STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Remdesivir in Participants with Severely Reduced Kidney Function who are Hospitalized for COVID-19	
Name of Test Drug:	Remdesivir	
Study Number:	GS-US-540-5912	
Protocol Version (Date):	Original:	07 December 2020
	Amendment 1:	28 January 2021
	Amendment 2:	02 August 2021
	Amendment 3:	27 August 2021
Analysis Type:	Final Analysis	
Analysis Plan Version:	SAP v1.0	
Analysis Plan Date:	22 July 2022	
Analysis Plan Author(s):	PPD & PPD	

CONFIDENTIAL AND PROPRIETARY INFORMATION

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AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CKD	chronic kidney disease
CMH	Cochran-Mantel-Haenszel
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
DAIDS	Division of AIDS
DAVG	Time-weighted average change from baseline
DMC	data monitoring committee
ED	Emergency department
ESKD	end-stage kidney disease
ET	early termination
FAS	Full Analysis Set
Hb	Hemoglobin
HLT	high-level term
HLGT	high-level group term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IMV	Invasive mechanical ventilation
IV	Intravenous
IXRS	interactive voice or web response system
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PCR	polymerase chain reaction
PK	pharmacokinetics
PT	preferred term
PTM	Placebo to match
Q1, Q3	first quartile, third quartile
RDV	remdesivir
RRT	renal replacement therapy

SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SBECD	sulfobutylether-beta-cyclodextrin
SCr	serum creatinine
SD	standard deviation
SI (units)	international system of units
SOC	system organ class
SpO_2	oxygen saturation
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-540-5912. This SAP is based on the study protocol Amendment 3 dated 27 August 2021 and the electronic case report form (eCRF). This SAP will be finalized before data finalization and unblinding. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate whether remdesivir (RDV) reduces the composite risk of death or invasive mechanical ventilation (IMV) through Day 29 in participants with severely reduced kidney function who are hospitalized for coronavirus disease 2019 (COVID-19)

The secondary objectives of this study are as follows:

- To evaluate whether RDV reduces the risk of death through Day 29
- To evaluate whether RDV reduces the risk of IMV through Day 29
- To evaluate the time to recovery (defined as satisfying category 1, 2, or 3 by an 8-point ordinal scale)
- To evaluate the effect of RDV on clinical status assessed by an 8-point ordinal scale at Day 15 and Day 29
- To evaluate the effect of RDV on renal replacement therapy (RRT)-free days (among those without end-stage kidney disease [ESKD]) through Day 29
- To evaluate the effect of RDV on recovery through Day 29
- To evaluate the safety and tolerability of RDV in participants with severely reduced kidney function who are hospitalized for COVID-19

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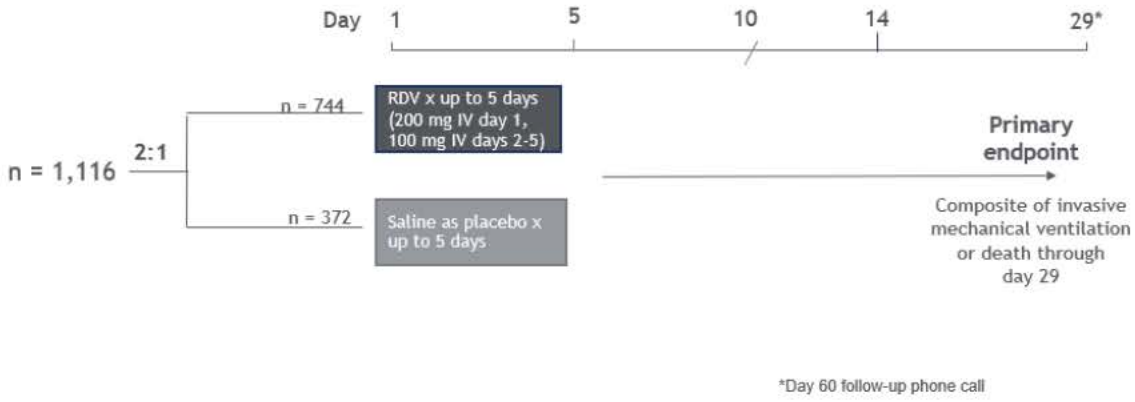
1.2. Study Design

This is a Phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluating the efficacy and safety of RDV therapy in participants with severely reduced kidney function who are hospitalized for COVID-19.

Figure 1-1. Study Schema



Approximately 1,116 eligible participants are planned to be randomized in a 2:1 ratio to receive RDV or saline as placebo, according to the following treatment regimen, in addition to standard of care therapy:

Treatment Group A (N = 744): IV RDV 200 mg on Day 1 followed by IV RDV 100 mg once daily from Day 2 up to Day 5

Treatment Group B (N = 372): IV saline as placebo on Day 1 followed by IV saline as placebo once daily from Day 2 up to Day 5

Randomization will be stratified by:

- ESKD requiring chronic dialysis
- High-flow oxygen requirement
- Region (United States [US] vs. ex-US)

All participants will be requested to continue assessments during study hospitalization and any subsequent re-hospitalization to the same institution during Days 1 through 29 and attend the Day 60 phone follow-up (whether hospitalized or as an outpatient).

The schedule of assessments is provided as an appendix (Appendix 1).

1.3. Sample Size and Power

A total of approximately 1116 participants are planned to be randomized in a 2:1 ratio to 2 groups (744 in the RDV group and 372 in the saline as placebo group).

This sample size achieves approximately 85% power to detect a hazard ratio of 0.70 at a two-sided alpha level of 0.05. In the sample size calculation, it is assumed that the event rate in the saline as placebo group is 35%. The hazard ratio and event rate in the saline as placebo group are based on the most conservative estimates of the primary endpoint (composite of all-cause mortality or IMV) and the key α-controlled secondary endpoint (all-cause mortality) through Day 29 among a subset of participants with eGFR < 60 mL/min in the Division of Microbiology and Infectious Diseases Protocol 20-0006 Adaptive COVID-19 Treatment Trial (ACTT)-1 (hazard ratio of 0.67 and placebo rate of 33%).

The sample size calculation was done using software EAST (Version 6.5, module for log-rank test given accrual duration [120 days] and study duration [149 days] and 1 interim analysis at 50% information fraction using the Lan-Demets approach with O'Brien-Fleming type spending function).

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

Prior to the final analysis, interim analyses may be conducted, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

2.2. DMC Analyses

Two formal DMC meetings were planned for this study and were specified in protocol Sections 8.2 and 8.10. The first meeting has occurred and was conducted after the first 100 participants completed the Day 29 assessment. The purpose of this meeting was to review safety data, including renal and hepatic toxicity. The second meeting was planned after 50% of participants completed the Day 29 assessment. The purpose of this meeting was to review safety and provide a formal evaluation of futility and efficacy. However, this analysis was not performed due to the stop of study enrollment prior to reaching 50% of planned enrollment.

In addition to the above mentioned 2 formal DMC analyses, the DMC was provided with blinded safety listings including Grade 3 or higher AEs and SAEs every week for the first 2 weeks after the first participant was enrolled followed by every 2 weeks thereafter.

All details on DMC analyses are documented in the approved DMC charter.

2.3. Final Analysis

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

The analysis of the primary endpoint of all-cause mortality or IMV through Day 29 and the key α-controlled secondary endpoint of all-cause mortality through Day 29 will be conducted at the final analysis (see Section 3.5 for prespecified testing strategy). The overall Type I error rate will be controlled at the two-sided 0.05 significance level.

2.4. Change from Protocol-Specified Analyses

The second formal DMC analysis was not performed due to the stop of study enrollment prior to reaching 50% of planned enrollment. The reason for stopping enrollment was that it became clear the study would not fully enroll in a reasonable timeframe even after implementing enrollment mitigation strategies. The decision to stop study enrollment was documented in the 16 December 2021 Study Management Team meeting minutes.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-participant listings will be presented for all participants in the All Randomized Analysis Set and sorted by participant identification (ID) number, visit date, and time (if applicable). Data collected on log forms, such as adverse events (AEs), will be presented in chronological order for each participant. The treatment group to which participants were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. Participants included in each analysis set will be determined before the study blind is broken for analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by participant.

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3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all participants who were randomized in the study.

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 the study, and (2) have received at least 1 dose of study drug.

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 the study and (2) have received at least 1 dose of study drug.

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3.1.7. Virology Analysis Set

The Virology Analysis Set will include all participants who (1) are randomized into the study, (2) have received at least 1 dose of RDV, and (3) have positive SARS-CoV-2 viral load at baseline (a result of "No SARS-CoV-2 detected" is considered as negative, results of Inconclusive, < limit of quantitation (LOQ) SARSCoV2 detected, and numerical results are considered as positive).

3.2. Participant Grouping

For analyses based on the All Randomized Analysis Set and FAS, participants will be grouped according to the treatment to which they were randomized. For analyses based on Safety Analysis Set,CCI [redacted] Virology Analysis Set and CCI [redacted] participants will be grouped according to the actual treatment they received.

