# STATISTICAL ANALYSIS PLAN

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| **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™) |
| **Study Number:** | GS-US-540-5774 |
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| **Analysis Plan Author(s):** | PPD |

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BIPAP | bilevel positive airway pressure |
| BMI | body mass index |
| CI | confidence interval |
| CPAP | continuous positive airway pressure |
| CRF | case report form |
| CSR | clinical study report |
| DMC | data monitoring committee |
| ECMO | extracorporeal membrane oxygenation |
| ET | early termination |
| FAS | Full Analysis Set |
| Hb | hemoglobin |
| HLT | high-level term |
| ICH | International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use) |
| ITT | intent to treat |
| LTT | lower-level term |
| LOQ | limit of quantitation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PCR | polymerase chain reaction |
| PP | per protocol |
| PT | preferred term |
| Q1, Q3 | first quartile, third quartile |
| RDV | remdesivir |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SOC | standard of care |
| TEAE | treatment-emergent adverse event |
| TFLs | tables, figures, and listings |
| ULN | upper limit of normal |
| WHO | World Health Organization |

# 1. INTRODUCTION

This Phase 3 study is conducted in two parts. In Part A, approximately 600 participants who meet all eligibility criteria may be 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 final analysis of Part A 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-labeled, multi-center study of RDV therapy in participants with moderate COVID-19.

**Treatment Groups**

For Part A, approximately 600 participants who meet all eligibility criteria may be 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 participants who meet all of the eligibility criteria may 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.

If the 5-day dosing regimen used in Treatment Group 1 of Part A is selected for Part B instead of the 10-day dosing regimen, all participants in the Extension Treatment Group and all new participants will be reassigned to receive treatment for a total of 5 days.

**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
- $SpO_2$ > 94% on room air at screening
- Radiographic evidence of pulmonary infiltrates

**Schedule of Assessments**

The date of randomization will be considered Day 1 and all participants randomized to receive RDV should receive their initial dose on Day 1.

On Days 1 through 14 or until discharge, whichever is earlier, 7-point ordinal scale of clinical status, 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 count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing being reported to the Sponsor.

In addition, even if not performed as SOC, white blood cell 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.

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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**

Participants who meet eligibility criteria will be 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 will not be stratified.

**Sites**

Up to approximately 160 centers globally.

**Duration of Treatment**

Participants will receive study treatment with RDV for 5 days (Treatment Group 1), 10 days (Treatment Group 2) or no RDV (Treatment Group 3) in Part A, and either 5 or 10 days (Extension Treatment Group) in Part B. Treatment with RDV will stop if the participant is discharged prior to the end of assigned regimen.

**Discontinuation Criteria**

Study drug dosing in an individual subject 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 will be randomized in a 1:1:1 ratio to 3 treatment groups (200 participants per group).

The sample size computation is based on an assumed distribution of the 7-point ordinal scale on Day 11 for the 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, $\rho_i$ 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 $z_{\beta}$ 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).

# 2. TYPE OF PLANNED ANALYSIS

## 2.1. Interim Analyses

### 2.1.1. DMC Analysis

The DMC will review 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 analysis will be repeated in the Part A Final Analysis.

### 2.1.3. Part A Final Analysis

The final analysis for participants randomized in Part A will be performed after all these participants have completed Part A of the study or prematurely terminated from Part A of 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 Part A Final Analysis.

## 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 (Part A or Part B), outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. There will be a separate SAP for the Final Analysis.

# 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.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

By-subject listings will be presented for all participants in the All Randomized 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 subject. The treatment group to which participants were randomized will be used in the listings.

## 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 the primary analysis. 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 by treatment group and in total.

### 3.1.1. All Randomized Analysis Set

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

### 3.1.2. Full Analysis Set

The primary analysis set for efficacy analysis is defined as the **Full Analysis Set (FAS)**, which will include all participants who (1) are randomized into Part A of the study and (2) have received at least 1 dose of study treatment if randomized to 1 of the RDV treatment groups. Participants in the SOC arm who have had protocol Day 1 visit will be included in the FAS. Participants will be grouped according to the treatment to which they were randomized for Part A (RDV 5-day, RDV 10-day, or SOC).

