STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GS-5245 for the Treatment of COVID-19 in Participants With High-Risk for Disease Progression
Name of Test Drug:	Obeldesivir (ODV, GS-5245)
Study Number:	GS-US-611-6273
Protocol Version (Date):	Amendment 1 (29 March 2023)
Analysis Type:	Final Analysis
Analysis Plan Version:	1.0
Analysis Plan Date:	22 January 2024
Analysis Plan Author(s):	PPD
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
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
DMC	data monitoring committee
eGFR	estimated glomerular filtration rate
FAS	Full Analysis Set
FAPS	Full Analysis Positive Set
HLT	high-level term
ID	identification
IXRS	interactive voice or web response system
LLOQ	lower limit of quantification
LLT	lowest-level term
LOD	limit of detection
LOQ	limit of quantitation
MAVs	medically attended visits
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
PK	pharmacokinetic(s)
PT	preferred term
Q1, Q3	first quartile, third quartile
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SD	standard deviation
SIC	Symptoms of Infection with Coronavirus-19
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
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-611-6273. This SAP is based on the study protocol Amendment 1 dated 29 March 2023 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 objective of this study is as follows:

- To evaluate the efficacy of GS-5245 in reducing the rate of COVID-19–related hospitalization or all-cause death

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of GS-5245 administered in nonhospitalized participants with COVID-19
- To evaluate the efficacy of GS-5245 in reducing all-cause hospitalization
- To evaluate the efficacy of GS-5245 in reducing COVID-19–related medically attended visits (MAVs) or all-cause death
- To evaluate the efficacy of GS-5245 in reducing COVID-19–related MAVs
- To evaluate the efficacy of GS-5245 in reducing all-cause death
- To evaluate the efficacy of GS-5245 in reducing the duration and severity of COVID-19 symptoms
- To evaluate the antiviral activity of GS-5245 on SARS-CoV-2 nasal swab viral load at Day 5
- To evaluate the plasma pharmacokinetics (PK) of GS-441524 (metabolite of GS-5245)

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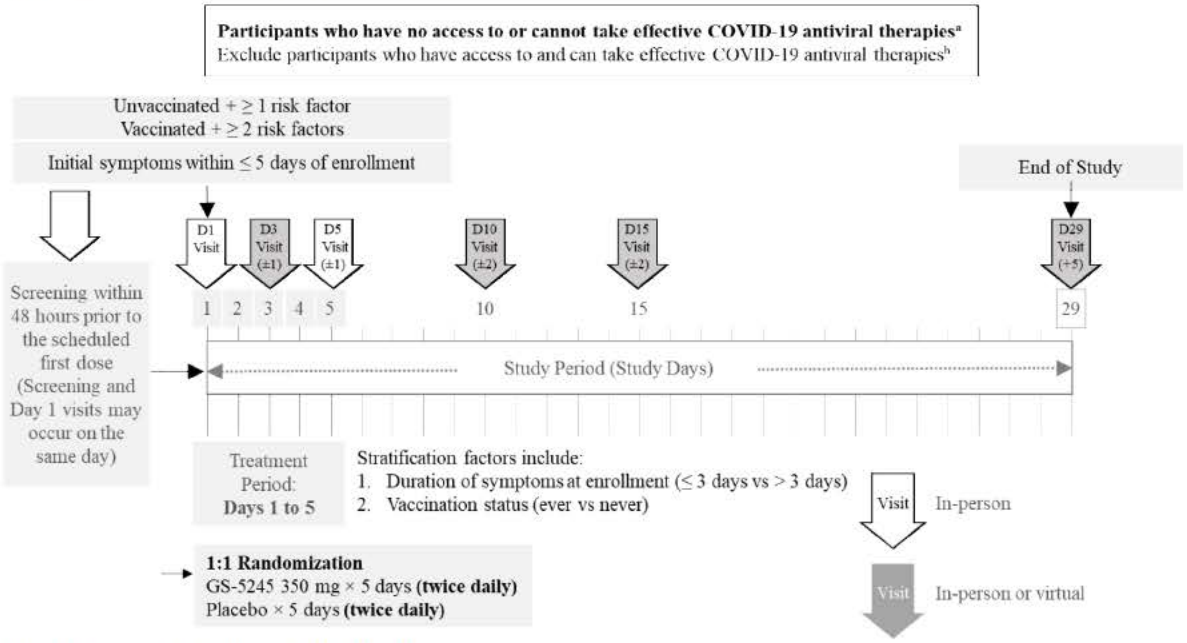
1.2. Study Design