The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

3.3. Strata and Covariates

Participants will be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 2:1 ratio using a stratified randomization schedule. Randomization will be stratified by:

- ESKD requiring chronic dialysis (Yes, No)
- High-flow oxygen requirement (Yes, No)
- Region (US, ex-US)

Stratification discrepancies between the IXRS and the clinical database will be reviewed and assessed. The values recorded in the clinical database will be used for analyses in case there are discrepancies. Based on the assessment of stratification discrepancies, a sensitivity analysis of the primary endpoint may be performed.

The primary efficacy endpoint and the key α-controlled secondary efficacy endpoint (see Section 6 for definition) will be evaluated in a stratified analysis based on the same 3 factors used for randomization, as specified in Section 6. In addition, observed imbalances between treatment groups in other baseline characteristics may be considered as covariates in sensitivity analyses of efficacy endpoints.

3.4. Examination of Participant Subgroups

The primary efficacy endpoint and the key α-controlled secondary efficacy endpoint will be examined for the following participant subgroups:

- Kidney disease status (defined as: AKI, CKD and ESKD.)
- High-flow oxygen requirement at baseline (Yes, No)
- Region (US, ex-US)
- Participant's age (≥18 - < 65, ≥ 65 years)
- Sex at birth: (a) male and (b) female
- Race: (a) Asian, (b) Black, (c)White, (d) Other
- Baseline risk factor (as applicable): Chronic lung disease (Yes, No), Hypertension (Yes, No), Cardiovascular or cerebrovascular disease (Yes, No), Diabetes mellitus (Yes, No), BMI (with categories: < 20, ≥ 20 - < 30, ≥ 30 kg/m^2), Immunocompromised state (Yes, No), Chronic liver disease (Yes, No), Current cancer (Yes, No)

In addition, the primary efficacy endpoint will be examined for duration of symptoms prior to first dose of study drug (<= 5 days vs >5 days) and baseline oxygen support status. Other subgroups may be considered based on imbalances between treatment groups observed in other baseline characteristics.

3.5. Multiple Comparisons

To control the overall Type I error in the evaluation of the primary efficacy endpoint and the key secondary efficacy endpoint, the hypothesis testing will be performed in sequential order.

The primary efficacy endpoint will be tested first at the significance level of 0.05. If the primary efficacy endpoint null hypothesis is rejected, the key secondary efficacy endpoint will be tested at the 0.05 significance level; otherwise, the key secondary efficacy endpoint will not be tested.

All other endpoints may be tested using 2-sided tests at the 0.05 significance level without multiplicity adjustment as they are considered secondary CCI endpoints.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

In this study, a missing pre-treatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

For missing last dose date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for concomitant medications in Section 7.4.

Imputation rules for the secondary efficacy endpoints related to the 8-point ordinal scale score are described in Section 6.2.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process. No sensitivity analyses to evaluate the impact of outliers on efficacy or safety outcomes are planned. Unless specified otherwise, all data will be included in the analyses.

3.7. Data Handling Conventions and Transformations

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived from 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. Age required for longitudinal and temporal calculations and analyses (e.g., estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

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

- 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.

Laboratory data that are continuous in nature but are less than the lower 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).

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Natural logarithm transformation will be used for analyzing concentrations. Concentration values that are BLQ will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postdose time points for summary purposes.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 participant has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."

- If more than 25% of the participants have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."

- If more than 50% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."

- If all participants have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

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

- For assessment dates on or after the first dosing date: Assessment Date – First Dosing Date + 1

- For assessment dates prior to the first dosing date: Assessment Date – First Dosing Date

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

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

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

Last Study Date is the latest of study drug start dates and end dates, the in-person or phone visit dates, the vital sign and the laboratory collection dates, including the Day 60 phone follow-up visit date. For participants who died during the study, the death date will be the Last Study Date. For participants who died after completing the study or after prematurely discontinuing the study, the death date will not be considered for the Last Study Date.

3.8.2. Analysis Visit Windows

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

The analysis windows for chemistry (except for SCr), hematology and coagulation laboratory tests are provided in Table 3-1. CCI [redacted]

Table 3-1. Analysis Visit Windows for Chemistry (Except for SCr), Hematology, and Coagulation Laboratory Tests

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1 (Pre Dose)
Day 3	3	1 (Post Dose)	3
Day 5	5	4	6
Day 8	8	7	10
Day 12	12	11	14
Day 16	16	15	18
Day 20	20	19	22
Day 24	24	23	26
Day 29	29	27	44

The 8-point ordinal scale will be collected daily from Day 1 through Day 29 or discharge, whichever is earlier, as well as at the Day 29 and Day 60 phone follow-up. The analysis visit window will coincide with each study day up to Day 44 with 1 exception: a Day 1 postdose record will be mapped to Analysis Day 2 visit (the 8-point ordinal scale will be collected twice on Day 1: predose and the worst score on Day 1 post-dose). If any additional records are collected after Day 44, the analysis window is provided in Table 3-3.

Table 3-3. Analysis Visit Window for 8-Point Ordinal Scale Collected after Day 44

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 60	60	45	(none)

Vital signs, and SCr will be collected daily from Day 1 through Day 29 or discharge, whichever is earlier, per protocol; therefore, the analysis visit window will coincide with each study day up to Day 29 with 1 exception: a Day 1 postdose record will be mapped to Analysis Day 2 visit.

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

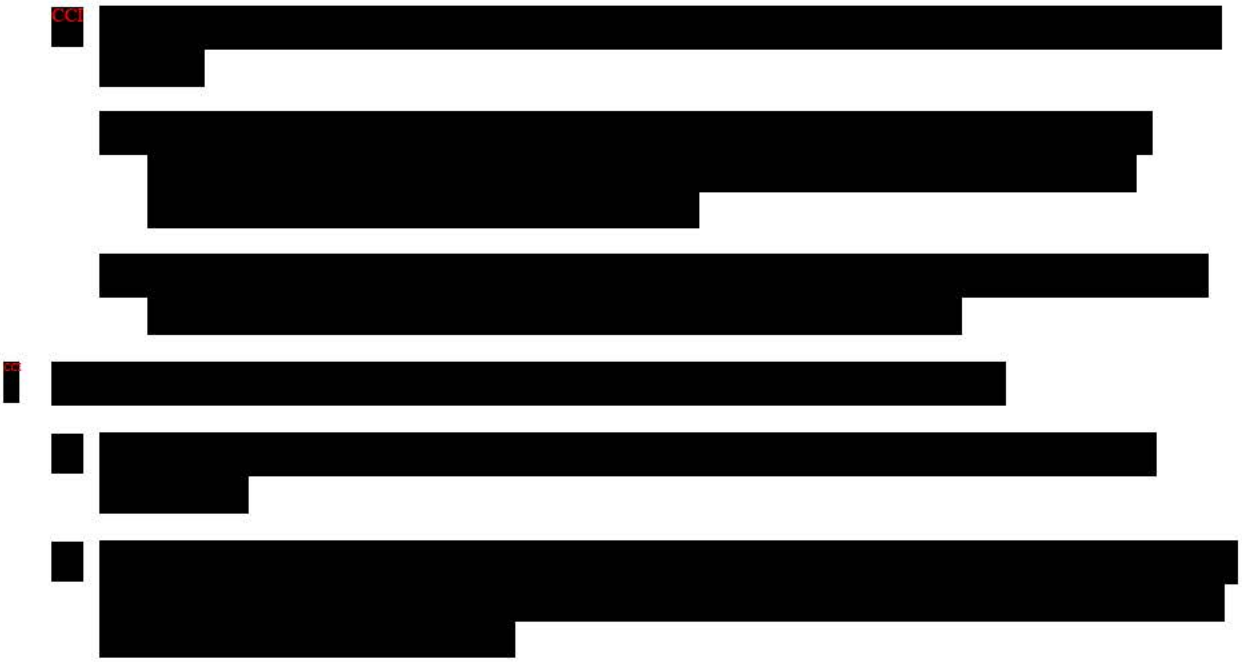
Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would use all data regardless of analysis window.

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

- For baseline, 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 selected as follows:
  - For continuous data:
    - CCI [redacted]
    - For other continuous data, the average of the measurements will be taken.
  - For categorical data:
    - For SARS-CoV-2 infection status, the highest severity (ie, a positive PCR result) will be selected.
    - For other categorical data, the lowest severity will be selected.

For the 8-point ordinal scale, only Screening and Day 1 predose values will be considered for baseline value selection.

[redacted]



In an analysis window (including baseline window), if both central lab and local lab results are available, then central lab results will be used for record selection instead of local lab results; local lab results will only be used for record selection if central lab results are missing.

3.9. Change from Protocol-Specified General Considerations

The multiplicity adjustment specified in the protocol Section 8.7 was changed because the interim analysis planned after 50% of participants completed the Day 29 assessment was not performed due to the stop of study enrollment prior to reaching 50% of planned enrollment. As there was no interim analysis, there was no alpha spent and the final analysis is planned at the 0.05 significance level (see Section 2.3).