### 3.1.3. Safety Analysis Set

The primary analysis set for safety analyses is defined as the **Safety Analysis Set**, which will include all participants who (1) are randomized into Part A of the study and (2) have received at least 1 dose of study treatment if randomized to 1 of the RDV treatment groups. Participants in the SOC arm who have had protocol Day 1 visit will be included in the safety analysis set. Participants will be grouped according to the treatment to which they were randomized for Part A (RDV 5-day, RDV 10-day, or SOC).

## 3.2. Subject Grouping

Participants will be grouped by randomized treatment (RDV for 5 days, RDV for 10 days, or SOC), regardless of the actual number of days of treatment.

### 3.2.1. Subject Subgroups for Efficacy Analyses

The primary endpoint will be analyzed for the following participant subgroups:

- Age (years): (a) < 65 and (b) ≥ 65
- Sex at birth: (a) male and (b) female
- Oxygen support status based on the 7-point ordinal scale: (a) invasive mechanical ventilation, (b) high flow oxygen, (c) low flow oxygen, and (d) 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.

### 3.2.2. 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
- Race: (a) Asian, (b) Black, (c) White and (d) Other. Other includes all races (including Not Permitted) other than Asian, Black and White.

## 3.3. Multiple Comparisons

To adjust for multiple comparisons, the primary efficacy analysis was conducted based on Bonferroni method detailed in Section 6.1.3.

## 3.4. Missing Data and Outliers

### 3.4.1. 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 would 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.

### 3.4.2. 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.

## 3.5. 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 Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the randomization 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 or above the upper limit of quantitation 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).

## 3.6. Analysis Visit Windows

### 3.6.1. Definition of Study Day

**Study Day 1/First Dose Date** is defined as follows:

- Participants randomized to RDV 5-day or RDV 10-day treatment groups: Study Day 1/First Dose Date is defined as the day when the first dose of RDV was taken, as recorded on the Study Drug Administration eCRF form.

- Participants randomized to the SOC group: Study Day 1 is defined as the Day 1 visit date recorded on the Visit Date eCRF.

**Study Days** are calculated relative to Study Day 1 and derived as follows:

- For postdose study days: Assessment Date  Study Day 1 + 1
- For days prior to the first dose: Assessment Date  Study Day 1

**Last Dose Date** is defined as follows:

- For participants randomized to RDV 5-day or RDV 10-day treatment groups: 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 data imputation, if necessary.
- For participants randomized to the SOC group: Last Dose Date is defined as missing.

**Last Study Date** is the latest of the study drug start dates and end dates, the clinic visit dates, death date (if applicable), and the laboratory visit dates, including the 28-day follow-up visit date, for participants who permanently 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 3.6.3).

### 3.6.2. Analysis Visit Windows

Subject 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 3.6.2 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 for participants in the RDV treatment groups 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; for participants in the SOC group, the baseline is the value from the record labeled as 'Day 1 Predose' on the Ordinal Scale Assessment eCRF. Results will be summarized for each Study Day without windows.

SARS-CoV-2 PCR results were to be reported (if collected) each day. However, windows in Table 3-1 will be assigned to account for missing data.

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

**Table 3-1. Analysis Windows for PCR and 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(pre dose)* |
| Day 3 | 3 | 1 (post dose)* | 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 summarized for treatment emergent laboratory presentations only

### 3.6.3. 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 would not require 1 value per Study Day/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 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.

  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 selected value will be the highest severity (ie, highest value or positive result).

- For laboratory values (other than PCR) and SpO2 and 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 randomized at each investigator site will be summarized by treatment group (RDV 5-day, RDV 10-day, and SOC) and overall using the Safety Analysis Set. The denominator for this calculation will be the number of participants in the Safety Analysis Set.

The summary of subject disposition will be provided by treatment group (RDV 5-day, RDV 10-day, and SOC) and overall for all screened participants. This summary will include the number of participants screened, screen failure participants who were not randomized, participants who met all eligibility criteria and were not randomized, participants randomized, participants randomized but never treated, participants in the Safety Analysis Set, and participants in the FAS.

