STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting
Name of Test Drug:	Remdesivir
Study Number:	GS-US-540-9012
Protocol Version (Date):	Amendment 4: 14 January 2021
Analysis Type:	Final Analysis
Analysis Plan Version:	1.0
Analysis Plan Date:	12 August 2021
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
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
ET	early termination
FAS	Full Analysis Set
FLU-PRO©	InFLUenza Patient-Reported Outcome
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)
IV	Intravenous
IXRS	interactive voice or web response system
LLT	lower-level term
LOD	Limit of detection
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PCR	polymerase chain reaction
CCI	[redacted]
PT	preferred term
PTM	Placebo to match
Q1, Q3	first quartile, third quartile
RDV	remdesivir (GS-5734™)
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
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
WHO	World Health Organization

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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-540-9012. This SAP is based on the study protocol amendment 4 dated 14 January 2021 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To evaluate the efficacy of RDV in reducing the rate of COVID-19 related hospitalization or all-cause death in non-hospitalized participants with early stage COVID-19
- To evaluate the safety of RDV administered in an outpatient setting

The secondary objectives of this study are as follows:

- To evaluate the efficacy of RDV in reducing the rate of COVID-19 related medically attended visits (MAVs; medical visits attended in person by the participant and a health care professional) or all-cause death in non-hospitalized participants with early stage COVID-19
- To determine the antiviral activity of RDV on SARS-CoV-2 viral load
- To assess the impact of RDV on symptom duration and severity

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1.2. Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of RDV therapy for outpatients with early stage COVID-19 who are at higher risk of disease progression.

Participants who meet all eligibility criteria may be randomized in a 1:1 ratio to RDV or placebo. Randomization will be stratified by participants who reside in a skilled nursing facility, by participant's age (< 60 vs ≥60 years), and by region (United States [US] vs. ex-US):

Treatment Group A: single dose of IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2 and 3 (RDV group)

Treatment Group B: IV placebo-to-match (PTM) RDV on Days 1 to 3 (PTM group)

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Willing and able to provide written informed consent (participants ≥ 18 years of age) or assent (participants ≥ 12 and < 18 years of age) prior to performing study procedures. Participants aged ≥ 18 years may be enrolled with the consent of a legal representative where permitted according to local law and approved nationally and by the relevant institutional review board (IRB) or independent ethics committee (IEC). For participants ≥ 12 and < 18 years of age, a parent or legal guardian must be willing and able to provide written informed consent prior to performing study procedures

2) Either:

   — Age ≥ 18 years (at all sites) or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved nationally and by the relevant IRB or IEC) with at least 1 of the following pre-existing risk factors for progression to hospitalization:

      a) Chronic lung disease: chronic obstructive pulmonary disease, moderate-to-severe asthma, cystic fibrosis, pulmonary fibrosis

      b) Hypertension: systemic or pulmonary

      c) Cardiovascular or cerebrovascular disease: coronary artery disease, congenital heart disease, heart failure, cardiomyopathy, history of stroke, atrial fibrillation, hyperlipidemia

      d) Diabetes mellitus: Type 1, type 2, or gestational

      e) Obesity (BMI ≥ 30)

f) Immunocompromised state; having a solid organ transplant, blood, or bone marrow transplant; immune deficiencies; HIV with a low CD4 cell count or not on HIV treatment; prolonged use of corticosteroids; or use of other immune weakening medicines

g) Chronic mild or moderate kidney disease

h) Chronic liver disease

i) Current cancer

j) Sickle cell disease

— OR age ≥ 60 years, regardless of the presence of other pre-existing risk factors for progression

3) SARS-CoV-2 infection confirmed by molecular diagnostics (nucleic acid [eg, PCR] or antigen testing) ≤ 4 days prior to screening

4) Presence of ≥ 1 symptom(s) consistent with COVID-19 for ≤ 7 days prior to randomization (such as fever, cough, fatigue, shortness of breath, sore throat, headache, myalgia/arthralgia)

5) Not currently receiving, requiring, or expected to require supplemental oxygen

6) Not currently requiring hospitalization (hospitalization defined as ≥ 24 hours of acute care)

7) Participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception

Exclusion criteria for participation include:

1) Participation in any other clinical trial of an experimental treatment and prevention for COVID-19

2) Prior hospitalization for COVID-19 (hospitalization defined as ≥ 24 hours of acute care)

3) Treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 or administration of any SARS-CoV-2 (or COVID-19) vaccine

4) Criterion removed

5) Requiring oxygen supplementation

6) ALT or AST ≥ 5 × upper limit of normal (ULN) at screening or within 90 days of screening
Note: if per local practice only ALT is routinely measured, exclusion criteria will be evaluated on ALT alone

7) Creatinine clearance < 30 mL/min at screening or within 90 days of screening using the Cockcroft-Gault formula in participants ≥ 18 years of age or estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 at screening or within 90 days of screening using the Schwartz formula in participants < 18 years of age (see Section 6.7.2 of protocol)

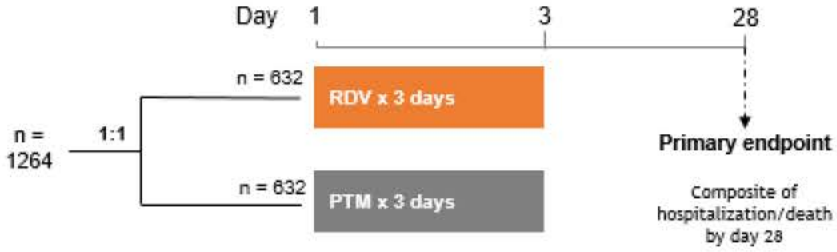
8) Currently breastfeeding (nursing)

9) Known hypersensitivity to the study drug, metabolites, or formulation excipient

10) Use or planned use of exclusionary medications (refer to Section 5.4 of protocol)

Participants will receive study treatment with RDV for 3 days (Treatment Group A) or PTM for 3 days (Treatment Group B).