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

A table of key study dates will be provided, including first participant screened, first participant enrolled, last participant enrolled, last participant last visit for the primary endpoint, and last participant last visit.

The number and percentage of participants enrolled at each investigator site and country will be summarized by treatment group and overall. The denominator for this calculation will be the number of participants analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of participants in the stratum will be the total number of participants in the Safety Analysis Set. If there are discrepancies in the value used for stratification assignment between the IXRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of participants with discrepancies in the value used for stratification assignment between the IXRS and the clinical database at the time of data finalization will be provided.

A summary of participant 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 but were not randomized, participants randomized, participants randomized but never treated, participants in the Safety Analysis Set, and Full Analysis Set (FAS).

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

- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed study
- Did not complete study with reasons for premature discontinuation of study

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

No inferential statistics will be generated. A data listing of reasons for premature study drug/study discontinuation will be provided.

A summary of analysis sets will also be provided by treatment group and overall.

4.2. Extent of Study Drug Exposure

Number of doses received will be summarized by treatment group for the Safety Analysis Set.

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 and the total number of important protocol deviations by deviation reason (eg, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the FAS. A by-participant listing will be provided for those participants with important protocol deviations.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic data (eg, sex, race, race category, ethnicity, age, and age group [< 18, ≥ 18 - < 65, ≥ 65 years]) and baseline characteristics (eg, body weight, height, body mass index [BMI] and BMI group [< 20, ≥ 20 - < 30, ≥ 30 kg/m^2]) 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 characteristics will be provided for the Safety Analysis Set.

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data and row mean scores differ statistic for ordinal data) 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: kidney disease status (as defined in Section 3.4), high-flow oxygen requirement (Yes, No), and region (US vs. ex-US).

A by-participant 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:

- Kidney disease status (as defined in Section 3.4)
- High-flow oxygen requirement (Yes, No)
- Region (US, ex-US)
- Clinical status (8-point ordinal scale)
- Oxygen support status
- RRT at baseline
- Duration of hospitalization prior to first dose of study drug
- Duration of symptoms prior to first dose of study drug (as a continuous variable, and a categorical variable with categories of <= 5 and > 5)
- Duration from SARS-CoV-2 positive result to first dose of study drug

[redacted]

- Alanine aminotransferase (ALT)
- Baseline risk factor (as defined in Section 3.4 except BMI)
- COVID-19 vaccine (See Appendix 2) status

For categorical data, the CMH test (ie, general association statistic for nominal data and row mean scores differ statistic for ordinal data) 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: kidney disease status (as defined in Section 3.4), high-flow oxygen requirement (Yes, No), and region (US vs. ex-US).

A by-participant listing will also be provided.

5.3. 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. A listing of medical history will be provided.

A by-participant listing of kidney transplant history will also be provided.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary endpoint is the composite of all-cause mortality or IMV from date of first dose through Day 29.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

Null hypothesis: There is no difference between treatment groups in the probability of all-cause mortality or IMV through Day 29.

Alternative hypothesis: The probability of all-cause mortality or IMV through Day 29 is different between treatment groups.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The primary endpoint will be analyzed using a stratified log-rank test stratified by the randomization strata. P value and the proportion of all-cause mortality or IMV at Day 29 from Kaplan-Meier estimate will be provided.

The hazard ratio and 95% confidence interval (CI) will be estimated using a Cox model with stratification factors as covariates.

Participants with missing outcomes for the primary endpoint due to premature discontinuation of the study on or prior to Day 29 will be censored at the last study day.

Additionally, the difference in proportions of all-cause mortality or IMV at Day 29 between treatment groups and the 95% CI for the difference will be provided based on the stratum-adjusted Mantel-Haenszel (MH) proportion as described in {Koch 1989} in Appendix 2.

The FAS will be the primary analysis set for efficacy endpoint evaluation.

6.1.4. Secondary Analyses of the Primary Efficacy Endpoint

The primary endpoint will also be analyzed for each of the subgroups defined in Section 3.4.

Sensitivity analyses maybe conducted using the following alternative approaches for the primary endpoint.

- A CMH test including stratification factors as strata for the statistical comparison between treatment groups. If a participant prematurely discontinues from the study prior to Day 29 with no event before discontinuation or the IMV/death status is missing, the participant will be considered as with no IMV/death.

- In rare occasions, a participant may be unblinded to site for safety considerations (Gilead remains blinded). Data for such participants after site unblinding may be censored for a sensitivity evaluation.

The sensitivity analyses are for the purposes of evaluating the robustness of the estimates of the primary analysis.

6.2. Secondary Efficacy Endpoints

The key α-controlled secondary endpoint is all-cause mortality through Day 29.

Other secondary endpoints include:

- Initiation of IMV through Day 29
- Time to recovery through Day 29
- Clinical status assessed by the 8-point ordinal scale at Day 15 and Day 29
- RRT-free days (among those without ESKD at baseline) through Day 29
- Proportion of participants with recovery through Day 29

Recovery is defined as achieving category 1, 2, or 3 on the 8-point ordinal scale score, for participants with a baseline score ≥ 4.

6.2.1. Analysis of Secondary Efficacy Endpoints

The key α-controlled secondary endpoint of all-cause mortality through Day 29 will be analyzed in a similar manner to the primary endpoint.

Initiation of IMV through Day 29 and time to recovery through Day 29 will also be analyzed in a similar manner to the primary endpoint except that a competing risk analysis approach will be used with death as the competing risk.

For analysis on time to recovery through Day 29, two sets of analyses will be conducted:
(1) Time to recovery through Day 29, in which the first recovery without further worsening in the ordinal scale score (ie, a score of > 4) by Day 29 will be considered an event; (2) Time to recovery through Day 29, in which the first recovery (regardless of further worsening or not) will be considered an event.

The clinical status assessed by the 8-point ordinal scale at Day 15 and Day 29 will be analyzed using a proportional odds model including treatment as the independent variable. Two models will be explored; one with baseline score as a continuous covariate and one without baseline score as a covariate. The odds ratio and 95% CI will be provided. 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. Clinical status by study day and change from baseline up to Day 29 will also be summarized by treatment group.

For participants without ESKD at baseline, the number of RRT-free days will be calculated between date of first dose and Day 29. The number of RRT-free days will be calculated as the number of full days from Day 1 to Day 29 that the participant was alive and did not receive RRT. The number of RRT-free days will be summarized by treatment group, and compared between treatment groups using Wilcoxon rank sum test.

The proportion of participants with recovery through Day 29 will be summarized by treatment group, and compared between treatment groups using the CMH test stratified by randomization strata. Similar for time to recovery analysis, two sets of analyses will be conducted: (1) The proportion of participants with recovery through Day 29, in which recoveries without further worsening by Day 29 is considered; (2) The proportion of participants with recovery through Day 29, in which recoveries regardless of worsening status by Day 29 is considered.

The key α-controlled secondary endpoint of all-cause mortality through Day 29 will also be analyzed for each of the subgroups defined in Section 3.4. Other secondary endpoints may also be analyzed for each of the stratification factor subgroups.