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

- Completed 5-day or 10-day treatment on study drug as recorded on the Study Drug Completion form (for Treatment Groups 1 and 2)
- Prematurely discontinued study drug prior to completion of 5 days of dosing (Treatment Group 1) or 10 days of dosing (Treatment Group 2) with summary of reasons for discontinuing study drug as recorded on the Study Drug Completion form
- Completed study
- Prematurely discontinued from study prior to the data cut date (with summary of reasons for discontinuing study) as recorded on the Study Drug Completion form.

The denominator for the percentages of participants in each category will be the number of participants in the Safety Analysis Set.

No inferential statistics will be generated. 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 by treatment group for participants randomized to RDV 5-day or RDV 10-day treatment groups in the Safety Analysis Set.

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier method by treatment group for participants randomized to RDV 5-day or RDV 10-day treatment groups. Participants who completed study drug will be censored at the last dose date.

### 4.2.2. Protocol Deviations

A listing will be provided for all randomized 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 by treatment group (RDV 5-day, RDV 10-day, and SOC) for the FAS. A by-subject listing will be provided for those participants with important protocol deviations.

# 5. BASELINE CHARACTERISTICS

## 5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, sex, race/ethnicity, and age) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized by treatment group and overall 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 subject characteristics will be provided for the Safety Analysis Set.

Age group ($< 50$, $\geq 50$ to $< 65$, $\geq 65$ to $< 75$ and $\geq 75$) will be summarized by treatment group and overall.

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data and row mean scores for ordinal data [age group]) will be used to compare the 3 treatment groups. For continuous data, the 2-sided Kruskal-Wallis test will be used to compare the 3 treatment groups.

A by-subject demographic listing will be provided.

## 5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics:

- Clinical status (7-point ordinal scale)
- Duration of hospitalization prior to Study Day 1
- Duration of symptoms prior to Study Day 1
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Oxygen support status based on the 7-point ordinal scale (invasive mechanical ventilation, high-flow oxygen, low-flow oxygen, room air)

For categorical data, the CMH test (row means scores differerence statistic for ordinal data [oxygen support status]) will be used to compare the 3 treatment groups. For clinical status and continuous data, the 2-sided Kruskal-Wallis test will be used to compare the 3 treatment groups.

## 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. It will be coded, using the current version of MedDRA, and summarized. The 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.

# 6. EFFICACY ANALYSES

## 6.1. Primary Efficacy Endpoint

The analysis of primary efficacy endpoint was done previously, but will be repeated in the Part A Final Analysis for completeness.

### 6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is clinical status assessed by a 7-point ordinal scale on Day 11. The endpoint will be derived by combining the available death, hospital discharge, and ordinal scale assessment reported by the site, where death supersedes discharge and discharge supersedes the ordinal scale score reported by the site. The proportion of participants for each ordinal scale category by treatment group is expressed as percentages for presentation purpose.

Sites were instructed to report the worst ordinal scale category for each day. Therefore, the ordinal scale category on the day the participant was discharged does not necessarily reflect Not hospitalized ( 7). The definition of the 7-point ordinal scale endpoint for the efficacy analyses 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.

### 6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

**Null hypothesis:** The odds of improvement for either the RDV 5-day treatment group (Treatment Group 1) or 10-day treatment group (Treatment Group 2) is the same as the odds of improvement for the SOC treatment group (Treatment Group 3) with respect to clinical status assessed by a 7-point ordinal scale on Day 11.

**Alternative hypothesis:** The odds of improvement for the RDV 5-day treatment group (Treatment Group 1) or 10-day treatment group (Treatment Group 2) is different from the odds of improvement for SOC treatment group (Treatment Group 3) with respect to clinical status assessed by a 7-point ordinal scale on Day 11.

