STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19
Name of Test Drug:	Remdesivir (RDV; GS-5734™)
Study Number:	GS-US-540-5773
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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
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
eCRF	Electronic case report form
FAS	Full Analysis Set
HLT	high-level term
LLN	lower limit of normal
LLT	lowest level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PCR	polymerase chain reaction
PT	preferred term
Q1, Q3	first quartile, third quartile
RDV	remdesivir
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal

1. INTRODUCTION

This Phase 3 study is conducted in two parts. In Part A, approximately 400 participants who meet all eligibility criteria and who are not mechanically ventilated are randomized to one of two treatment groups. Part B starts after Part A is completed and includes up to approximately 5600 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 A of Study GS-US-540-5773. This SAP is based on the study protocol Amendment 3.0 dated 12 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 severe COVID-19.

The primary objective of this study is as follows:

- To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14.

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of RDV.

1.2. Study Design

This is a Phase 3 randomized, open-labeled, multi-center study of RDV therapy in participants with severe COVID-19.

Treatment Groups

For Part A, approximately 400 participants who meet all eligibility criteria and who are not mechanically ventilated may be randomized in a 1:1 ratio into one of the following treatment groups:

- **Treatment Group 1:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5

- **Treatment Group 2:** continued standard of care 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

Part B will enroll participants on mechanical ventilation and, after enrollment to Part A is complete, any additional participants. In Part B, up to an additional approximately 5600 participants who meet all of the eligibility criteria will be enrolled, based on whether they are mechanically ventilated at enrollment, to receive:

Mechanically Ventilated Treatment Group: continued standard of care 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

Extension Treatment Group: continued standard of care 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, 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
- SpO2 ≤ 94% on room air or requiring supplemental oxygen at screening
- Radiographic evidence of pulmonary infiltrates

Schedule of Assessments

The date of randomization is considered Day 1 and it is expected that all randomized 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 standard of care 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. Clinical status will be recorded on the 7-point ordinal scale for each day.

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

CCI [redacted]

Randomization

Participants who meet eligibility criteria are randomized in a 1:1 ratio to 1 of 2 treatment groups on Day 1 using an IWRS and assigned a subject number. Randomization is not stratified.

Sites

Up to approximately 160 centers globally.

Duration of Treatment

Participants will receive study treatment with RDV for 5 days (Treatment Group 1) or 10 days (Treatment Group 2) in Part A, and 10 days (Mechanically Ventilated Treatment Group), or either 5 or 10 days (Extension Treatment Group) in Part B. 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 < 30mL/min

Discontinuation of study medication is not a seriousness criterion.

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 400 participants will be randomized in a 1:1 ratio to 2 groups (200 participants per group).

The sample size computation is based on an assumed distribution of the 7-point ordinal scale on Day 14 for Part A Treatment Group 1. The odds ratio represents the odds of improvement in the ordinal scale for Treatment Group 2 relative to Treatment Group 1. 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 both treatment groups) of being in the ith 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 400 participants (200 in each group) achieves > 85% power to detect an odds ratio of 1.75 using a two-sided significance level of 0.05. In this sample size calculation, it is assumed that the probability distribution of the ordinal scale at Day 14 for Treatment Group 1 is as follows:

1. Death, 2%
2. Hospitalized, on invasive mechanical ventilation or ECMO, 4%
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices, 7%
4. Hospitalized, requiring low flow supplemental oxygen, 13%
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 16%
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration), 20%
7. Not hospitalized, 38%

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 analysis of the Day 14 snapshot.

2.1.2. Primary Analysis

The primary analysis will be performed after availability of data from participants in Part A of the study who have completed 14 days or prematurely terminated from Part A of the study on or prior to Day 14.

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 analysis of Part A.

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.

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 RDV. Participants will be grouped according to the treatment to which they were randomized.

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 RDV. Participants will be grouped according to the treatment to which they were randomized for Part A.

3.2. Subject Grouping

Participants will be grouped by randomized treatment (RDV for 5 Days and RDV for 10 Days), 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 subject 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)
- Country: (a) USA, (b) Italy, and (c) ex-Italy

3.2.2. Subject Subgroups for Safety Analyses

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

- Age (years): (a) < 65 and (b) ≥ 65
- Sex at birth: (a) male and (b) female
- Country: (a) USA, (b) Italy, and (c) ex-Italy

Survival will be summarized for the following subject subgroups:

- Age (years): (a) < 65, further broken down by (a1) < 50 and (a2) ≥ 50 to < 65, and (b) ≥ 65, further broken down by (b1) ≥ 65 to < 75 and (b2) ≥ 75
- Sex at birth: (a) male and (b) female
- Country: (a) USA, (b) Italy, and (c) ex-Italy

3.3. Multiple Comparisons

No prespecified multiplicity adjustments are planned for confidence intervals or statistical tests.