Figure 1-1. Study Schema



On study Days 1 through 3, vital signs including respiratory status and SpO_2 will be measured, and adverse events (AEs) and concomitant medications will be documented. Laboratory tests for safety (hematology, coagulation and chemistry) will be performed on Days 1, 3, 7, and 14. Nasopharyngeal swabs and sputum samples will be collected on Days 1, 2, 3, 7, and 14 for SARS-CoV-2 quantitative reverse transcriptase polymerase chain reaction viral load testing and possible resistance testing.

On study Day 14 physical examination findings, vital signs including temperature, respiratory rate, and SpO_2, AEs and concomitant medications will be documented.

Symptom severity will be assessed daily from Day 1 through Day 14 using the COVID-19 adapted FLU-PRO Plus questionnaire (if available). On study Day 28, there will be an in-person or phone visit. Physical examination, vital signs including temperature, respiratory rate, and SpO_2, AEs, MAV information and concomitant medications will be documented (only AEs, MAV information and concomitant medications needed if performed by phone).

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1.3. Sample Size and Power

The total sample size of the study will be approximately 1264 participants.

The sample size computation is based on proportions of COVID-19 related hospitalization or all-cause death by Day 28 for the RDV and placebo treatment groups. The sample size needed for a 1:1 randomization using a 2-tailed test at level α is given by:

$$\frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{P(1-R^2)\sigma^2 B^2}$$

Where P is the overall rate of COVID-19 related hospitalization or all-cause death, B is the log hazard ratio, σ is the standard deviation of treatment indicator variable, R is the R-Squared that is obtained when treatment indicator variable is regressed on the other covariates, and $z_{1-\alpha/2}$ and $z_{1-\beta}$ are the 1-α/2 and 1-β quantiles of the standard normal distribution.

A sample size of 1264 participants (632 in each group with 1:1 randomization) achieves > 90% power to detect a ratio of 0.55 (RDV to placebo) in proportion of COVID-19 related hospitalization or all-cause death, which is equal to a hazard ratio of 0.534) using a two-sided significance level of 0.05 assuming the overall COVID-19 related hospitalization or all-cause death rate is 9.3% (12% in the placebo group and 6.6% in the RDV group) and a 5% drop out rate. The sample size provides approximately 80% power to detect a smaller treatment effect size with a ratio of 0.60 (RDV to placebo), assuming a 2-sided significance level of 0.05 and the overall COVID-19 related hospitalization or all-cause death rate is 9.6% (12% in the placebo group and 7.2% in the RDV group) and a 5% drop out rate. The proportion of patients with COVID-19-related hospitalizations or emergency department (ED) visits was 13.5% in high risk patients (age ≥ 65 or BMI ≥ 35) who received placebo{Gottlieb 2021}, 12% is assumed for the study to account for decrease in hospitalization rate in recent months.

The sample size calculation was done using software PASS (Version 14.0, module of Cox regression for survival).

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.

2.1.1. DMC Analysis

One external multidisciplinary DMC was planned to review the progress of the study and to perform interim reviews of the efficacy (futility assessment) and safety data. However, this DMC analysis was not performed due to the stop of study enrollment after 584 participants randomized and prior to reaching the planned DMC analysis schedule (ie, approximately 50% of the total 1264 planned participants have completed Day 28 assessment).

2.2. 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. This SAP describes the analysis plan for the final analysis.

2.3. Changes from Protocol-Specified Analyses

The DMC analysis was not performed due to the stop of enrollment on 08 April 2021 after less than 50% of the participants were randomized. The reasons of stopping enrollment were due to significant changes in the epidemiology of COVID-19 from a combination of lower hospitalization rates and high vaccine rates in high-risk patients, and a change in the unmet patient need for convenient at home options for non-hospitalized patients with COIVD-19. The decsion to stop study ernollment was documented on 06-APR-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.

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

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

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

3.1.3. Modified Full Analysis Set

A modified full analysis set (mFAS) includes all participants who (1) are randomized into the study, and (2) have received at least 1 dose of study treatment, and (3) enrolled under protocol amendment 2 or later. Participants will be grouped according to the treatment to which they were randomized.

3.1.4. 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 treatment. Participants will be grouped according to the treatment which they received.

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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 study treatment, and (3) have positive SARS-CoV-2 viral load at baseline (result of 'No SARS-CoV-2 detected' is considered as negative, results of 'Inconclusive', "<2228cp/mL SARSCoV2 detected" and numerical results are considered as positive).

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set, FAS, mFAS or Virology Analysis Set, participants will be grouped according to the treatment to which they were randomized. For the safety analysis set, the actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

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3.3. Strata and Covariates

Participants will be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- Region: US vs. ex-US
- Participant's age: < 60 vs ≥ 60 years
- Resident of skilled nursing facility: Yes vs. No

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

The primary efficacy endpoint will be evaluated in a stratified analysis based on the same 3 factors used for randomization, as specified in Section 6.1.3. 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 Subject Subgroups

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

- region (US vs. ex-US)
- participant's age (<18, 18≤ - < 60, ≥ 60 years),
- participants who reside in a skilled nursing facility (Yes, No),
- Sex at birth: (a) male and (b) female
- Race: (a) Asian, (b) Black, (c)White, (d) other
- Baseline risk factor: Chronic lung disease (Yes, No), Hypertension (Yes, No), Cardiovascular or cerebrovascular disease (Yes, No), Diabetes mellitus (Yes, No), Obesity (Yes, No), Immunocompromised state (Yes, No), Chronic mild or moderate kidney disease (Yes, No), Chronic liver disease (Yes, No), Current cancer (Yes, No), Sickle cell disease (Yes, No)
- Common COVID-19 symptoms at baseline: absence or presence for each of the following symptoms: Stuffy or runny nose; Sore throat; Shortness of breath (difficulty breathing); Cough; Low energy or tiredness; Muscle or body aches; Headache; Chills or shivering; Feeling hot or feverish; Nausea; Vomit; Diarrhea; Loss of Smell; Loss of taste.

In addition, other subgroups may be considered based on imbalances between treatment groups observed in other baseline characteristics.