### 6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The primary endpoint will be analyzed using a proportional odds model, to compare each RDV (5-day or 10-day) group with the SOC group, including treatment as the independent variable. A separate model will be provided for each comparison. The odds ratio, 95% confidence interval, and p-value for comparing treaments will be provided. The corresponding SAS code is as following:

```
proc logistic data=example;
class trt(ref='SOC')/ param=ref order=data;
model outcome(descending)= trt;
run;
```

To control for Type I error rate, the statistical significance of RDV treatment effect will be assessed based on the Bonferroni method. Each hypothesis (5-day RDV vs. SOC and 10-day RDV vs. SOC) will be tested at alpha level of 0.025.

The proportion of participants in each category will be summarized by treatment group. The assumption of odds proportionality will be assessed using a score test and reported. The FAS will be the primary analysis set for efficacy endpoint evaluation. The primary endpoint will be analyzed for each of the subgroups defined in Section 3.2.1.

### 6.1.4. Secondary Analysis of the Primary Efficacy Endpoint

As supportive analyses of the primary endpoint, the following will be conducted for each RDV (5-day or 10-day) treatment group compared to the SOC arm:

- The primary endpoint will be analyzed using a proportional odds model including treatment as the independent variable and baseline clinical status as a nominal covariate. Due to small number of participants with baseline clinical status of 3 and 6, those with baseline clinical status of 3 or 4 will be combined into one category and those with baseline clinical status of 5 or 6 will be combined into one category.

- The clinical status at Day 11 will be compared between each RDV (5-day or 10-day) group and the SOC group using a 2-sided Wilcoxon Rank sum test.

The change from baseline on Days 5, 7, 11, 14, 28 and last available assessment in clinical status category will be summarized by treatment groups using descriptive statistics. Change from baseline will be compared between the treatment groups (5-day RDV vs. SOC and 10-day RDV vs. SOC) using a 2-sided Wilcoxon Rank sum test. This analysis will use the primary endpoint as specified in Section 6.1.1.

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 last available assessment will be summarized by treatment group. These results will be summarized using two methods: (1) the clinical status definition specified in Section 6.1.1 and (2) the clinical status definition specified in Section 6.1.1 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 by treatment group using the definition specified in Section 6.1.1.

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 3.2.1. These descriptive summaries will be based on the primary endpoint as specified in Section 6.1.1.

The above analyses will be conducted using the FAS.

## 6.2. Other Endpoints of Interest

The other endpoints of interest include:

- Clinical status assessed by a 7-point ordinal scale on Day 14
- Number and percent of participants with negative SARS-CoV-2 PCR on Days 5 and 10
- Number of days of oxygen support through discharge alive, death, or Day 14 based on clinical status reported values. This summary will present results separately for participants who died on or prior to Day 14 and those who were discharged alive on or before 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 on or prior to Day 14, 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). For the final Part A analysis, duration of hospitalization is calculated through Day 28 for participants who were discharged alive prior to Day 28. 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

The following endpoints are based on the daily assessment of clinical status (7-point ordinal scale) as defined in Section 6.1.1:

- Time to recovery 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
- Proportion of participants with recovery on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment
- Time to modified recovery where modified recovery is defined as an improvement from a baseline score of 2 through 4 to a score of 5, 6, or 7, or an improvement from a baseline score of 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7
- Proportion of participants with modified recovery on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment
- Time to ≥ 2-point improvement from baseline clinical status or discharged alive
- Proportion of participants with a ≥ 2-point improvement on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment
- Time to ≥ 1-point improvement from baseline clinical status
- Proportion of participants with a ≥ 1-point improvement on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment
- Time to room air defined as an improvement from a baseline score of 2 through 4 to a score of 5, 6, or 7
- Proportion of participants with improvement to room air on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment

### 6.2.1. Analysis of Other Endpoints of Interest

Similar to the primary endpoint, each RDV (5-day or 10-day) group will be compared with the SOC group using the FAS. The comparisons with SOC for each endpoint listed in Section 6.2 are detailed in this section.

The clinical status on Day 14 will be analyzed using a proportional odds model including treatment as the independent variable to compare each RDV (5-day or 10-day) group with the SOC group. A separate model will be provided for each comparison. The odds ratio, 95% confidence interval, and p-value for comparing treaments will be provided.