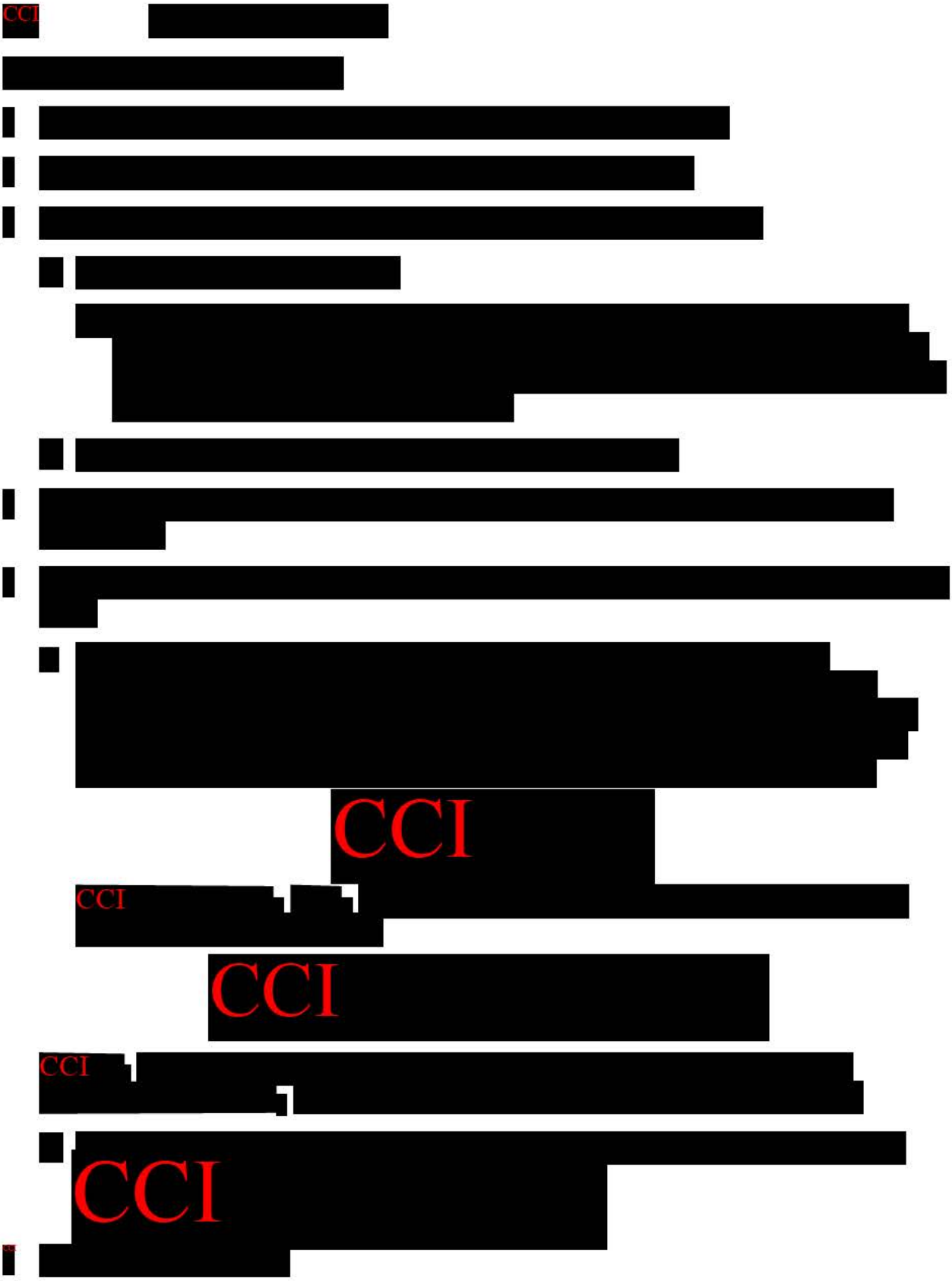
For time to event analysis of secondary endpoints, participants with missing outcomes due to premature discontinuation of the study on or prior to Day 29 will be censored at the date of last known status for that endpoint.

Clinical status assessed by the 8-point ordinal scale 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.

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. The definition of clinical status based on the 8-point ordinal scale is defined as follows:

- If a participant dies on or prior to Day 29, clinical status on the day of death and all subsequent days through Day 29 will be set as 8 (death)
- If a participant is discharged alive on or prior to Day 29, clinical status on the day of discharge alive will be set to 2 (not hospitalized, limitation on activities and/or requiring home oxygen), which is the worst score for a non-hospitalized participant
- If a participant is discharged alive and subsequently re-admitted on or prior to Day 29, and the 8-point ordinal score is not reported on the day of re-admission, the clinical status on the day of the re-admission will be imputed to 7 (hospitalized, on IMV or ECMO), which is the worst score for a hospitalized participant
- For other missing ordinal scores from Day 2 through Day 29, the clinical status will be imputed using the previous day's score (either reported score or imputed score as applicable)

The FAS will be the primary analysis set for the secondary efficacy endpoints.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6.4. Changes from Protocol-Specified Efficacy Analyses

The primary analysis specified in the protocol Section 8.2.2 and the final analysis will be combined into one final analysis due to early study closure with smaller than planned sample size.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

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

Adverse events are graded by the investigator as Grade 1 (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.

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

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

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

7.1.5.2. Incomplete Dates

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

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

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

7.1.6. Summaries of Adverse Events and Deaths

TEAEs will be summarized based on the Safety Analysis Set.

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

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

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

For other AEs described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs with Grade 3 or higher
- TE study drug-related AEs
- TE study drug-related AEs with Grade 3 or higher
- TE SAEs
- TE study drug-related SAEs
- AEs leading to premature discontinuation of study drug

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

In addition to the above summary tables, all TEAEs, TEAEs with Grade 3 or higher, TE study drug-related AEs, TE study drug-related AEs with Grade 3 or higher, and TE SAEs will be summarized by PT only, in descending order of total frequency.

The above summary tables may also be provided for one or more of the following subgroups: kidney disease status (as defined in Section 3.4), high-flow oxygen requirement (Yes, No), and/or region (US, ex-US).

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

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

Listing of renal and hepatic adverse events will be provided. Hypersensitivity including infusion-related reactions adverse events will also be summarized and listed (See Appendix 2).

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days. The analysis will be based on values reported in conventional units. When values are below or above the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

Because RRT may significantly impact certain lab values such as SCr and BUN, a sensitivity analysis will be conducted, in which records and/or participants may be excluded from analysis as follows:

- SCr and BUN will only be analyzed for participants who are not on RRT at baseline. If RRT is used during the study, any records from RRT start to end + 3 days will be excluded from analysis.

RRT started within 3 days before first dose is considered RRT at baseline.

Anticoagulation medications can impact coagulation lab parameters, such as aPTT, PT, and INR. Sensitivity analysis will be conducted for coagulation lab parameters. Any coagulation lab records under the influence of these medications will be excluded from analysis. For anticoagulation medications in the Warfarin class, coagulation lab records with a date in between the start and 5 + the stop date of the medication will be excluded; for other anticoagulation medications, records with a date in between the start and 1 + the stop date of the medication will be excluded.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, coagulation, serum chemistry, CCI [redacted] Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the DAIDS Grading Scale (see Section 7.2.2) will be flagged in the data listings, as appropriate.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for selected laboratory test specified in the study protocol as follows:

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

A baseline laboratory value will be defined as the last nonmissing measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1. 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 3.8.3.

In an analysis window (including baseline window), if both central lab and local lab results are available, then central lab results will be used instead of local lab results; local lab results will only be used if central lab results are missing.

7.2.2. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 (July 2017) (see Section 7.1.2) 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 (i.e., increased, decreased) will be presented separately.

For baseline, if both central lab and local lab results are available, then central lab results will be used to determine baseline toxicity grade; local lab results will only be used if central lab results are missing. For postbaseline laboratory abnormalities, both central lab and local lab results will be used.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

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

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

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 or 4 laboratory abnormalities

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

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

7.2.3. Liver-Related Laboratory Evaluations

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

- Alanine aminotransferase (ALT): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Aspartate aminotransferase (AST): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- ALT or AST: (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Total bilirubin: (a) > 1 × ULN, (b) > 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN
- ALT or AST > 3 × ULN and total bilirubin: (a) > 1.5 × ULN, (b) > 2 × ULN
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN

For individual laboratory tests, participants will be counted once based on the most severe postbaseline value. For both the composite endpoint of ALT or AST and total bilirubin, and the composite endpoint of ALT or AST, total bilirubin, and ALP, participants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of participants in the Safety Analysis Set with nonmissing postbaseline value of the tests in evaluation at the same postbaseline visit date.

Listings of liver-related laboratory tests will be provided.

7.3. Vital Signs and Respiratory Status

Descriptive statistics will be provided by treatment group for vital signs (including pulse rate, respiratory rate and 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 in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-participant listing of vital signs (including pulse rate, temperature, blood pressure, height, weight, and respiratory rate) and respiratory status (including SpO_2) will be provided by participant ID number and visit in chronological order.

7.4. Concomitant Medications

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

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 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 will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.5. Other Safety Measures

Renal replacement therapy during the study will be listed.

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

7.6. Changes from Protocol-Specified Safety Analyses

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

[redacted]

CCI [redacted]

9. 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.

10. SOFTWARE

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

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Study Procedures Table

	Screening	Baseline/ Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9, 10, 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17, 18, 19	Day 20	Day 21	Day 22, 23	Day 24	Day 25, 26, 27, 28	Day 29*	Day 29 and Day 60 Phone Follow-up Visits (+ 5 days)
Written Informed Consent	X																						
Inclusion/Exclusion Criteria	X																						
Focused Medical History, including SCr values[a]	X																						
Documentation of SARS-CoV-2 Infection[b]	X																						
Complete Physical Examination	X																						
Height	X																						
Weight	X																						
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Respiratory Status[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Invasive Mechanical Ventilation[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pulmonary Radiographic Imaging[e]	X																						
8-Point Ordinal Scale[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[g]	X																						
Chemistry[h,r]	X	X		X		X			X		X				X		X			X		X	
Hematology[i,r]	X	X		X		X			X		X				X		X			X		X	
Coagulation[j,r]	X	X		X		X			X		X				X		X			X		X	
Serum Creatinine[r,s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Screening	Baseline/ Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9, 10, 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17, 18, 19	Day 20	Day 21	Day 22, 23	Day 24	Day 25, 26, 27, 28	Day 29*	Day 29 and Day 60 Phone Follow-up Visits (+ 5 days)
Urinalysis[t]	X																						
RRT Assessment[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Virologic Testing[l]		X		X		X		X					X					X				X	
CCI																							
CCI																							
Investigational Drug Dosing		X	X	X	X	X																	
Adverse Events	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X
Mortality																							X
Hospital Readmission Rate																							X