3.5. Multiple Comparisons

There will be no multiplicity adjustment in the final analysis. Efficacy will be evaluated using the primary efficacy endpoint at the significance level of 0.05. All other efficacy endpoints are exploratory in nature and will be tested using 2-sided tests at the 5% significance level without multiplicity adjustment.

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.

Participants with missing outcomes for the primary endpoint due to premature discontinuation of the study will be censored at last study date.

In this study, a missing pre-treatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary. The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2, and for prior and concomitant medications in Section 7.4.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process. 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 based on date of birth and the first dose date will be used instead. If an enrolled participant was not dosed with any study drug, the 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 limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

SARS-COV2 viral load results that are below LOQ but have a positive signal will be reported as "<2228cp/mL SARSCoV2 detected" and those that are below lower limit of detection(LOD) and negative will be reported as "No SARS-CoV2 detected". The data will be imputed as follows:

- A value of 1114 copies/ml (half of the LOQ 2228 copies/ml) will be used to calculated descriptive statistics if the datum is reported as "<2228cp/mL SARSCoV2 detected".

- A value of 746.5 copies/ml (1/2 of the LOD 1493 copies/ml) will be used to calculated descriptive statistics if the datum is reported as "No SARS-CoV2 detected"

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

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

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3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

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

- For postdose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 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. Refer to Appendix 2 for missing date imputation, if necessary.

Last Study Date is the latest of the study drug start dates and end dates, the in-person or phone visit dates, the vital sign or respiratory status collection dates, Flu-PRO Plus questionnaire collection date and the laboratory collection dates, including the 28-day follow-up visit date, and the death date (if applicable, only for participants who prematurely discontinued study according to the Study Completion eCRF).

Baseline value is defined as the last value obtained on or prior to the first dose date (and time, if available) unless otherwise specified (see Section 3.8.3).

3.8.2. Analysis Visit Windows

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

The analysis windows for Vital signs are provided in Table 3-1.

Table 3-1. Analysis Visit Windows for Vital signs

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1 (Pre Dose)*
Day 1	1	1 (Post Dose) *	1 (Post Dose)
Day 2#	2	2	2
Day 3#	3	3	4
Day 7	7	5	9
Day 14	14	10	21
Day 28	28	22	(none)

* For baseline, the upper limit includes values collected at or prior to the first dose date/time. For Day 1, the lower limit includes values collected after the first dose date/time on Day 1.

The pre dose and post dose timepoints for Days 2 and 3 will be based on nominal time point.

The analysis windows for Weight, and Respiratory status are provided in Table 3-2.

Table 3-2. Analysis Visit Windows for Weight, SpO_2 and Respiratory status

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1 (Pre Dose)*
Day 2	2	1 (Post Dose) *	2
Day 3	3	3	4
Day 7	7	5	9
Day 14	14	10	21
Day 28	28	22	(none)

* For baseline, the upper limit includes values collected at or prior to the first dose date/time. For Day 2, the lower limit includes values collected after the first dose date/time on Day 1.

The analysis windows for PCR are provided in Table 3-3.

Table 3-3. Analysis Visit Windows for PCR

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1 (Pre Dose)
Day 2	2	1 (Post Dose)	2
Day 3	3	3	4
Day 7	7	5	9
Day 14	14	10	21
Post Day 14	22	22	none

The analysis windows for Chemistry and Hematology laboratory parameters are provided in Table 3-4.

Table 3-4. Analysis Visit Windows for Hematology, Coagulation and Chemistry 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)	4
Day 7	7	5	9
Day 14	14	10	(none)

FLU-PRO Plus Questionnaire were to be collected daily from Day 1 through Day 14; therefore, windows are not assigned and results will be summarized for each Study Day.

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 the average of the measurements for continuous data, or the measurement with the lowest severity for categorical data.
  - For baseline, if both local lab and central lab results are available, central lab results will be selected first for baseline, local lab results will be used when central lab results are missing.
  - For FLU-PRO Plus data, if there are multiple records on Day 1, the baseline value will be selected as follows:
    - The record closest to the dosing day will be selected.
    - If there are more than 1 records on the selected day with different times, the least severe score will be selected as baseline. If there are multiple records with same severity, the measurement with the lowest severity at later time will be selected.

- For postbaseline values (other than PCR negative confirmation and PCR for time-weighted average change from baseline (DAVG)):
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, values will be selected for analysis as follows:
    - For PCR, if there is more than 1 record on the selected day, the latest value will be selected. If there are multiple records with the same time or no time recorded on the same day, the geometric mean value (copies/mL) will be taken. For laboratory values (other than PCR) and SpO_2, if there is more than 1 record on the selected day, the average value will be selected.
    - For FLU-PRO Plus data, if there are more than 1 record on the same day, the worst value will be selected.
    - For RBC Morphology result, if there is more than 1 record on the selected day, all results will be selected.
    - For vital signs, the pre dose and post dose timepoints for Days 2 and 3 will be summarized by nominal time point. If there is more than 1 record on a time point, the average will be taken.
    - For other parameters, if there is more than 1 record on the selected day, the average will be taken for continuous data and the worst severity will be taken for categorical data, unless otherwise specified.
- For postbaseline values of PCR negative confirmation:
  - All available data will be used to derive negative confirmation except if there are multiple records on the same day, the worst value will be used for negative confirmation for that day
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
- For postbaseline values PCR for DAVG calculation:
  - All values from different days within an analysis windows will be used for DAVG calculation.

— If there is more than 1 record on a study day, the latest value will be selected. If there are multiple records with the same time or no time recorded on the same day, the geometric mean value (copies/mL) will be taken.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

The number and percentage of participants randomized at each investigator site will be summarized by treatment group and overall using the Safety Analysis Set and All Randomized Analysis Set. The number and percentage of participants enrolled by randomized stratum will be summarized using stratum assignment captured in the IXRS. Discrepancy between IXRS and clinical database will be noted if applicable. The denominator for this calculation will be the number of participants in the Safety Analysis Set.