Number and percent of participants with negative SARS-CoV-2 PCR on Days 5 and 10 will be summarized. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided.

Number of days of oxygen support status modes (invasive mechanical ventilation, high flow oxygen, low flow oxygen) will be compared between each RDV (5-day or 10-day) group and the SOC group using the Wilcoxon Rank sum test. Number of days 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.

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 assessment will be included.

Duration of hospitalization will be calculated only for participants who are discharged alive on or prior to Day 28 and will be compared between each RDV (5-day or 10-day) group and the SOC group using the Wilcoxon Rank sum test.

All-cause mortality will be estimated using the Kaplan-Meier product limit method with all available data. Each RDV (5-day or 10-day) group will be compared to the SOC group using the log-rank test, and hazard ratios and 95% confidence intervals will be provided. Participants who did not die will be censored on the last study day.

A competing risk analysis approach will be used to estimate time to i) recovery, ii) modified recovery, iii) $\geq$ 2-point improvement, iv) $\geq$ 1-point improvement, and v) room air, with death considered as the competing risk. The hazard ratio and 95% confidence interval will be provided. Participants without the endpoint being analyzed will be censored on the day of the last non-missing ordinal scale assessment.

The number and percentage of participants with i) recovery, ii) modified recovery, iii) $\geq$ 2-point improvement, iv) $\geq$ 1-point improvement, and v) improvement to room air will be presented with 95% confidence intervals on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided. Comparisons between each RDV (5-day or 10-day) group and the SOC group will be performed using a Fisher's Exact test. Point estimates of treatment differences in percentages and 95% confidence intervals will be provided.

### 6.3. Changes from Protocol-Specified Efficacy Analyses

The protocol stated that the primary endpoint will be analyzed using a proportional odds model including baseline clinical status as a covariate; however, a proportional odds model including treatment as the independent variable (dropping baseline clinical status as a covariate) will be used.

Clinical status on Day 14 was not listed in the protocol but has been added in this SAP as an other endpoint of interest.

# 7. SAFETY ANALYSES

Safety data will be summarized for the participants in the safety analysis set. All safety data collected on or after the date that study drug was first dispensed through 30 days after last dose for the RDV (5-day or 10-day) groups and all safety data collected for the SOC group will be summarized by treatment group for the Safety Analysis Set, unless specified otherwise. All safety data will be included in data listings.

## 7.1. Secondary Endpoint

The secondary endpoint of the proportion of participants with any treatment emergent adverse events will be compared between each RDV (5-day or 10-day) group and the SOC group using a Fisher's Exact test. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided.

## 7.2. Adverse Events and Deaths

### 7.2.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of 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 Pharmacovigilance and Epidemiology (PVE) Department before data finalization.

### 7.2.5. Treatment-Emergent Adverse Events

#### 7.2.5.1. Definition of Treatment-Emergent Adverse Events

For participants randomized to either of the RDV (5-day or 10-day) groups, 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.

For participants randomized to the SOC group, all AEs reported on or after protocol Day 1 visit will be considered as treatment-emergent.

#### 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 for the RDV groups or the protocol Day 1 visit date for the SOC group, 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 for the RDV groups:

- 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

For the SOC group, the event is considered treatment emergent if the month and year (or year) of the AE onset is the same as or after the month and year (or year) of the protocol Day 1 visit date.

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 for the RDV groups or the protocol Day 1 visit date for the SOC group, 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 for participants randomized to the RDV groups, and 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 protocol Day 1 visit date will be considered treatment emergent for participants randomized to the SOC group.

### 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, PT, and treatment group. For other AEs described below, summaries will be provided by system organ class, PT, and treatment group using the Safety Analysis Set:

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

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

For each of the categories, the proportion of participants reporting AEs will be compared between each RDV (5-day or 10-day) group and the SOC group using a Fisher's Exact test. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided.

For participants randomized to either of the RDV (5-day or 10-day) groups, treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive). For participants randomized to the SOC group, all deaths reported on or after protocol Day 1 visit will be considered as treatment-emergent.