This Phase 3 study is a randomized, double-blind, placebo-controlled study comparing the safety and efficacy of oral GS-5245 with placebo in nonhospitalized participants with COVID-19 who are at high risk of progression to hospitalization.

Randomization will be stratified by duration of symptoms at enrollment (≤ 3 days versus > 3 days) and vaccination status (ever versus never).

An overview of the study design is shown in Figure 1.

Figure 1. Study Schema



COVID-19 = coronavirus disease 2019; D = Day
a Access determined at the site level by the principal investigator and participant.
b Effective COVID-19 antiviral therapies such as nirmatrelvir/ritonavir, molnupiravir, ensitrelvir, intravenous remdesivir, monoclonal antibodies, or any other locally authorized/approved direct-acting therapy against SARS-CoV-2.

Approximately 2300 participants were planned to be randomized into the study. After screening procedures, eligible participants are randomized in a 1:1 ratio to receive treatment with GS-5245 or placebo.

The schedule of study procedures is presented in Appendix 1.

1.3. Sample Size and Power

A total sample size of approximately 2300 participants provides approximately 90% power to detect a ratio of 0.25 (GS-5245 to placebo) in the primary endpoint (proportion of COVID-19-related hospitalization or all-cause death by Day 29), which is equal to a hazard ratio of 0.25 using a 2-sided significance level of 0.05 assuming the placebo event rate is 2% in the placebo group. The estimate of 2% in the placebo group is based on the placebo event rate for COVID-19 in the EPIC-SR study {Pfizer Inc 2022} and vaccine efficacy data from the Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report {Ferdinands 2022, Thompson 2022}.

The sample size calculation was performed using software East® (Version 6.5, module for log-rank test given accrual duration and study duration and 1 or 2 interim analyses using the Lan DeMets approach with O'Brien-Fleming type spending function, with sample size re-estimation).

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. DMC Analysis

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will make recommendations to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are provided in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

The initial review was conducted after the first 200 participants completed the Day 29 assessment or prematurely discontinued from the study.

A second DMC meeting to evaluate safety, futility, and efficacy was planned after 50% of the total planned participants had completed the Day 29 assessment or prematurely discontinued from the study, or 50% of expected primary endpoint events had occurred. However, the interim futility and efficacy analysis was not performed due to the stop of study enrollment prior to reaching the planned number of participants and events.

2.2. Final Analysis

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

2.3. Changes from Protocol-Specified Analyses

The DMC meeting to formally evaluate futility and efficacy was not performed due to the stop of enrollment at close of business on 06 October 2023 after less than 50% of the participants were randomized. The reasons for stopping enrollment were due to lower-than-expected event rate for the primary endpoint.

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 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.

SARS-CoV-2 viral load will be used throughout the SAP for SARS-CoV-2 RT-qPCR viral load.

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. 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 and overall.

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 Full Analysis Set (FAS) includes all randomized participants who received at least 1 dose of study drug.

3.1.3. Full Analysis Positive Set

The Full Analysis Positive Set (FAPS) includes all randomized participants who received at least 1 dose of study drug and are SARS-CoV-2 positive at baseline as confirmed by Cepheid's Xpert Xpress CoV-2/Flu/RSV plus test or SARS-CoV-2 RT-qPCR test from central lab. This is the primary analysis set for efficacy analyses.

3.1.4. Virology Analysis Set

The Virology Analysis Set includes all randomized participants who received at least 1 dose of study drug and had baseline SARS-CoV-2 viral load ≥ lower limit of quantification (LLOQ). Refer to Section 3.7 for the definition of LLOQ.