3.4. Missing Data and Outliers

3.4.1. Missing Data

Missing data can have an impact upon the interpretation of the 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

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

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

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a subject, then age derived based on date of birth and the first dose date will be used instead. If a randomized subject 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 (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).

3.6. Analysis Visit Windows

3.6.1. 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, and the laboratory visit dates, including the 28-day follow-up visit date, 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 3.6.3).

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 3.6.1 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 through the earliest of discharge date or Day 14 was to be recorded. For subjects 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.

SARS-CoV-2 PCR results were to be reported (if collected) each day. However, the 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 eGFR)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	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 considered 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 or analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis does not require 1 value per Study Day or analysis window.

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

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

  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 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 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 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 randomized 5-day or 10-day treatment on study drug as recorded on the Study Drug Completion form
- Prematurely discontinuing 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
- Still on study up to the data cut date (if applicable)
- Completed study
- Prematurely discontinuing from study (prior to the data cut date for the primary analysis only) 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 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 the Safety Analysis Set.

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier method by treatment group. Subjects who completed study drug will be censored at the last dose date.

4.3. 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 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 groups (< 50, ≥ 50 to < 65, ≥ 65 to < 75 and ≥ 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 groups]) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

Similar summaries will be produced for the following subgroups: USA, Italy and ex-Italy.

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 first dose of RDV
- Duration of symptoms prior to first dose of RDV
- 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 differ statistic for ordinal data [oxygen support status]) will be used to compare the 2 treatment groups. For clinical status and continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

Similar summaries will be produced for the following subgroups: USA, Italy and ex-Italy.

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. A summary table will present the percentages of participants reporting each medical history preferred term, sorted first in alphabetical order by system organ class (SOC) and then by preferred term (PT) in descending order of total frequency within SOC.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

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 14. 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 endpoint 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 result on the day the participant was discharged alive 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 subject 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 the 5-day treatment group (Treatment Group 1) is the same as the odds of improvement for the 10-day treatment group (Treatment Group 2) with respect to clinical status assessed by a 7-point ordinal scale on Day 14.

Alternative hypothesis: The odds of improvement for the 5-day treatment group (Treatment Group 1) is different from the odds of improvement for the 10-day treatment group (Treatment Group 2) with respect to clinical status assessed by a 7-point ordinal scale on Day 14.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The primary endpoint will be analyzed using a proportional odds model including treatment as the independent variable and baseline score as a continuous covariate. The odds ratio and 95% confidence interval will be provided. The corresponding SAS code is as following:

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

The percentage 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. It will be concluded that 10-day treatment is superior to 5-day treatment if the lower bound of the 2-sided 95% CI of the odds ratio (10-day / 5-day) on Day 14 is more than 1.

6.1.4. The FAS will be the primary analysis set for efficacy endpoint evaluation. Secondary Analyses of the Primary Efficacy Endpoint

As supportive analyses of the primary endpoint, the following will be conducted:

- The primary endpoint will be analyzed using a proportional odds model including treatment as the independent variable (dropping baseline score as a covariate).

- The clinical status at Day 14 will be compared between treatment groups using a 2-sided Wilcoxon Rank sum test, stratified on baseline clinical status.

The change from baseline in clinical status category on Days 5, 7, 11, 14, 28 and last available assessment will be summarized by treatment groups using descriptive statistics. Change from baseline will be compared between the treatment groups using a 2-sided Wilcoxon Rank sum test. This analysis will use 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 using the last available assessment will be summarized by treatment group. These results will be summarized using the clinical status definition in Section 6.1.1 and two methods: (1) with the definition specified in Section 6.1.1 and (2) with the 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 results will use the definition 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:

- Number of subjects with negative PCR on Days 5 and 10
- 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 subjects 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 subject was in the hospital, if a subject was discharged alive and died afterwards, the subject will be included only in the summary for subjects discharged alive.

- 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 primary analysis, duration of hospitalization through Day 14 is calculated for subjects who were discharged alive on or prior to Day 14. For the final Part A analysis, duration of hospitalization is calculated through Day 28 for subjects who were discharged alive prior to Day 28. If subjects 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
- 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 in Section 6.1.1.
- Percentage of subjects with a ≥ 2-point improvement or discharged alive based on the 7-point ordinal scale using the definition specified in Section 6.1.1 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 in Section 6.1.1.
- Percentage of subjects with a ≥ 1-point improvement based on the 7-point ordinal scale using the definition specified in Section 6.1.1 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 specified in Section 6.1.1, 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 subjects with recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment
- Time to modified recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1, 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
- Percentage of subjects with modified recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment
- Time to room air (for subjects not on room air at baseline) based on the 7-point ordinal scale using the definition specified in Section 6.1.1, defined as an improvement from a baseline score of 2 through 4 to a score of 5, 6 or 7
- Percentage of subjects with improvement to room air based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment

6.2.1. Analysis of Other Endpoints of Interest

The number and percent of subjects with negative PCR on Days 5 and 10 will be summarized. The point estimate of the treatment difference and the associated 95% confidence intervals will be constructed based on an unconditional exact method using 2 inverted 1-sided tests.