Multiple events will be counted only once per subject 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 subject 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 (RDV groups only), treatment-emergent study drug-related AEs with Grade 3 or higher (RDV groups only), and treatment-emergent SAEs will be summarized by PT only, in descending order of total

frequency. Treatment-emergent AEs and study-drug related treatment-emergent AEs (RDV groups only) will also be summarized by highest grade.

Data listings will be provided for the following:

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

## 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 Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for the RDV (5-day or 10-day) groups. For the SOC group all laboratory data will be included. 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 3.2.2.

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 by treatment group for each laboratory test as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window
- Percentage change from baseline to each postbaseline analysis window (if specified)

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 for the RDV (5-day or 10-day) groups. For the SOC group a baseline laboratory value will be defined as the last nonmissing value obtained on or prior to the protocol Day 1 visit date. 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; SD values will be displayed to the reported number of digits plus 1. Baseline and change from baseline will be compared between each RDV (5-day or 10-day) group and the SOC group using the 2-sided Wilcoxon Rank sum test.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.3.

### 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 for either of the RDV (5-day or 10-day) groups. For participants randomized to the SOC group, all postbaseline laboratory abnormalities in this study will be considered as treatment-emergent.

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

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 visit.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by laboratory test and treatment group; 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 for the RDV (5-day or 10-day) groups and the number of participants with nonmissing postbaseline values for the SOC group.

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 by treatment group for body weight, BMI, 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 for the RDV (5-day or 10-day) groups. For the SOC group a baseline value will be defined as the last nonmissing value obtained on or prior to the protocol Day 1 visit date. 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 3.6.3. No formal statistical testing is planned.

Temperature will not be summarized due to different methods of measuring temperature. $SpO_2$ and $PaO_2$ will not be summarized due to collection under different oxygen support statuses.

A by-subject listing of body weight, BMI, and vital signs (including heart rate, respiratory rate, temperature, blood pressure) will be provided by subject ID number and visit in chronological order.

## 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 such as approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, interferon, etc is prohibited in participants receiving RDV.

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 treatment group. 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 for the RDV 5-day or 10-day groups) 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 for the RDV 5-day or 10-day groups) 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 for the RDV 5-day or 10-day groups 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 of concomitant medications will be provided for the Safety Analysis Set. Participants with any concomitant medications will be listed. No inferential statistics will be provided.

### 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 3.2.2 using the safety analysis set.

### 7.8. Changes from Protocol-Specified Safety Analyses

No change from the protocol-specified safety analysis is planned.

# 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 (DD MMM YYYY) | 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[12] 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~~.~~; data collection other than adverse events and concomitant medications should stop at Day 14 or discharge, whichever is earlier.
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.

## 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 protocol the participant was consent to.

4) Participants in the randomized analysis set are defined as participants randomized into the study. IXRSRAND is the source to determine whether the participant is randomized (ie, participant with non-missing RGMNDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN "Yes" in ENROLL dataset).

5) Randomized treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if participant took at least 1 dose of study drug and assigned as blank if the participant was never dosed for RDV groups, and is assigned as the randomized treatment if participant had protocol Day 1 visit and assigned as blank if the participant did not have protocol Day 1 visit for the SOC group.

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<br>Lowest result if any <LLN and none >ULN<br>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) SAS codes for the treatment comparison for demographics and baseline characteristics tables.

CMH test for nominal variable (Y), the p-value from the general association test should be used for nominal variables:

```
proc freq;
tables trt * Y /cmh; /*general association test*/
run;
```

CMH test for ordinal variable (Y), the p-value from the row mean score test should be used for ordinal variables:

```
proc freq;
tables trt * Y / cmh2 ; /*row mean score test*/
run;
```

Kruskal-Wallis test for continuous variable (Y):

```
proc npar1way wilcoxon;
class trt;
var Y;
run;
```

10) For race and ethnicity, “Not Permitted”, “Missing”, or “Other” will be excluded from percentage calculation and also excluded for p-value generation for categorical data analysis.