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

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

- Completed randomized treatment on study drug as recorded on the Study Drug Completion form
- Prematurely discontinuing study drug prior to completion with summary of reasons for discontinuing study drug as recorded on the Study Drug Completion form
- Completed study
- Prematurely discontinuing from study (with summary of reasons for discontinuing study) as recorded on the Study Completion form

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

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

4.2. Extent of Study Drug Exposure and Adherence

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 (e.g., nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the FAS. A by-subject listing will be provided for those participants with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic data (eg, sex, race/ethnicity, age, and age group (<18, ≥18 - < 60, ≥ 60) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of participants for categorical data. The summaries of demographic data and baseline participant 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 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: region (US vs. ex-US), participant's age (< 60 vs ≥ 60 years), and participants who reside in a skilled nursing facility (Yes, No).

A by-subject demographic listing will be provided.

5.2. Other Baseline Characteristics

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

- Baseline risk factor as defined in Section 3.4
- Duration of symptoms prior to first dose of study drug
- Duration from SARS-CoV-2 nucleic acid/antigen confirmation to first dose of study drug
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Baseline SARS-CoV-2 viral Load (as a continuous variable, and a categorical variable with categories of < median and ≥ median)
- Baseline respiration rate

For categorical data, the CMH test (general association statistic for nominal 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: region (US vs. ex-US), participant's age (< 60 vs ≥60 years), and participants who reside in a skilled nursing facility (Yes, No).

Categorical baseline COVID-19 symptoms from Flu-PRO Plus will be summarized by treatment group separately from other baseline characteristics.

5.3. Medical History

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

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary endpoint of the study is the composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28. The endpoint will be derived by combining the available all-cause death and COVID-19 related hospitalization reported by the site. The first COVID-19 related hospitalization will be used for the proportion of COVID-19 related hospitalization or all-cause death.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

Null hypothesis: The hazard ratio of COVID-19 related hospitalization or all-cause death by Day 28 between the 2 treatment groups equals to 1.

Alternative hypothesis: The hazard ratio of COVID-19 related hospitalization or all-cause death by Day 28 between the 2 treatment groups does not equal to 1.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The hazard ratio of COVID-19 related hospitalization or all-cause death between the two treatment groups will be estimated using a Cox model with stratification factors as covariates.

If a participant prematurely discontinues from the study prior to Day 28 or the hospitalization status is missing, the participant is censored at last study date or day 28 whichever is earlier. If a participant has a COVID-19 related hospitalization first and then dies, then date of the COVID-19 related hospitalization and status will be used for the primary analysis for this participant. If a participant has a non COVID-19 related hospitalization first and then dies without experiencing a COVID-19 related hospitalization, then date of the death and status will be used for the primary analysis for this participant.

The hazard ratio, p-value, 95% CI for the hazard ratio from Cox model, and proportion of COVID-19 related hospitalization or all-cause death at Day 28 from Kaplan-Meier estimate will be provided.

The FAS will be the primary analysis set for efficacy endpoint evaluation. The primary endpoint may be analyzed for each of the subgroups defined in Section 3.3.

6.1.4. Secondary Analyses of the Primary Efficacy Endpoint

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

- A CMH test including baseline stratification factors as strata for the statistical comparison between the two treatment groups. If a participant prematurely discontinues from the study prior to Day 28 with no event before discontinuation or the hospitalization/death status is missing, the participant will be considered as with no hospitalization/death.

The analysis is for the purposes of evaluating the robustness of the estimates of the primary analysis.

6.2. Secondary Endpoints

The other endpoints of interest include:

- Composite endpoint of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or all cause death by Day 28
- All-cause mortality by Day 28
- Proportion of participants hospitalized (COVID-19 related) by Day 28
- Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 14
- Composite endpoint of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or death by Day 14
- Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7
  - The time-weighted average change from baseline to study Day 7 ($DAVG_7$) in SARS-CoV-2 viral load (log_{10} copies/mL) is defined as the time-weighted average between the first postbaseline value through the last available value up to Day 7 minus the baseline value in SARS-CoV-2 viral load (log_{10} copies/mL). $DAVG_7$ is calculated using the trapezoidal rule and the area-under-the-curve (AUC) concept as follows:

$$DAVG_7 = \frac{AUC_{t_1-t_7}}{(t_7 - t_1)} - Y_0$$

The AUC between t_1 and t_n in a time (ie, day) versus SARS-CoV-2 viral load (log10 copies/mL) plot is calculated as

$$AUC_{t_1-t_n} = \sum_{i=1 \; to \; (n-1)} \frac{1}{2}(Y_i + Y_{i+1}) \times (t_{i+1} - t_i)$$

Where Y_i is the SARS-CoV-2 viral load (log10 copies/mL) at time t_i, t_1 is the first postbaseline time, and Y_0 is the baseline SARS-CoV-2 viral load (log10 copies/mL).

— For subject with SARS-CoV-2 viral load data only available up to Day x ($x < 7$), $DAVG_7$ is defined as $DAVG_7 = \frac{AUC_{t_1-t_x}}{(t_x - t_1)} - Y_0$

— If baseline viral load is missing or there is no post-baseline data, then the participant will be excluded from the analysis. If there is one post-baseline data value Y_i, $DAVG_7 = Y_i - Y_0$. If a participant receives additional COVID-19 treatments (see Appendix 2), the viral load from the start of additional treatment will be excluded.

- Time to alleviation (mild or absent) of baseline COVID-19 symptoms as reported on the COVID-19-adapted FLU-PRO Plus

  — The alleviation of baseline COVID-19 symptoms, i.e. overall alleviation of all symptoms scored 1 or higher at baseline for each participant, is defined as:

    ■ Symptoms scored as 2 or higher at baseline are scored as 0 or 1 at postbaseline, AND

    ■ Symptoms scored as 1 at baseline are scored as 0 at postbaseline, AND

    ■ for two consecutive days.

  — Time to alleviation of baseline COVID-19 symptoms is defined (in days) as:

    First Date of the two consecutive dates achieving alleviation - First dose Date + 1

    If a participant has not achieved symptom alleviation at last FLU-PRO Plus assessment or early discontinuation of study, the participant will be censored at last FLU-PRO Plus assessment date. Last assessment date is the last date when at least one of the baseline symptoms is assessed.