* All assessments to be completed through Day 29, or until discharge, whichever is earlier. If participant is discharged prior to Day 29, a phone follow-up is to be completed at Day 29 and Day 60.

a Focused medical history will include date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics, concomitant medications, kidney or other transplant history, and allergies. If available, up to 3 SCr values prior to COVID-19 illness (eg, within the previous 6 months) should be provided. Document COVID-19 vaccine status. (Note: It should be documented whether participant is fully or partially vaccinated, including any booster[s] received, if applicable.)

b Positive as determined by PCR via 1 validated assay at a local laboratory, if not performed within the last 4 calendar days.

c Includes heart rate, temperature, and blood pressure.

d Respiratory status includes respiratory rate and oxygenation: see protocol Sections 6.2.1, 6.2.2, and 6.4.

e Pulmonary radiographic imaging may be performed within 72 hours, if not already available and if needed to satisfy eligibility criteria.

f Ordinal scale to be performed twice on Day 1: prior to randomization (for baseline predose score) and the worst score on Day 1.
g Serum pregnancy test will only be done for women of childbearing potential. Women < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range > 40 IU/L and they are not using hormonal contraception or hormonal replacement therapy. Results from within 48 hours prior to screening are acceptable.
h Chemistry: alkaline phosphatase, AST, ALT, total bilirubin, total protein, albumin, lactate dehydrogenase, creatine phosphokinase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lipase, magnesium, phosphorus, potassium, sodium, uric acid. Results from within 48 hours prior to screening are acceptable.
i Hematology: complete blood count with differential, hemoglobin and/or hematocrit, platelets. Results from within 48 hours prior to screening are acceptable.
j Coagulation performed by central lab: international normalized ratio, prothrombin time, activated partial thromboplastin time, D-dimer, fibrinogen. Results from within 48 hours prior to screening are acceptable.
k RRT will be measured at screening through Day 29 or until discharge from inpatient hospitalization, as well as at the Day 60 phone follow-up.
l Nasopharyngeal swab collection for virologic (SARS-CoV-2) testing for participants on Days 1, 3, 5, 7, 14, 21, and 29 or until discharge, whichever is earlier.
[redacted]
q If on invasive mechanical ventilation at screening, participant should be excluded from the study.
r For participants on intermittent RRT, laboratory safety assessments should be drawn before dialysis on the day of dialysis.
s Refer to protocol Inclusion Criterion #5 to determine the need for a confirmatory SCr evaluation.
t Participants who are oliguric are not required to provide a urine sample.

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.

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) TEAE

Events with Missing Onset Day and/or Month

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

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

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

iii. End date is as follows:

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

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

End date is completely missing

Events with Completely Missing Onset Date

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

9) Baseline risk factor

Selected medical history will be summarized as baseline risk factor and be included as subgroups in analysis. The risk factor of "current cancer" for a participant is defined as a medical history of one of these diseases:

— At least 1 ongoing medical history record with MedDRA PT (mh.MDRPT) in the following selected PT listing for the corresponding disease with start date on or prior to the first dose date;

— At least 1 ongoing AE record with MedDRA PT (ae.MDRPT) in the following selected PT listing for the corresponding disease with start date on or prior to the first dose date.

Other risk factors for a participant is defined as a medical history of one of these diseases:

— At least 1 medical history record with MedDRA PT (mh.MDRPT) in the following selected PT listing for the corresponding disease with start date on or prior to the first dose date;

— At least 1 AE record with MedDRA PT (ae.MDRPT) in the following selected PT listing for the corresponding disease with start date on or prior to the first dose date. If the start date is incomplete but the month and year (or year alone) of the start date is the same as or before the month and year (or year alone) of the first dosing date of study drug, the event will be included. If the start date is completely missing, the event will be included.

If the ongoing status is missing for an event:

- If the end date is completely missing and start date is the same as or before the first dosing date of the study drug, the event will be included;
- If the end date is completely missing and start date is after the first dosing date of the study drug, the event will not be included;
- If the end date is incomplete but the month and year (or year alone) of the end date is the same as or after the month and year (or year alone) of the first dosing date of study drug, the event will be included;
- If the end date is incomplete but the month and year (or year alone) of the end date is before the month and year (or year alone) of the first dosing date of study drug, the event will not be included.

A variable for each of the risk factors will be added to raw Medical History and Adverse Events datasets. A medical history or an AE record will be flagged for a risk factor if its MedDRA PT is included in the prespecified PT list for the corresponding disease of interest, which includes all PTs from the narrow or broad search of the following SMQs under MedDRA 25.0 provided by

Gilead GLPS and reviewed by Gilead medical monitors.

Disease of Interest	SMQ or MedDRA HLT Source
Chronic lung disease	HLT of bronchospasm and obstruction
Hypertension	Hypertension (SMQ)
Cardiovascular or cerebrovascular disease	Ischaemic central nervous system vascular conditions (SMQ); Myocardial infarction (SMQ); Other ischaemic heart disease (SMQ)
Diabetes mellitus	Hyperglycaemia/new onset diabetes Mellitus (SMQ)
Immunocompromised state	HLGT for “Immunodeficiency syndromes”
Chronic liver disease	search name “Chronic liver disease excluding transient_acute events and nonspecific signs_symptoms”
Current cancer	Malignancies (SMQ)

10) Details on SCr and BUN record exclusion for sensitivity analysis

SCr and BUN will only be analyzed for participants who are not on RRT at baseline.

<u>RRT at baseline</u>:

RRT started within 3 days of first dose is considered RRT at baseline. An RRT record with an end date prior to the first dose date - 3 days (or 72 hours if time available) or a start date/time after the first dose date/time will not be considered a baseline RRT record; otherwise, the record will be considered baseline.

SCr/BUN record exclusion (for participants who are not on RRT at baseline):

Any SCr/BUN records from an RRT start to end + 3 days will be excluded from analysis.

If both date and time are collected for RRT and labs, only date will be used, with 1 exception below:

If an SCr/BUN record is collected on the first dose date and prior to first dose time, and the participant's first RRT starts on the first dose date but after first dose time, then this lab record will not be excluded.

RRT date:

A missing end date of a hemodialysis record will be imputed using the hemodialysis start date.

If an end date is missing for a CVVH record:

- If this record is followed by another RRT (CVVH or hemodialysis) record, then the end date of this CVVH record will be imputed as the start date of the subsequent RRT record;
- If this record is the last available or the only RRT record for a participant:
  - If the participant died after the start of this CVVH record, then the end date of this CVVH record will be imputed as the death date;
  - Otherwise, the end date of this CVVH record will not be imputed, and all the SCr and BUN records after the start date of this CVVH record will be excluded from analysis.

11) Details on coagulation lab record exclusion for sensitivity analysis

Any coagulation lab records under the influence of anticoagulation medications will be excluded from analysis. For coagulation lab record exclusion, the start/end date of anticoagulation medications will be used. An anticoagulation medication may be taken chronically prior to and/or during the study.

Anticoagulation medication date:

If a medication end date is missing, the medication will be considered as "ongoing", and all coagulation lab records after the medication start date will be excluded from analysis.

If a medication start date is missing, all coagulation lab records will be considered after the medication start date.

For a partial medication end date:

- If only date is missing, then the date will be imputed as the last date of the month;

- If both month and date is missing, then the month and date will be imputed as December 31st of the year.

For a partial medication start date:

- If only date is missing, then the date will be imputed as the first date of the month;
- If both month and date is missing, then the month and date will be imputed as January 1st of the year.

