15) Ordinal scale and oxygen support status

The oxygen support status is derived from the ordinal scale:

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

16) Censoring rules

Time to death: participants are censored at the last known date alive (last study day)

Time to ≥ 2-point improvement, time to ≥ 1-point improvement, time to recovery; if a participant does not experience the event of interest and does not die, the participant is censored at the last non-missing ordinal scale assessment date.

17) 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	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	ALT	Increase	ALT (Increased)
	AST	Increase	AST (Increased)
	Creatinine	Increase	Creatinine (Increased)
	Creatinine Clearance	Decrease	Creatinine Clearance (Decreased)
	Serum Glucose	Increase	Serum Glucose (Hyperglycemia)
	Serum Glucose	Decrease	Serum Glucose (Hypoglycemia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)

Appendix 3. Renal Events

An adverse event record will be flagged as a renal event if its MedDRA PT is included in this pre-specified PT list, which includes all PTs from the broad and narrow search of the acute renal failure SMQ under MedDRA v22.1 provided by GLPS (search name: Acute Renal Failure (SMQ)) and reviewed by Gilead medical monitors.

SMQ Source	Preferred Term
Acute Renal Failure (SMQ)	Albuminuria
	Anuria
	Azotaemia
	Blood creatinine abnormal
	Blood creatinine increased
	Blood urea abnormal
	Blood urea increased
	Creatinine renal clearance decreased
	Glomerular filtration rate abnormal
	Glomerular filtration rate decreased
	Haemodialysis
	Nephritis
	Nephropathy toxic
	Oliguria
	Peritoneal dialysis
	Proteinuria
	Renal failure
	Renal failure neonatal
	Renal transplant
	Renal tubular disorder
	Renal tubular necrosis
	Urea renal clearance decreased
	Tubulointerstitial nephritis
	Oedema due to renal disease
	Renal impairment neonatal
	Neonatal anuria
	Renal tubular dysfunction
	Blood urea nitrogen/creatinine ratio increased
	Haemofiltration

SMQ Source	Preferred Term
	Protein urine present
	Creatinine urine decreased
	Urine output decreased
	Dialysis
	Renal function test abnormal
	Renal impairment
	Hypercreatininaemia
	Continuous haemodiafiltration
	Creatinine renal clearance abnormal
	Kidney injury molecule-1
	Acute kidney injury
	Acute phosphate nephropathy
	Creatinine urine abnormal
	Crystal nephropathy
	Prerenal failure
	Intradialytic parenteral nutrition
	Fractional excretion of sodium
	Hyponatriuria
	Renal tubular injury
	Foetal renal impairment
	Subacute kidney injury
	Neutrophil gelatinase-associated lipocalin increased

Appendix 4. Hepatic Events

An adverse event record will be flagged as a hepatic event if its MedDRA PT is included in this pre-specified PT list, which includes the following 152 PTs for acute and non-infectious liver events under MedDRA v22.1 provided by GLPS (search name: Acute and non-infectious liver events_simple) and reviewed by Gilead medical monitors.

Search Term	Preferred Term
Acute and Non-infectious Liver Events	5'nucleotidase increased
	Acute hepatic failure
	Alanine aminotransferase abnormal
	Alanine aminotransferase increased
	Ammonia abnormal
	Ammonia increased
	Aspartate aminotransferase abnormal
	Aspartate aminotransferase increased
	Asterixis
	Autoimmune hepatitis
	Bilirubin conjugated increased
	Biopsy liver abnormal
	Blood bilirubin increased
	Blood bilirubin unconjugated increased
	Blood cholinesterase abnormal
	Blood cholinesterase decreased
	Blood fibrinogen abnormal
	Blood fibrinogen decreased
	Blood thrombin abnormal
	Blood thrombin decreased
	Blood thromboplastin abnormal
	Blood thromboplastin decreased
	Bromosulphthalein test abnormal
	Cholestasis
	Coagulation factor decreased
	Coagulation factor IX level decreased
	Coagulation factor V level decreased
	Coagulation factor VII level decreased
	Coagulation factor X level decreased