Number of days of oxygen support status modes (invasive mechanical ventilation, high flow oxygen, low flow oxygen) will be compared between the treatment groups 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 status will be provided. For the primary analysis, the last available assessment on or prior to Day 14 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 the treatment groups using the Wilcoxon Rank sum test.

All-cause mortality will be estimated using the Kaplan-Meier product limit method with all available data. The treatment groups will be compared using the log-rank test stratified by baseline clinical status. The hazard ratio and 95% confidence interval will be provided based on a stratified proportional hazards model. Participants who did not die will be censored at the last study day.

Days to clinical improvement will be estimated using a competing risk analysis approach, with death as the competing risk. Baseline score will be included in the model as a continuous covariate. The hazard ratio and 95% confidence interval will be provided. Subjects without clinical improvement will be censored on the day of the last non-missing ordinal scale assessment.

Days to recovery, days to modified recovery and days to room air will be estimated using a competing risk analysis approach, with death as the competing risk. Baseline score will be included in the model as a continuous covariate. The hazard ratio and 95% confidence interval will be provided. Subjects without recovery will be censored on the day of the last non-missing ordinal scale assessment.

The number and percent of subjects with $\geq$ 1-point improvement, $\geq$ 2-point improvement, recovery, modified recovery, and improvement to room air will be presented with 95% confidence intervals on Day 5, Day 7, Day 11 and Day 14. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided. For the number of subjects on room air, only subjects on room air at baseline will be included.

Point estimates of treatment differences in percentages and 95% confidence intervals will be calculated based on stratum-adjusted Mantel-Haenszel proportion where the stratum is baseline clinical status {Koch 1989} (see Appendix 2). Comparisons between treatment groups will be performed using the CMH test stratified on baseline clinical status.

Analyses will be performed using the FAS.

6.3. Changes from Protocol-Specified Efficacy Analyses

The protocol stated that participants who have missing clinical status information on Day 14 will be excluded from the primary analysis; however death and discharge alive information as well as last known clinical status will be used for Day 14 (see Section 6.1.1).

The protocol stated that endpoints that are measured as time to first event will be compared between treatment groups using the log-rank test; however, a competing risk approach (with death as the competing risk) will be used. Treatment groups will be compared using the hazard ratio with 95% confidence interval.

The endpoint of interest of time to $SpO_2 > 94\%$ on room air was changed to time to room air because SpO_2 was not collected routinely for participants on room air.

The endpoint of interest of time to first negative PCR was updated to the number of subjects with negative PCR on Days 5 and 10 because PCR was not collected on a routine basis.

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 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 percentage of participants with any treatment emergent adverse events will be compared between the 2 groups using the CMH test stratified on baseline clinical status. The point estimate of the treatment difference and the associated 95% confidence intervals will be calculated based on stratum-adjusted Mantel-Haenszel proportion where the stratum is baseline clinical status (see Appendix 2).

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. SOC, high-level group term (HLGT), high-level term (HLT), PT, and lowest-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 Department 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 SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group using the Safety 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 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 percentage of participants reporting AEs will be compared between the 2 groups using the CMH test stratified on baseline clinical status. The point estimate of the treatment difference and the associated 95% confidence intervals will be calculated based on stratum-adjusted Mantel-Haenszel proportion where the stratum is baseline clinical status (see Appendix 2).

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 subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity 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, 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. 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

7.3. 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. 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. 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 the treatment groups 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. 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.

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.

7.3.3. Liver-Related Laboratory Evaluations

Subjects with AST or ALT > 3 × ULN will be listed.

7.4. Body Weight, and Vital Signs

Descriptive statistics will be provided by treatment group 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 3.6.3. 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 multiple measures through varying oxygen supplementation methods.

A by-subject listing of body weight, BMI, and vital signs (including heart rate, respiratory rate, temperature, blood pressure, SpO_2 and PaO_2) 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 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 subject 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 subject 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 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

The protocol stated that the secondary endpoint of particpants with treatment emergent AEs would be compared between the treatment groups using a Fisher's Exact test. However, a CMH test stratified on baseline clinical status will be used to account for differences in baseline clinical status.

8. REFERENCES

Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1989:pp. 414-21.