  Similar endpoints of time to alleviation of all symptoms or selected symptoms as reported on the COVID-19-adapted FLU-PRO Plus may be included.

- Worsening after alleviation of baseline COVID-19 symptoms

  — The worsening after alleviation of baseline COVID-19 symptoms is defined as:

    ■ For a participant who has achieved alleviation of baseline COVID-19 symptoms

    ■ If any symptom scored as 2 or higher at baseline is scored as 2 or higher postbaseline after achieved alleviation, or

    ■ Any symptom scored as 1 at baseline are scored as 1 or higher postbaseline after achieved alleviation.

- Proportion of participants progressing to requiring oxygen supplementation by Day 28

6.2.1. Analysis of Secondary Endpoints

The FAS will be the primary analysis set for secondary endpoints. The mFAS will be used for secondary endpoints of composite endpoint of COVID-19 related MAVs or death.

All-cause mortality by Day 28 will be compared between the 2 treatment groups using the Fisher exact test. If a participant prematurely discontinues from the study prior to Day 28 or the Death status is missing, the participant will not be included in the analysis.

The secondary endpoint of COVID-19 related hospitalization or all-cause death by Day 14, COVID-19 related MAVs or death by Day 28, and COVID-19 related MAVs or death by Day 14 will be analyzed using the same method as used for the primary endpoint, described in Section 6.1.3.

The proportion of participants hospitalized (COVID-19 related) by Day 28 will be estimated using the Kaplan-Meier method and compared between the 2 treatment groups using a log-rank test. Hazard ratio and two-sided 95% CI estimated using the Cox regression with baseline stratification factors as covariates will be provided.

Number and percentage of participants progressing to requiring oxygen supplementation by Day 28 will be summarized and compared between treatment groups using the Fisher Exact test. Participants discontinued from the study before progressing to requiring oxygen supplementation will be considered as not requiring oxygen supplementation.

The Kaplan-Meier product limit method will be used to estimate and log-rank test will be used to compare treatment groups for the time to alleviation of baseline COVID-19 symptoms. Hazard ratio and two-sided 95% CI estimated using the Cox regression with baseline stratification factors as covariates will be provided. Number and proportion of participants with worsening after alleviation of baseline COVID-19 symptoms will be summarized.

Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7 will be summarized by treatment groups and compared between treatment groups using an ANCOVA model with baseline viral load as covariate, the analysis will be based on the Virology Analysis Set.

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6.4. Change from Protocol Specified Efficacy Analyses

The protocol states that the proportion of participants progressing to requiring oxygen supplementation by Day 28 will be estimated using the Kaplan-Meier method and compared between the 2 treatment groups using a log-rank test. In the SAP, the number and percentage of participants progressing to requiring oxygen supplementation by Day 28 will be summarized and compared between treatment groups using the Fisher Exact test due to very small number of participants progressing to requiring oxygen supplementation.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

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

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (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-subject data listings will show the relationship as missing.

7.1.4. Relationship of Adverse Events to Study Procedure

Study procedure-related AEs are those for which the investigator selected “Yes” on the AE CRF to the question of “Related to Study Procedures.” Events for which the investigator did not record relationship to study procedure will be considered as missing. No summary table for relationship of AE to study procedure will be presented.

7.1.5. 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.

7.1.6. Treatment-Emergent Adverse Events

Proportion of participants with treatment-emergent AEs (TEAEs) is the primary safety endpoint of the study. No statistical comparison will be provided for proportion of participants with TEAE.

7.1.6.1. 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.

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

7.1.7. Summaries of Adverse Events and Deaths

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

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, High lever term (HLT), PT, and treatment group. For other AEs described below, summaries will be provided by system organ class, PT, and treatment group:

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

TEAE and study drug related TEAE will summarized by system organ class, PT, Severity and treatment group.

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described above, and treatment emergent deaths will be provided by treatment group. Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of 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 treatment-emergent AEs, treatment-emergent AEs with Grade 3 or higher, treatment-emergent study drug-related AEs, and treatment-emergent study drug-related AEs with Grade 3 or higher, will be summarized by PT only, in descending order of total frequency.

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

- All AEs
- Study-Drug-Related AEs
- AEs with severity of Grade 3 or higher
- SAEs

- Study-Drug-Related SAEs
- Deaths
- AEs leading to premature discontinuation of study drug

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.. SAR-COV-2 PCR result of "Inconclusive" will not be included in numeric summary and will be considered as not negative result for PCR negative confirmation.

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

7.2.1. Summaries of Numeric Laboratory Results

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

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

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

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

7.2.2. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 (July 2017) will be used 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 local lab and central lab results are available, central lab results will be selected first for baseline toxicity grade, local lab results will be used when central lab results are missing.

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 with the exception of Glucose (See Appendix 2 for details.)

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

Abnormalities in coagulation parameters will be graded for international normalized ratio (INR) and aPTT.

For the international normalized ratio (INR) of prothrombin time (PT) and aPTT, protocol specified toxicity grading scale depends on the upper limit of normal range (ULN). While the ULN of INR and aPTT depends on whether the subject is taking anticoagulant medication or not (ie, Not taking oral anticoagulant: 0.8 – 1.2; Taking oral anticoagulant: 2.0 – 3.0), this information is not collected by the reference laboratory. As a result, INR and aPTT will be graded by assuming subject is not taking an oral anticoagulant, which is a conservative approach that may lead to over-reporting of abnormalities for INR and aPTT.

7.3. Body Weight, Vital Signs and Respiratory Status

Descriptive statistics will be provided by treatment group for body weight and vital signs (including heart rate, respiratory rate on room air and blood pressure) as follows:

- Baseline value
- Values at each postbaseline analysis window for rate respiratory rate on room air or at each timepoint for heart rate and blood pressure
- Change from baseline at each postbaseline analysis window for rate respiratory rate on room air or at each timepoint for heart rate and blood pressure

Similar descriptive statistics will be provided by treatment group for SpO_2 on room air.