11) Proportional Odds

A proportional odds model is used for the primary efficacy endpoint:

```
proc logistic;
class trt (ref  'SOC')/ param  ref order  data;
model outcome(descending)   trt;
run;
```

where outcome is the ordinal scale response at Day 11.

12) Confidence Interval for single percentage

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

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

13) Treatment difference in percentages

The percentage difference between two treatment groups and its 95% CIs are calculated based on the unconditional exact method using 2 inverted 1-sided tests in SAS v9.3 or above.

The following SAS code will be used to compute cell counts and p-values.

```
data example;
input  grp trt $  outcome $ count ;

datalines;
1      Treat-A      2-Fail      x
1      Treat-A      1-Succ     xxx
1      Treat-B      2-Fail      x
1      Treat-B      1-Succ     xxx
run;

proc freq data    example;
table trt*outcome /riskdiff(CL  (exact)) alpha  0.05;
weight count; exact RISKDIFF(METHOD  SCORE);
output out  ciexact(keep  _RDIF1_ XL_RDIF1 XU_RDIF1 _RSK11_  _RSK21) riskdiff;
run;
```

```
data final(keep  A1 B1 Estimate LowerCL UpperCL ocharc1);
set ciexact;
label Estimate   "Percentage Difference"
LowerCL    "95% Lower Confidence Limit"
UpperCL    "95% Upper Confidence Limit"
A1    "Percentage of Success in Treat-A"
B1    "Percentage of Success in Treat-B";
Estimate  100*  RDIF1  ;
LowerCL    100*XL  RDIF1;
UpperCL    100*XU _RDIF1;
A1    100*  RSK11  ;
B1    100*  RSK21  ;
ocharc1    right(compress(put(Estimate,8.1)) || '% (' || compress(put(LowerCL,8.1)) || '%
to ' || compress(put(UpperCL,8.1)) || '%)');
run;
```

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

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

Fisher's exact test for categorical response, where trt is the treatment, and response is the categorical response. P-value from 2-sided Fisher's exact test should be used.

```
proc freq;
tables trt*response/ fisher; /*p value from Fisher's exact test*/
run;
```

14) Log-rank test

Log-rank test for time to death between treatment groups:

```
proc lifetest;
strata trt;
time days*censor(0);
run;
```

The binary indicator variable (CENSOR) with a value of 1 indicates the time to the event of interest is complete or 0 indicates the time to the event is censored. DAYS is a time to event variable.

15) Hazard ratio

The following SAS code will be used to compute hazard ratio (HR) and its 95% CI:

```
proc phreg;
class trt;
model days*censor(0)    trt / rl;
run;
```

16) Competing risk analysis

The following SAS code will be used to generate the cause-specific hazard ratio and 95% confidence intervals for the competing risk analysis:

```
proc phreg;
class trt;
model days*event(0, 2)    trt/ rl;
hazardratio "Cause-specific hazard" trt;
run;
```

where EVENT 1 if the participant had the event; EVENT 2 if the participant died prior to having the event, and EVENT 0 if the participant 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;
```

17) SAS code for Wilcoxon Rank sum test:

```
proc npar1way wilcoxon;
class trt;
var Y;
run;
```

18) TEAE

**Events with Missing Onset Day and/or Month**

An event is considered treatment emergent if 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.

19) The number of decimal places in reporting p-values should be as follows:

a) values less than 0.001 → < 0.001

b) values 0.001 to less than 1.000 → 4 decimal places (no rounding)

20) 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 CRF.

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.

21) Last dose date is not expected to be missing for RDV (5-day or 10-day) groups. 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.

22) 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) |

23) 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 |

24) 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; time to modified recovery; time to room air: 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.

# GS-US-540-5774_Part_A_Final_SAP_v1

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy hh:mm:ss) |
|---|---|---|
| PPD | Biostatistics eSigned | 06-Jul-2020 19:47:00 |
| PPD | Regulatory Affairs eSigned | 06-Jul-2020 20:20:55 |
| PPD | Clinical Research eSigned | 07-Jul-2020 02:50:56 |