12) Treatment difference in percentages not adjusted by stratum

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;
```

13) Difference in proportions between treatment groups adjusted by stratum

The 95% confidence interval for difference in between treatment groups will be calculated based on the stratum-adjusted Mantel-Haenszel (MH) proportion as described as follows {Koch 1989}, where the stratification factors include ESKD (Yes, No), High-flow oxygen requirement (Yes, No), and region (US, ex-US):

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

where

- $(P_1 - P_2) = \frac{\sum w_h d_h}{\sum w_h}$, is the stratum-adjusted MH proportion difference, where $d_h = p_{1h} - p_{2h}$ is the difference in the proportions of Treatment Groups 1 and 2 in stratum *h*.
- $w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$, 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*.
- $SE(P_1 - P_2) = \sqrt{\frac{\sum \left[\frac{p^*_{1h}(1-p^*_{1h})}{n_{1h}-1} + \frac{p^*_{2h}(1-p^*_{2h})}{n_{2h}-1} \right]}{(\sum w_h)^2}}$, 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 participants with event interest at Day 29 in Treatment Groups 1 and 2 in stratum *h*.
- $\alpha = 0.05$ for this study
- $Z_{(1-\alpha/2)} = Z_{0.975} = 1.96$ 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.

To facilitate SAS macro use, a single stratum variable could be defined as:

ESKD requiring chronic dialysis	High-flow oxygen requirement	Region	Stratum
Yes	No	US	1
Yes	No	ex-US	2
Yes	Yes	US	3
Yes	Yes	ex-US	4
No	No	US	5
No	No	ex-US	6
No	Yes	US	7
No	Yes	ex-US	8

14) Clarification for SE(P1-P2) Calculation in 13).

- if n1h or n2h > 1 the denominator n1h − 1 or n2h − 1 was calculated as indicated in the formula;
- if n1h or n2h =1, the corresponding n1h or n2h will be adjusted to 2, then corresponding denominator [(n1h − 1) or (n2h − 1)] is 1;
- if n1h or n2h = 0, then the corresponding stratum will be ignored, will not be included in the calculation, thus the proportion difference and 95% CI are still calculable.

15) Kidney disease status definition

Kidney disease data at baseline are collected in this study, including: history of CKD and ongoing AKI from the Medical History CRF form, ESKD status at Screening from the ENROLLMENT CRF form, and renal transplant history from the Transplant History CRF form.

Expected data patterns are as follows (renal transplant history can be present or absent for any of these combinations):

	Ongoing AKI (from MH CRF question)	History of CKD (from MH CRF question)	ESKD status at Screening (from ENROLLMENT CRF)	Kidney Disease Status
1	Yes	Any	No	AKI
2	No	Yes	No	CKD
3	Any	Any	Yes	ESKD

Kidney disease status is defined as:

- AKI: the 1st row of the above table, ie, ongoing AKI with or without history of CKD
- CKD: the 2nd row of the above table, ie, history of CKD without ongoing AKI
- ESKD: the 3rd row of the above table.

16) For demographics tables, "Not Permitted" will be excluded from percentage for detailed race categories summary (ie, race categories collected on eCRF). For combined Race Category (e.g. Asian, White, Black, Other), "Not Permitted" is included in "Other" and "Other" will be included in the count of percentage.

17) For calculation of peak serum creatinine (SCr) through Day 29 (among those without ESKD at baseline), (1) baseline records will not be included; (2) Day 1 postdose is included in the calculation; (3) for multiple records within one day, the observed record with max SCr will be selected; (4) For multiple days has the same highest value, the earliest will be picked.

18) Death date imputation

For a partial death date where the year and month are available but the date is missing, the following imputation will be performed:

- If the latest clinical date (ie, the latest of study drug start dates and end dates, the in-person or phone visit dates, the vital sign and the laboratory collection dates, including the Day 60 phone follow-up visit date) falls into the same year/month of death, then this latest clinical date will be used to impute the date of death;
- If the latest clinical date falls into the same year, but a prior month of death, then the 1st of the month of death will be the imputed date of death;
- If the latest clinical date falls into a prior year of death, then the 1st of the month of death will be the imputed date of death.

19) 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.

    If records for the same lab use different decimal places, the decimal place with majority records would be used.

    Exceptions may be considered.

20) 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)
	Lymphocytes	Decrease	Lymphocytes (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose	Increase	Serum Glucose (Hyperglycemia)
	Serum Glucose	Decrease	Serum Glucose (Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
Coagulation	Prothrombin Intl. Normalized Ratio (INR)	Increase	Prothrombin Intl. Normalized Ratio (Increased)
	Prothrombin Time (PT)	Increase	Prothrombin Time (Increased)
	Activated partial thromboplastin time (aPTT)	Increase	Activated partial thromboplastin time (Increased)

21) 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;
```

22) Proportional Odds

A proportional odds model including treatment as the independent variable and baseline score as a continuous covariate to compare the treatment groups:

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

A proportional odds model including treatment as the independent variable to compare the treatment groups (without covariate):

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

where outcome is the ordinal scale response at Day 15 and Day 29.

23) Cox model :

a) with stratification factors as covariates

```
proc phreg;
class trt strat1 strat2 strat3;
model aval*cnsr(1) = trt strat1 strat2 strat3 /risklimits = wald;
ods output  ParameterEstimates=Est1 ModelANOVA = pvout1;
run;
```

b) with no stratification factors as covariates

```
proc phreg;
class trt;
model aval*cnsr(1) = trt /risklimits = wald;
ods output  ParameterEstimates=Est1 ModelANOVA = pvout1;
run;
```

24) log-rank test

Log-rank test between treatment groups:

```
proc lifetest;
time aval*cnsr(1);
strata trt;
run;
```

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

25) Stratified log-rank test

Log-rank test between treatment groups:

```
proc lifetest;
time aval*cnsr(1);
strata strat1 strat2 strat3/group=trt;
run;
```

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

26) 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 strat1 strat2 strat3;
model aval* cnsr (1, 2) = trt strat1 strat2 strat3 / rl;
hazardratio "Cause-specific hazard" trt;
run;
```

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

SAS codes 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 aval* cnsr (1) / failcode = 0;*Note: this produces data for the event of interest only;
run;
```

SAS code to obtain support tables:

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

27) 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.

28) SAS code for ANCOVA:

```
ods output ParameterEstimates=out1 LSMeans=out2 LSMeanCL=out3
LSMeanDiffCL=out4;

proc glm data=dat1 plots=none;
  class trt;
  model DAVG = trt base / solution;
  lsmeans trt / stderr cl pdiff;
  run;
ods output close; quit;
```

29) SAS code for CMH test and estimates with stratification factors adjustment:

```
proc freq data=dat1;
  tables strat1*strat2*strat3*trt*Y/ list cmh;
ods output cmh=cmhpval CommonRelRisks=risk;
run;
```

30) Renal and hepatic adverse events include preferred terms from search term list 'Acute Renal Failure (SMQ)' and search term list 'Acute and non-infectious liver events' MedDRA 25.0.

31) Vital signs, and SCr collected after Day 29, PCR collected after day 44 will be assigned to "Post Day 29".

CCI [redacted]

33) For coagulation laboratory tests, both local and Covance lab records are collected in the data. In a visit where both Covance and local lab records are collected, Covance records will be picked over local lab records.

34) Reference ranges are based on Covance laboratory reference ranges.

35) COVID-19 medications include the following drugs:

Drug name
Chloroquine
Hydroxychloroquine
Lopinavir/ritonavir
Ribavirin
Remdesivir
Bamlanivimab/ etesevimab
Casirivimab/Imdevimab
Molnupiravir
Monoclonal antibodies
Convalescent plasma
Sotrovimab
Nirmatrelvir
Paxlovid
Regdanivimab
Tixagevimab/cilgavimab

with preferred term codes (WHODrug BMAR2022):

Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes
15665101001	14055301001	13983301001	13980301001	14248901001
15585401001	14068301001	14000901001	15847201001	08968801001
00001001001	15250901001	15337902001	08030701001	08342801001
00001002001	15379801001	15337901001	05699301001	15494501001
00001003001	15925301001	09304301001	14780501001	15646401001
00001004001	15701601001	15684201001	14780502001	15341201001
00001005001	15290701001	06356701001	15945601001	15633201001
00001006001	15251201001	14011101001	15395601001	15396501001
00001007001	15251601001	14033401001	14026001001	14048001001
00001008001	15416301001	15770001001	14056001001	01555211001
11198301001	15343501001	14182301001	14053601001	14057701001
11198302001	15665101001	14659001001	15356801001	14049401001
11282901001	15774801001	13408901001	14031801001	14010801001
11282902001	14037301001	15401601001	14492001001	01555207001
11617101001	14036401001	14816501001	14036601001	14548401001
11617102001	14052601001	14999701001	08032001001	14548402001
11724901001	14022401001	14033301001	01555212001	15400501001
11724902001	14148201001	14149501001	14164901001	15322701001
11725001001	13980701001	15350401001	13981101001	08969201001
11725002001	14022501001	15585401001	13983101001	08969202001
11725101001	15719902001	15710301001	15796001001	01402501001
11725102001	15719901001	15139201001	14691701001	01402503001
11725201001	13947301001	14183001001	14691702001	01402507001
11725202001	14152101001	14181701001	14057401001	01402502001
11725301001	13983001001	13999801001	15342201001	01402506001
11725302001	01555201001	15429101001	14039101001	01402504001
11725401001	01555202001	15616901001	14547901001	14055601001
11725402001	01555206001	13981201001	13978101001	14666201001
13117801001	01555205001	14004701001	08342601001	14346101001
13118301001	01555203001	14005201001	01555210001	07222101001
13118401001	12336402001	14031101001	14397901001	01555213001

Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes
13183901001	14396302001	14001401001	14030401001	07244601001
13480201001	14396401001	07841501001	14585201001	06331801001
13480202001	14396501001	09304401001	14155601001	07209901001
14001301001	14396502001	09304402001	13979801001	15464401001
14001302001	14397801001	01445608001	15350501001	15429001001
14001303001	13975801001	12759302001	01445601001	01759101001
15363001001	14849201001	14033001001	01445604001	14359501001
15363002001	13776401001	12759301001	01445609001	15267901001
15616901001	14398601001	14148601001	01445605001	
00072601001	14398701001	14148501001	01445606001	
00072602001	15290001001	15603201001	01445607001	
00072603001	15868501001	13982501001	01445602001	
11725301001	13157101001	12734302001	01445603001	
11725302001	14404701001	12759102001	15960101001	
12881901001	14399701001	12689502001	12771001001	
14693401001	14399801001	13111502001	13947001001	
15440701001	15378701001	14040601001	07251001001	
15469801001	14847801001	12734301001	07339901001	
15470001001	12336401001	12759101001	09018701001	
15326101001	14848001001	14152701001	09018702001	
15892101001	14396301001	14165501001	14213701001	
15748501001	13826001001	14053001001	14031901001	
15892101001	14400001001	13109601001	13981601001	
15400501001	14400002001	12689501001	14165301001	
14269001001	13840901001	13111501001	14055901001	
00816701001	15900001001	14228101001	14055902001	
06821701001	13696801001	14151501001	15334201001	
12751901001	14982301001	14279401001	15583201001	
12751902001	15578501001	14182701001	08745601001	
13389401001	14400101001	14031501001	14741401001	
13485001001	14400102001	14048101001	15325601001	
13633501001	14955501001	13111401001	01555208001	
13709401001	14400201001	14279402001	08290701001	

Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes
13769601001	14400202001	14216301001	14194301001	
13769901001	15502802001	13110601001	15269501001	
13770201001	15502801001	13111503001	14410101001	
13770901001	14400301001	13981901001	14183101001	
13771401001	14400302001	13982601001	14039401001	
13772801001	15868401001	13110701001	13980401001	
15464401001	01402505001	13110702001	01555209001	
01612901001	01612906001	14000501001	15500901001	
01612904001	01555204001	14030001001	15261201001	
01612903001	14193001001	14023901001	07872901001	
01612907001	14054001001	14034301001	15520801001	
01612911001	14054801001	15927901001	15539901001	
01612902001	14181501001	13980101001	15578201001	
01612909001	12759202001	14032301001	15628001001	
01612910001	14666301001	14032501001	15536601001	
01612905001	14000401001	15388901001	07252301001	
01612908001	12759201001	14407901001	01601501001	
14022001001	14032001001	14997401001	14972001001	
14156901001	14032401001	14151801001	13978201001	
14149701001	15632601001	13979301001	15586901001	

36) Hypersensitivity including Infusion-Related Reaction includes MedDRA Terms (MedDRA 25.0) listed in the following table:

MedDRA Term Name	MedDRA Term Name	MedDRA Term Name	MedDRA Term Name
Acquired C1 inhibitor deficiency	Cross sensitivity reaction	Injection site urticaria	Skin necrosis
Acute generalised exanthematous pustulosis	Cutaneous vasculitis	Injection site vasculitis	Skin reaction
Administration related reaction	Dennie-Morgan fold	Instillation site hypersensitivity	Skin test positive
Administration site dermatitis	Dermal filler reaction	Instillation site rash	Solar urticaria
Administration site eczema	Dermatitis	Instillation site urticaria	Solvent sensitivity

MedDRA Term Name	MedDRA Term Name	MedDRA Term Name	MedDRA Term Name
Administration site hypersensitivity	Dermatitis acneiform	Interstitial granulomatous dermatitis	Stevens-Johnson syndrome
Administration site rash	Dermatitis allergic	Intestinal angioedema	Stoma site hypersensitivity
Administration site recall reaction	Dermatitis atopic	Iodine allergy	Stoma site rash
Administration site urticaria	Dermatitis bullous	Kounis syndrome	Stridor
Administration site vasculitis	Dermatitis contact	Laryngeal oedema	Swelling face
Allergic bronchitis	Dermatitis exfoliative	Laryngitis allergic	Swelling of eyelid
Allergic colitis	Dermatitis exfoliative generalised	Laryngospasm	Swollen tongue
Allergic cough	Dermatitis herpetiformis	Laryngotracheal oedema	Symmetrical drug-related intertriginous and flexural exanthema
Allergic cystitis	Dermatitis infected	Limbal swelling	Throat tightness
Allergic eosinophilia	Dermatitis psoriasiform	Lip oedema	Tongue oedema
Allergic gastroenteritis	Device allergy	Lip swelling	Toxic epidermal necrolysis
Allergic hepatitis	Dialysis membrane reaction	Mast cell activation syndrome	Toxic skin eruption
Allergic keratitis	Distributive shock	Mast cell degranulation present	Tracheal oedema
Allergic lymphangitis	Documented hypersensitivity to administered product	Medical device site dermatitis	Type I hypersensitivity
Allergic oedema	Drug eruption	Medical device site eczema	Type II hypersensitivity
Allergic otitis externa	Drug hypersensitivity	Medical device site hypersensitivity	Type III immune complex mediated reaction
Allergic otitis media	Drug provocation test	Medical device site rash	Type IV hypersensitivity reaction
Allergic pharyngitis	Drug reaction with eosinophilia and systemic symptoms	Medical device site recall reaction	Urticaria
Allergic reaction to excipient	Eczema	Medical device site urticaria	Urticaria cholinergic
Allergic respiratory disease	Eczema infantile	Mouth swelling	Urticaria chronic

MedDRA Term Name	MedDRA Term Name	MedDRA Term Name	MedDRA Term Name
Allergic respiratory symptom	Eczema nummular	Mucocutaneous rash	Urticaria contact
Allergic sinusitis	Eczema vaccinatum	Multiple allergies	Urticaria papular
Allergic stomatitis	Eczema vesicular	Nephritis allergic	Urticaria physical
Allergic transfusion reaction	Eczema weeping	Nikolsky's sign	Urticaria pigmentosa
Allergy alert test positive	Encephalitis allergic	Nodular rash	Urticaria vesiculosa
Allergy test positive	Encephalopathy allergic	Nutritional supplement allergy	Urticarial dermatitis
Allergy to immunoglobulin therapy	Eosinophilic granulomatosis with polyangiitis	Oculomucocutaneous syndrome	Urticarial vasculitis
Allergy to surgical sutures	Epidermal necrosis	Oculorespiratory syndrome	Vaccination site dermatitis
Allergy to vaccine	Epidermolysis	Oedema mouth	Vaccination site eczema
Anal eczema	Epidermolysis bullosa	Oral allergy syndrome	Vaccination site exfoliation
Anaphylactic reaction	Epiglottic oedema	Orbital swelling	Vaccination site hypersensitivity
Anaphylactic shock	Erythema multiforme	Oropharyngeal blistering	Vaccination site rash
Anaphylactic transfusion reaction	Erythema nodosum	Oropharyngeal oedema	Vaccination site recall reaction
Anaphylactoid reaction	Exfoliative rash	Oropharyngeal spasm	Vaccination site urticaria
Anaphylactoid shock	Eye allergy	Oropharyngeal swelling	Vaccination site vasculitis
Anaphylaxis treatment	Eye oedema	Palatal oedema	Vaccination site vesicles
Angioedema	Eye swelling	Palatal swelling	Vaginal ulceration
Anti-neutrophil cytoplasmic antibody positive vasculitis	Eyelid oedema	Palisaded neutrophilic granulomatous dermatitis	Vancomycin infusion reaction
Antiallergic therapy	Face oedema	Palpable purpura	Vascular access site dermatitis
Antiendomysial antibody positive	Fixed eruption	Pathergy reaction	Vascular access site eczema
Application site dermatitis	Flushing	Perioral dermatitis	Vasculitic rash
Application site eczema	Generalised bullous fixed drug eruption	Periorbital dermatitis	Vasodilatation
Application site hypersensitivity	Giant papillary conjunctivitis	Periorbital oedema	Vernal keratoconjunctivitis
Application site rash	Gingival oedema	Periorbital swelling	Vessel puncture site rash

MedDRA Term Name	MedDRA Term Name	MedDRA Term Name	MedDRA Term Name
Application site recall reaction	Gingival swelling	Pharyngeal oedema	Vessel puncture site vesicles
Application site urticaria	Gleich's syndrome	Pharyngeal swelling	Vulval eczema
Application site vasculitis	Haemorrhagic urticaria	Polymers allergy	Vulval ulceration
Arthritis allergic	Hand dermatitis	Post procedural fever	Vulvovaginal rash
Aspirin-exacerbated respiratory disease	Heart rate decreased	Procedural shock	Vulvovaginal ulceration
Atopic cough	Henoch-Schonlein purpura	Pruritus allergic	Vulvovaginitis allergic
Atopy	Henoch-Schonlein purpura nephritis	Pseudoallergic reaction	
Blepharitis allergic	Heparin-induced thrombocytopenia	Radioallergosorbent test positive	
Blood immunoglobulin E abnormal	Hyperhidrosis	Rash	
Blood immunoglobulin E increased	Hypersensitivity	Rash erythematous	
Blood pressure decreased	Hypersensitivity myocarditis	Rash follicular	
Blood pressure diastolic decreased	Hypersensitivity pneumonitis	Rash macular	
Blood pressure diastolic increased	Hypersensitivity vasculitis	Rash maculo-papular	
Blood pressure increased	Hypertension	Rash maculovesicular	
Blood pressure systolic decreased	Hypotension	Rash morbilliform	
Blood pressure systolic increased	Idiopathic urticaria	Rash neonatal	
Bone cement allergy	Immediate post-injection reaction	Rash papulosquamous	
Bradyarrhythmia	Immune thrombocytopenia	Rash pruritic	
Bradycardia	Immune tolerance induction	Rash pustular	
Bromoderma	Implant site dermatitis	Rash rubelliform	
Bronchial obstruction	Implant site hypersensitivity	Rash scarlatiniform	
Bronchospasm	Implant site rash	Rash vesicular	
Bullous haemorrhagic dermatosis	Implant site urticaria	Reaction to azo-dyes	