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
15 May 2020	3.6.2, 7.4	SpO_2 and PaO_2 summaries removed	Removed because they were collected under various oxygen support statuses
	3.6.3, 4.1, 6.1.3	Minor updates to wording and formats	Clarity and consistency
	5,1	Age groups added to list of baseline variables to be summarized	Clarity and consistency
	6.1.4	Day 28 and last available assessment were added to summaries	Omission
	6.2	Other endpoints of interest were clarified	Clarity and consistency
	6.2.1, 7.1, 7.8, Appendix 2	Analyses adjusting for baseline clinical status were added	Clarity and consistency
	7.3.2.2	Description of listing was updated	Clarity and consistency
	7.3.3	Listing added	Omission

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													
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, SpO2 at rest, and body weight. Body weight collected on screening and Day 1 and otherwise if available.
b Assessments need not be repeated if performed the same calendar day as screening procedures.; data collection other than adverse events should stop Day 14 or discharge whichever is earlier.
c Day 28 evaluations completed if the visit is conducted in person. Only AEs, ordinal scale, and concomitant medication review completed if visit conducted by phone.
CCI

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 subject 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 subject 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 subject is randomized (ie, subject 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 subject took at least 1 dose of study drug and assigned as blank if the subject 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) 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;
```

Wilcoxon rank sum test for continuous variable (Y), the p-value from the normal approximation two-sided test should be used for continuous variables:

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

10) Please note, "Not Permitted", "Unknown", or missing categories will be excluded from percentage calculation and also excluded for p-value generation for categorical data analysis (eg, CMH test or Fisher exact test).

11) Proportional Odds

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

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

where outcome is the ordinal scale response at Day 14.

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 not adjusted by baseline clinical status

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;
```

14) Treatment difference in percentages adjusted by baseline clinical status

The baseline stratum weighted difference in rate (P_1 P_2) and its 95% CI will be calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion as described as follows {Koch 1989}, where the stratification factor is baseline clinical status:

$$P_1 \quad P_2 \pm Z_{(1\ \alpha/2\ )} * SE(P_1 \quad P_2),$$

where

- $(P_1 \quad P_2) \quad \frac{\sum w_h d_h}{\sum w_h}$, is the stratum-adjusted MH proportion difference, where $d_h \quad p_{1h} \quad p_{2h}$ is the difference in the response rate between the Treatment Groups 1 and 2 in stratum h (h 1 to 4).

- $w_h \quad \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$, is the weight based on the harmonic mean of sample size per treatment group for each stratum where n_{1h} and n_{2h} are the sample sizes of the Treatment Groups 1 and 2 in stratum h.

- SE(P_1 P_2) $\sqrt{\frac{\sum w_h^2\left[\frac{p_{1h}^*(1 \quad p_{1h}^*)}{n_{1h} \quad 1}+\frac{p_{2h}^*(1 \quad p_{2h}^*)}{n_{2h} \quad 1}\right]}{(\sum w_h)^2}}$, where p_{1h}^* $\frac{m_{1h}+0.5}{n_{1h}+1}$ and p_{2h}^* $\frac{m_{2h}+0.5}{n_{2h}+1}$. m_{1h} and m_{2h} are the number of subjects with the event in Treatment Groups 1 and 2 in stratum *h*.

- α 0.05

- $Z_{(1\ \alpha/2)}$ $Z_{0.975}$ 1.96 is the 97.5th percentile of the normal distribution

Note that if the computed lower confidence bound is less than 1, the lower bound is defined as 1. If the computed upper confidence bound is greater than 1, the upper bound is defined as 1.

15) CMH test for difference in percentages

The following SAS code will be used to test percentages adjusting for baseline status:

```
proc freq;
tables base*trt*response/cmh; * p-value from general association;
run;
```

16) Log-rank test

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

```
proc lifetest;
strata base;
time days*censor(0);
test trt;
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.

17) 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;
hazardratio '10 vs 4' trt;
strata base;
```

```
run;
```

18) 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 base/ 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 subject did not have the event and did not die. BASE baseline value.

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;
```

19) SAS code for stratified 2-sided Wilcoxon Rank sum test (stratified on baseline result)

```
proc freq;
  table base*trt*aval/cmh2 scores  modridit;
run;
```

where BASE is the baseline value.

20) 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.

21) 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)

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

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

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

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

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

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

24) 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

25) Censoring rules

Time to death: subjects 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 subject does not experience the event of interest and does not die, the subject is censored at the last non-missing ordinal scale assessment date.

26) 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)

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Regulatory Affairs eSigned	19-May-2020 02:51:23
PPD	Biostatistics eSigned	19-May-2020 03:20:19
PPD	Clinical Research eSigned	19-May-2020 16:57:30