Search Term	Preferred Term
	Coma hepatic
	Gamma-glutamyl transferase abnormal
	Gamma-glutamyl transferase increased
	Hepaplastin abnormal
	Hepaplastin decreased
	Hepatic encephalopathy
	Hepatic failure
	Hepatic function abnormal
	Hepatic necrosis
	Hepatic pain
	Hepatitis
	Hepatitis acute
	Hepatitis cholestatic
	Hepatitis fulminant
	Hepatitis toxic
	Hepatocellular injury
	Hepatomegaly
	Hepatorenal failure
	Hepatorenal syndrome
	Hepatosplenomegaly
	Hepatotoxicity
	Hyperammonaemia
	Hyperbilirubinaemia
	Hypocoagulable state
	Hypoprothrombinaemia
	Icterus index increased
	International normalised ratio abnormal
	International normalised ratio increased
	Jaundice
	Jaundice cholestatic
	Jaundice hepatocellular
	Leucine aminopeptidase increased
	Liver disorder

Search Term	Preferred Term
	Liver function test abnormal
	Liver tenderness
	Protein C decreased
	Prothrombin level abnormal
	Prothrombin level decreased
	Prothrombin time abnormal
	Prothrombin time prolonged
	Prothrombin time ratio increased
	Ultrasound liver abnormal
	Yellow skin
	Cholaemia
	Glutamate dehydrogenase increased
	Antithrombin III decreased
	Urine bilirubin increased
	Protein S decreased
	Hypofibrinogenaemia
	Thrombin time abnormal
	Guanase increased
	Bile output decreased
	Bile output abnormal
	Thrombin time prolonged
	Protein S abnormal
	Hepatopulmonary syndrome
	Foetor hepaticus
	Perihepatic discomfort
	Transaminases increased
	X-ray hepatobiliary abnormal
	Subacute hepatic failure
	Ocular icterus
	Blood bilirubin abnormal
	Hypothrombinaemia
	Hypothromboplastinaemia
	Blood alkaline phosphatase increased

Search Term	Preferred Term
	Blood alkaline phosphatase abnormal
	Galactose elimination capacity test abnormal
	Galactose elimination capacity test decreased
	Hepatic enzyme increased
	Bilirubin excretion disorder
	Coagulation factor IX level abnormal
	Coagulation factor V level abnormal
	Coagulation factor VII level abnormal
	Coagulation factor X level abnormal
	Prothrombin time ratio abnormal
	Liver scan abnormal
	Hepatobiliary disease
	Hepatic enzyme abnormal
	Transaminases abnormal
	Cholestatic pruritus
	Total bile acids increased
	Hepatic infiltration eosinophilic
	Mitochondrial aspartate aminotransferase increased
	Hepatobiliary scan abnormal
	Hepatic encephalopathy prophylaxis
	Mixed liver injury
	Molar ratio of total branched-chain amino acid to tyrosine
	Liver injury
	Bilirubin conjugated abnormal
	Cholestatic liver injury
	Hypertransaminasaemia
	Child-Pugh-Turcotte score increased
	Acquired protein S deficiency
	Urobilinogen urine increased
	Acute yellow liver atrophy
	Allergic hepatitis
	Deficiency of bile secretion
	Drug-induced liver injury

Search Term	Preferred Term
	Parenteral nutrition associated liver disease
	Acquired antithrombin III deficiency
	Hyperfibrinolysis
	Portal tract inflammation
	Liver palpable
	Minimal hepatic encephalopathy
	Hepatic hypertrophy
	Liver dialysis
	Child-Pugh-Turcotte score abnormal
	Model for end stage liver disease score abnormal
	Model for end stage liver disease score increased
	Acute on chronic liver failure
	Bilirubin urine present
	Anti factor X activity abnormal
	Anti factor X activity increased
	Liver function test increased
	Computerised tomogram liver abnormal
	Immune-mediated hepatitis
	Hepatic lymphocytic infiltration
	Acquired factor VIII deficiency
	Acquired factor XI deficiency
	Acquired factor IX deficiency
	AST/ALT ratio abnormal
	Magnetic resonance imaging liver abnormal

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	18-Sep-2020 15:02:08
PPD	Biostatistics eSigned	21-Sep-2020 16:21:23