Two types of baseline will be defined for vital signs. An overall baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Day 1 pre-dose baseline is defined the same as the overall baseline. A pre-dose baseline per day for each of dosing days 2-3 will use the "Pre-infusion" record on that day as baseline. Change from overall baseline to a postbaseline visit and change from pre-dose baseline for dosing days will be defined as the postbaseline value minus the respective 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-subject listing of body weight, BMI, vital signs (including heart rate, temperature, and blood pressure), and respiratory status (including respiratory rate and SpO_2) will be provided by subject ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

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

Concomitant medications are defined as medications taken while a participant took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of participants for each treatment group. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred term in

descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug 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

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.

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9. REFERENCES

Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA 2021.

Muller HH, Schafer H. A general statistical principle for changing a design any time during the course of a trial. Stat Med 2004;23 (16):2497-508.

10. SOFTWARE

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

Phoenix WinNonlin® 8.2. Pharsight Corporation, Princeton, NJ, USA.

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Study Procedures Table[a]

	Screening	Baseline/ Day 1	Day 2	Day 3	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 28[t] Follow-up (± 5 days)
Written Informed Consent	X						
Medical History[b]	X						
Complete Physical Examination[c]	X	X				X	
Clinical Symptom-Directed Physical Examination[d]			X	X	X		X
Height	X						
Vital Signs[e] and Weight	X	X[f]	X[f]	X[f]	X	X	X
Respiratory Status[g]	X	X	X	X	X	X	X
ALT, AST, Serum Creatinine, and Creatinine Clearance/eGFR[h]	X						
Chemistry[i], Hematology[j], and Coagulation[k] Panels		X		X	X	X	
CCI							
Urine Pregnancy Test[m]	X						
SARS-CoV-2 RT-qPCR Testing and Potential Resistance Testing[n]		X	X	X	X	X	
Documentation of SARS-CoV-2 Infection	X						
CCI							
Medically Attended Visit Information[r]		X	X	X	X	X	X
FLU-PRO Plus Questionnaire[s]		X	X	X	X	X	
Study Drug Dosing		X	X	X			
Adverse Events and Concomitant Medications	X	X	X	X	X	X	X

a Study visits may be performed in an outpatient setting, at the participant's home via tele-health, virtually or remotely, as permitted by local and institutional regulations. The Day 28 visit may be performed via a phone call.
b Medical history will include the date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics, allergies and all other medical history.
c A complete physical examination must include source documentation of general appearance and the following body systems: Head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; and neurological. Urogenital and reproductive examination should only be completed if clinically indicated.
d Clinical symptom-directed physical examination will include at least cardiac and respiratory evaluation.
e Vital signs include heart rate, temperature, and blood pressure.

f On Days 1, 2 and 3, vital signs to be completed pre-infusion, postinfusion, and when postinfusion observation is completed; weight from Screening may be used at Days 1-3.
g Respiratory status includes respiratory rate and SpO_2 on room air.
h Obtain ALT (and AST where available), serum creatinine, and creatinine clearance (calculated using Cockcroft-Gault or Schwartz formula; see Protocol Section 6.7.2) if not available within 90 days of screening, using a local laboratory.
i 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.
j Hematology: Complete blood count with differential.
k Coagulation: INR, PT, aPTT
[redacted]
m Urine pregnancy test will only be done for women of childbearing potential.
n Nasopharyngeal swab and sputum samples will be collected and stored for SARS-CoV-2 RT-qPCR and potential resistance testing.
[redacted]
r Medically attended visit information includes any interactions with health care professionals other than study staff or designees including hospitalization; in-person emergency, urgent, or primary care visits; or any other in-person visit attended by the participant and a health care profession. Identify the nature and cause of the visit.
s FLU-PRO Plus questionnaire should be completed daily from Day 1 through Day 14 (if available).
t Only AEs, symptom assessment, medically attended visit information, and concomitant medications review are needed if the visit is done by phone.

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 consented to.

4) Participants in the randomized analysis set are defined as participants randomized into the study. IXRSRAND is the source to determine whether the subject is randomized (ie, 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) For demographics tables, "Not Permitted" will be excluded from percentage for detailed race categories summary (i.e. 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 include in the count of percentage.

9) 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.

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

Raw measurements will be reported the same as the data captured electronically or on the eCRF for all but hematology and chemistry values.

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

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

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

Precision for derived parameters as follows:

Parameters	Decimal Places
log 10 of SARS-CoV-2 viral load	2
Time-weighted average change in SARS-CoV-2 viral load	2
BMI	2
CCI	

11) 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.

12) Incomplete death dates will be imputed as the maximum of the study drug start dates, study drug end dates , clinic or phone visit dates (lvis28dt), laboratory visit dates (llab28dt), including the 28-day follow-up visit date plus 1.

13) Censoring rules

Time to hospitalization/death: If a participant prematurely discontinues from the study prior to Day 28 or the hospitalization status is missing, the participant is censored at last study date or day 28 whichever is earlier.

Time to negative SARS-CoV-2 viral load, participants are censored at the last assessment day and participants are required to have at least one postbaseline assessment.

Time to alleviation of baseline COVID-19 symptoms:

- For overall baseline symptom alleviation, participants are censored at the last assessment day that at least one of the baseline symptoms was assessed. For baseline symptom alleviation for each domain, participants are censored at the last assessment day that at least one of the baseline symptoms within that domain was assessed

14) 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)
	Creatinine Clearance	Decrease	Creatinine Clearance (Decreased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, 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)
	Activated partial thromboplastin time (aPTT)	Increase	Activated partial thromboplastin time (Increased)

15) SAS code for ANCOVA:

```
ods output ParameterEstimates=out1 LSMeans=out2 LSMeanCL=out3
LSMeanDiffCL=out4;
proc glm data=dat1 plots=none;
  class trt01pn;
  model DAVG = trt01pn base / solution;
  lsmeans trt01pn / stderr cl pdiff;
  run;
```

```
ods output close; quit;
```

16) Symptom scores in the FLU-PRO questionnaire raw data start from 1 to n (total number of responses in a question), in the FLU-PRO user manual, symptom scores start from 0. In the analysis dataset, symptom scores will be re-mapped to match the scoring in the FLU-PRO user manual for proper calculation of total score and domain score.