MedDRA Term Name	MedDRA Term Name	MedDRA Term Name	MedDRA Term Name
Catheter site dermatitis	Incision site dermatitis	Reaction to colouring	
Catheter site eczema	Incision site rash	Reaction to excipient	
Catheter site hypersensitivity	Infusion related hypersensitivity reaction	Reaction to flavouring	
Catheter site rash	Infusion related reaction	Reaction to food additive	
Catheter site urticaria	Infusion site dermatitis	Reaction to preservatives	
Catheter site vasculitis	Infusion site eczema	Reaction to sweetener	
Chronic eosinophilic rhinosinusitis	Infusion site hypersensitivity	Rhinitis allergic	
Chronic hyperplastic eosinophilic sinusitis	Infusion site rash	Scleral oedema	
Circulatory collapse	Infusion site recall reaction	Scleritis allergic	
Circumoral oedema	Infusion site urticaria	Scrotal dermatitis	
Circumoral swelling	Infusion site vasculitis	Scrotal oedema	
Conjunctival oedema	Injection related reaction	Serum sickness	
Conjunctivitis allergic	Injection site dermatitis	Serum sickness-like reaction	
Contact stomatitis	Injection site eczema	Shock	
Contrast media allergy	Injection site hypersensitivity	Shock symptom	
Contrast media reaction	Injection site rash	Sinus bradycardia	
Corneal oedema	Injection site recall reaction	SJS-TEN overlap	

37) COVID-19 vaccines include the following preferred term codes (WHODrug BMAR2022):

Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes
00002001001	15268629001	15268666001
06201402001	15268630001	15268667001
06439204001	15268631001	15268668001
06559301001	15268632001	15268669001
06559307001	15268633001	15268670001
13195801001	15268634001	15268671001
13949502001	15268635001	15268672001
13950013001	15268636001	15268673001

Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes
14953401001	15268637001	15268674001
14953501001	15268638001	15268675001
15092101001	15268639001	15268676001
15268601001	15268640001	15268677001
15268602001	15268641001	15268678001
15268603001	15268642001	15268679001
15268604001	15268643001	15268680001
15268605001	15268644001	15268681001
15268607001	15268645001	15268682001
15268609001	15268646001	15268683001
15268610001	15268647001	15268684001
15268611001	15268648001	15268685001
15268612001	15268649001	15268686001
15268613001	15268650001	15268687001
15268614001	15268651001	15268688001
15268615001	15268652001	15268689001
15268616001	15268653001	15268690001
15268617001	15268654001	15268691001
15268618001	15268655001	15268692001
15268619001	15268656001	15268693001
15268620001	15268657001	90031301001
15268621001	15268658001	
15268622001	15268659001	
15268623001	15268660001	
15268624001	15268661001	
15268625001	15268662001	
15268626001	15268663001	
15268627001	15268664001	
15268628001	15268665001	

38) Antithrombotic medications include the following drugs:

Drug name
Direct factor Xa inhibitors
Direct thrombin inhibitors
Low molecular weight heparins (LMWH) and heparinoids
Other heparins
Other antithrombotic drugs
Platelet aggregation inhibitors, excluding heparin
Thrombolytic drugs
Vitamin K antagonists
Heparins

with preferred term codes (WHODrug BMAR2022):

Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes
06259501001	13765501001	12384902001	12353501001	13595102001	11890502001	12800601001
06324201001	13765502001	13825101001	12353502001	11902101001	12829002001	11012901001
06324202001	13766301001	13825102001	12354601001	11902102001	12779502001	13576201001
06297801001	15159701001	13824801001	12354201001	12382602001	12779503001	11885501001
06297802001	15159702001	12385301001	12354202001	12382402001	12779602001	13576701001
06297803001	12430501001	12385501001	12353602001	12382601001	11485302001	90045701001
01551201001	12430502001	12384901001	12353601001	12382401001	11756602001	13185301001
01551202001	11096401001	13824501001	13623001001	12382403001	12150301001	12189002001
05705201001	11096402001	11549402001	12150502001	13749001001	11923801001	12189003001
01369401001	11902001001	11549401001	12150503001	13707401001	12151101001	12189001001
01369402001	11902002001	10534502001	12150501001	13707402001	11902401001	13599601001
01506801001	13600801001	10534501001	11610504001	11890503001	11641801001	13599602001
01506802001	12150602001	12268601001	11610502001	12406404001	13629501001	11442802001
01633201001	12150601001	12268602001	11610002001	12406403001	12150201001	11442801001
01633202001	01384201001	12269902001	11610203001	12382702001	11492701001	12180302001
01633203001	01384202001	12283302001	11610202001	11578403001	13313701001	12646902001
01288601001	11097102001	11177702001	14527702001	11578402001	12151401001	12646901001
01346001001	11678602001	12283301001	12406402001	11096101001	10907301001	00889601001
01384201001	11678601001	12269901001	12456903001	11096102001	11052701001	00889603001
01384202001	11097101001	11177701001	12456902001	12416702001	12286502001	00889602001
07368201001	13431901001	14427201001	12156601001	12416701001	12286501001	11866102001
07368202001	11623502001	14421501001	12156602001	00027701001	13572501001	11866101001
01708301001	11623501001	14488101001	11699802001	00027702001	12150701001	00723702001

Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes	Prohibited PREF Codes
01708302001	13629801001	14488102001	11699803001	90006801001	12408701001	12344202001
01353901001	12181303001	01691801001	12186802001	00027705001	12406401001	11643102001
01353902001	12181302001	11699701001	11699602001	00027711001	12457201001	11012902001
06297801001	12181301001	11699702001	11699801001	00027710001	12456901001	13576202001
06297802001	07368201001	12475602001	12186801001	00027704001	12690401001	11885502001
06297803001	07368202001	12475601001	11699601001	00027708001	10999501001	01437701001
01707901001	12472001001	11375501001	14440702001	00027712001	12150901001	01437702001
01707902001	12472002001	11375502001	14440701001	00027707001	12382701001	07957701001
07957501001	11645802001	15876401001	01708201001	12150302001	12151201001	07957702001
07957502001	11645801001	15260602001	01708202001	11923802001	15778101001	00552101001
10679802001	10995602001	15260601001	12231802001	12151102001	12748001001	00552102001
13575901001	10995601001	12424001001	12231801001	11902402001	12517101001	11196102001
13575902001	12747502001	12424002001	11095802001	11641802001	11890501001	11657802001
10679801001	12747501001	10685602001	11095801001	13629502001	12829001001	11173402001
12601302001	12471001001	10685601001	11610503001	12150202001	14455101001	11196101001
12150802001	12471002001	01708301001	13472301001	11492702001	12779501001	11657801001
12150801001	11645702001	01708302001	13472302001	12151402001	12779601001	11173401001
12669701001	11645701001	01353901001	11718202001	10907302001	11485301001	13178201001
12669702001	11729402001	01353902001	11718201001	10907303001	15876301001	05509001001
11681801001	11729401001	07957801001	11610501001	11052702001	15878201001	05509002001
11681802001	12385504001	07957802001	11610001001	12150702001	11756601001	08069601001
12601301001	12385602001	07368001001	11610201001	12408702001	00723701001	08069602001
12430802001	12385601001	12190302001	14527701001	12457202001	13599501001	07579101001
13802202001	12385002001	12190301001	12382902001	12690402001	13720001001	07579102001
12431002001	12385001001	11514301001	12382302001	10999502001	13313601001	08336301001
12431001001	12479901001	11514302001	11885902001	12150902001	12180301001	01486301001
12430801001	12479902001	11732402001	12382301001	12151202001	12188202001	01063701001
13802201001	12385502001	11732301001	12382901001	12748002001	12188201001	00027709001
13802203001	12385503001	11732302001	11885901001	12748003001	12344201001	06563401001
15767701001	12385302001	11732401001	13595301001	12517103001	11643101001	06563402001
15767702001	12384903001	12354602001	13595101001	12517102001	11578401001	
01707901001	00075201001	00007401001	00014801001	00014803001	00014804001	
01707902001	00723901001	00062601001	00014805001	00014802001	00393001001	

39) Figures:

For figures, for a time point where n (sample size) is <= 5, data will not be displayed at that time point in the figure, but all data will be included in the corresponding table summary.

GS-US-540-5912-SAP-Final Analysis

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	26-Jul-2022 17:28:10
PPD	Clinical Research eSigned	27-Jul-2022 14:25:46