17) FLU-PRO Total Score and Domain Score:

The presence and severity of influenza signs and symptoms are assessed across 7 body systems: Nose (4 items), Throat (3 items), Eyes (3 items), Chest/Respiratory (7 items), Gastrointestinal (4 items), Body/Systemic (11 items), and Sense (2 itmes). For 29 of the items, the severity scale is as follows: 0 ("Not at all), 1 ("A little bit"), 2 ("Somewhat"), 3 ("Quite a bit"), and 4 ("Very much"). For 5 items, severity is assessed in terms of frequency, i.e., vomiting or diarrhea (0 times, 1 time, 2 times, 3 times, or 4 or more times); with frequency coughed up mucus or phlegm evaluated on a scale from 0 ("Never") to 4 ("Always"). For 2 items, severity is assessed as 0 ("No") or 1 ("Yes").

Domain	Items	Scoring	Minimum Data Requirement
Nose	Runny or dripping nose Congested or stuffy nose Sneezing Sinus pressure	Arithmetic mean of 4 items within **Nose** domain	Daily score for 3 of 4 items must be present to calculate domain score
Throat	Scratchy or itchy throat Sore or painful throat Difficulty swallowing	Arithmetic mean of 3 items within **Throat** domain	Daily score for 2 of 3 items must be present to calculate domain score
Eyes	Teary or watery eyes Sore or painful eyes Eyes sensitive to light	Arithmetic mean of 3 items within **Eyes** domain	Daily score for 2 of 3 items must be present to calculate domain score
Chest/Respiratory	Trouble breathing Chest congestion Chest tightness Dry or hacking cough Wet or loose cough Coughing Coughed up mucus or phlegm	Arithmetic mean of 7 items within **Chest/Respiratory** domain	Daily score for 5 of 7 items must be present to calculate domain score
Gastrointestinal	Felt nauseous Stomach ache How many times did you vomit? How many times did you have diarrhea?	Arithmetic mean of 4 items within **Gastrointestinal** domain	Daily score for 3 of 4 items must be present to calculate domain score
Body/Systemic	Headache Head congestion Felt dizzy Lack of appetite Sleeping more than usual	Arithmetic mean of 11 items within **Body/Systemic** domain	Daily score for 8 of 11 items must be present to calculate domain score

Domain	Items	Scoring	Minimum Data Requirement
	Body aches or pains Weak or tired Chills or shivering Felt cold Felt hot Sweating		
Sense*	Loss Smell Loss Taste	Arithmetic mean of 2 items within **Sense** domain	Daily score for 1 of 2 items must be present to calculate domain score
Total	All above 34 items	Arithmetic mean of all 34 items within FLU-PRO	In the presence of missing data, the above conditions for the calculation of all domain scores must be met in order to calculate the FLU-PRO total score.

* Added for COVID-19

18) Symptom alleviation and time to baseline symptom alleviation

1. Baseline symptoms: Baseline symptoms are the symptoms collected prior to dosing and score ≥1.

- Item 1 to 34 of the FLUPRO are symptoms. Global assessments (last 6 items in the questionnaire) are not symptoms.
- Each subject's baseline symptoms including number of symptoms likely are different.
- For alleviation of baseline symptoms, only need to follow the symptoms presented (≥1) at baseline
  - If a participant has 5 baseline symptoms, only the 5 symptoms will be followed to derive alleviation.
  - If a symptom (e.g. coughing) is not one of the baseline symptoms and has a score >1 post baseline, the symptom will be not considered to derive the subject's baseline symptom alleviation.
  - If participant has not symptom ≥1 at baseline, alleviation status for the participant is missing for all visit.
  - Baseline symptoms ≥1, symptoms from Day 2 and later are all missing, the alleviation status for the symptom is missing for all visits.

2. Alleviation of a symptom:

- Symptom scored as 2 or higher at baseline are scored as 0 or 1 at postbaseline
- Symptom scored as 1 at baseline are scored as 0 at postbaseline

- for two consecutive days - need to be confirmed with 2 visits
  - one missing day between two visits (that meets the alleviation definition) is allowed, but 2 or more days of missing is not considered reach alleviation
  - for Day 14 (or last assessment on Day x), if the symptom meets definition of alleviation, and day 13 (or Day x -1) also meets the definition of alleviation, then it is considered as confirmed. One missing day is allowed for the confirmation of Day 14 or last assessment, i.e if day 13 (or Day x-1) is missing and Day 12 (or Day x-2) meets the definition of alleviation, then it is considered as confirmed.

    Examples:

	Day														Alleviation for a symptom on day	
Example	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
1	2	2	2	1	1	1	0	0	0	0	0	0	0	0	4	*baseline 2 or higher needs to be 1 or 0*
2	2	2	2	0	1	1	0	0	0	0	0	0	0	0	4	*baseline 2 or higher needs to be 1 or 0*
3	2	2	2	0	2	1	1	0	0	0	0	0	0	0	6	*day 4 is not confirmed*
4	3	2	2	1	1	1	0	2	1	1	0	0	0	0	4	*still on day 4 if worsen after confirmation*
5	1	1	1	0	0	0	1	0	1	1	0	0	0	0	4	*Worsening on day7*
6	1	1	1	1	0	0	0	0	0	0	0	0	0	0	5	*baseline 1 needs to be 0*
7	2	2	2	1	.	1	0	0	0	0	0	0	0	0	4	*allow one missing*
8	2	2	2	1	.	.	1	1	.	0	0	0	0	0	7	*day 4 is not confirmed if there are two or more days' response missing, re-start the check for confirmation*
9	2	2	2	2	2	2	2	2	4	2	2	2	2	1	14	*censor*
10	2	2	2	2	2	2	2	2	2	2	2	2	1	.	13	*censor*
11	2	2	2	2	2	2	2	2	2	2	2	2	1	1	13	*Confirmed on day 13 and 14*
12	2	2	2	2	2	2	2	2	1	.	.	.	.	.	9	*censor*
13	2	2	2	2	2	2	2	2	1	1	.	.	.	.	9	*Confirmed on day 9 and 10*

Yellow - Confirmed alleviation, Tan - Not confirmed, Blue - Worsening

3. Alleviation of baseline symptoms for a participant

The alleviation status for a participant at each visit is

- Yes, if all confirmed baseline symptom alleviation status are Yes.
- if > 25% of symptoms are missing, then alleviation status is No, else ignore missing.
- No, if any baseline symptom alleviation status is No.

4. Tim to alleviation of baseline symptoms

First day of participant level alleviation status equals Yes. If a participant has not achieved symptom alleviation at last FLuPRO assessment, the participant will be censored at the date of last FLUpro assessment. For symptom alleviation of a domain, the last assessment date is only among those baseline symptoms within the domain.

19) Covid-19 medications include:

Chloroquine, Hydroxychloroquine, IV remdesivir, Bamlanivimab, Casirivimab/Imdevimab, Molnupiravir, Lopinavir-ritonavir, Ribavirin. Details of COVID-19 medications are provided in table below.

Drug name	ATC Code	WHODRUG Preferred Term
Chloroquine	P01BA	CHLOROQUINE
Hydroxychloroquine	P01BA	HYDROXYCHLOROQUINE
Lopinavir/ritonavir	J05AR	LOPINAVIR/RITONAVIR
Ribavirin	J05AP	RIBAVIRIN
Remdesivir	J05AB	REMDESIVIR
Bamlanivimab	--	BAMLANIVIMAB
Casirivimab/Imdevimab	--	CASIRIVIMAB/IMDEVIMAB
Molnupiravir	--	MOLNUPIRAVIR

ATC = anatomical therapeutic chemical

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

20) Baseline risk factor

Selected medical history will be summarized as baseline risk factor and be included as subgroups in analysis. A risk factor 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

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.

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 included in the prespecified PT list for the corresponding disease of interest, which include all PTs from the narrow or broad search of the following SMQs under MedDRA 24.0 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 mild or moderate kidney disease	Chronic kidney disease (SMQ)
Chronic liver disease	search name "Chronic liver disease excluding transient_acute events and nonspecific signs_symptoms
Current cancer	Malignancies (SMQ)
Sickle cell disease	HLGT "Haemoglobinopathies"

Risk factor of obesity will be defined as BMI >=30 kg/m^2 at baseline based on CRF data.

21) Common COVID-19 symptoms at baseline:

Common COVID-19 symptoms at baseline for each symptom will be considered as present if any of the corresponding FLU-PRO questionnaire items score 1 or higher at baseline.

Common COVID-19 symptoms	FLU-PRO questionnaire item
Stuffy or runny nose	Runny or dripping nose Congested or stuffy nose
Sore throat	Sore or painful throat
Shortness of breath (difficulty breathing)	Trouble breathing
Cough	Coughing
Low energy or tiredness	Weak or tired
Muscle or body aches	Body aches or pains
Headache	Headache
Chills or shivering	Chills or shivering
Feeling hot or feverish	Felt hot

Nausea	Felt nauseous (feeling like you wanted to throw-up)
Vomit	How many times did you vomit?
Diarrhea	How many times did you have diarrhea?
Loss of Smell	Loss of smell
Loss of taste	Loss of taste

22) SpO2 and respiration rate: -

Summary of SpO2 and respiration rate will include measurements obtained while participants are on room air. SpO2 and respiration rate obtained while participants are on supplemental oxygen will be listed.

23) Glucose:

Fasting is not required per protocol for collecting Glucose sample, mixed fasting Glucose and non-fasting Glucose results are presented in the dataset. Lab abnormality for Glucose will be summarized as follows:

- if fasting glucose is collected at baseline, max TE lab toxicity grade is selected for post-baseline fasting glucose, max post-baseline toxicity grade (i.e. not TE toxicity grade) is selected for the post-baseline glucose regardless of fasting status.
- if non-fasting glucose is collected at baseline, TE lab toxicity grade is selected for post-baseline non-fasting glucose, max post-baseline toxicity grade is selected for the post-baseline glucose regardless of fasting status.
- Max TE lab toxicity grade for fasting glucose and non-fasting glucose, max post-baseline toxicity grade for fasting glucose and non-fasting glucose will be summarized separately for Hyperglycemia, and Serum Glucose (regardless fasting or non-fasting status) for Hypoglycemia in the lab abnormality summary table.
- In the any TE lab toxicity section of the lab abnormality table, max post-baseline toxicity grade will be included.

24) SARs-CoV2 PCR data

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

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

i) Positive = any numeric result or "<LLOQ SARSCoV2 detected" - LLOQ could vary by sample type

ii) Negative = "No SARS-CoV2 detected"

iii) Inconclusive = "Inconclusive"

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

d) 2 negative results from the same day do not equal confirmation.

e) if last PCR sample is negative for participants completed the study or for participant withdrawn early from the study, then one negative PCR of last sample is considered as confirmed negative.

f) Categorical SARS-CoV2 and SARS-CoV2 negative summary will be separated out by sample type. There will be no combined Positive or negative category using 2 or more sample types.

25) SAS code for Cox model with Covariates

```
proc phreg;
class trt01p (ref="Placebo to match RDV") strat1 strat2 strat3;
model aval*cnsr(1) = trt01p strat1 strat2 strat3 /risklimits = wald;
ods output  ParameterEstimates=Est1 ModelANOVA = pvout1;
run;
```

Hazard ratio is the hazardratio, 95% Cis are HRLowerCL and HRUpperCL where Parameter = "TRT01P" from EST1 dataset; P-value is ProbChiSq where Effect = "TRT01P" from pvout1 dataset.

GS-US-540-9012 SAP final analysis v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	12-Aug-2021 20:53:51
PPD	Clinical Research eSigned	13-Aug-2021 11:55:23
PPD	Clinical Pharmacology eSigned	13-Aug-2021 17:22:10