3.1.5. Safety Analysis Set

The Safety Analysis Set includes all participants who received at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.6. Pharmacokinetic Analysis Set

The PK Analysis Set will include all randomized participants who received at least 1 dose of study drug and have at least 1 nonmissing concentration value reported by the PK laboratory. This is the primary analysis set for all PK analyses.

3.1.7. Pharmacokinetic Substudy Analysis Set

The PK Substudy Analysis Set will include all randomized participants who received at least 1 dose of study drug, participated in the PK substudy, and have at least 1 nonmissing postdose concentration. This is the primary analysis set for detailed PK analysis of intensive PK sampling.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set, FAPS, or Virology Analysis Set, participants will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, participants will be grouped according to the actual treatment 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.

For the PK Analysis Set and PK Substudy Analysis Set, participants will be grouped according to the actual treatment they received.

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:

- Duration of symptoms at enrollment: ≤ 3 days versus > 3 days
- Vaccination status: ever versus never

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

The primary efficacy endpoint will be evaluated using stratification factors as covariates or stratification variables for analyses, as specified in Section 6. If there is an imbalance in presumed prognostic baseline characteristics between treatment groups, efficacy evaluations may

be performed that include these baseline values in efficacy analysis models as covariates; these evaluations will be considered sensitivity analyses.

If 5 events or fewer across both treatment groups are observed within 1 or more stratum, the primary and key secondary endpoints will be evaluated in the same analyses without using the corresponding stratification factor(s).

3.4. Examination of Subject Subgroups

Subgrouping of participants based on randomization stratification factors will be explored for subgroup analyses. In addition, select efficacy endpoint(s) may be examined using the following subgroups:

- Baseline SARS-CoV-2 viral load: < 6 $\log_{10}$ copies/mL versus ≥ 6 $\log_{10}$ copies/mL

The safety endpoint(s) may be examined using the following subgroups:

- Age: ≥ 18 – < 65 years, ≥ 65 – < 75 years, ≥ 75 – < 85 years, ≥ 85 years
- Sex at birth: Male versus Female
- Race: (a) Asian, (b) Black, (c) White, (d) Other
- Region: Europe versus ex-Europe
- BMI: < 25 kg/m^2, ≥ 25 – < 30 kg/m^2, ≥ 30 kg/m^2
- BMI: < 30 kg/m^2 versus ≥ 30 kg/m^2
- Baseline estimated glomerular filtration rate (eGFR): Creatinine Clearance by Cockcroft-Gault: ≥ 90 mL/min, ≥ 60 – < 90 mL/min, ≥ 30 – < 60 mL/min, < 30 mL/min

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

3.5. Multiple Comparisons

The overall 2-sided type I error rate of 0.05 for the primary endpoint and key alpha-controlled secondary endpoints will be controlled using a gatekeeping testing strategy (ie, the primary efficacy endpoint will be tested first, and the key alpha-controlled secondary endpoints will be tested in a sequential manner only if the primary efficacy endpoint is met).

A gatekeeping approach will be used for testing the key secondary endpoints. The endpoints will be tested in the following sequential order in the final analyses:

1. Proportion of participants with all-cause hospitalization by Day 29.
2. Proportion of participants with COVID-19–related MAVs or all-cause death by Day 29.
3. Proportion of participants with COVID-19–related MAVs by Day 29.
4. Proportion of participants with all-cause death by Day 29.

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 from the study will be censored at the Last Study Date defined in Section 3.8.1.

For missing last dosing date of study drug, imputation rules are described in Section 4.2. The handling of missing or incomplete dates for adverse event (AE) onset is described in Section 7.1.5.2, 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, but no sensitivity analyses will be conducted. Unless specified otherwise, all data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

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

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

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, 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.

Non-PK 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 lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower 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 upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.

- The lower or upper 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 lower or upper LOQ, respectively).

SARS-CoV-2 viral load results that are below LLOQ 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 calculate descriptive statistics if the datum is reported as "<2228cp/mL SARSCoV2 detected".

- A value of 746.5 copies/mL (half of the LOD 1493 copies/mL) will be used to calculate descriptive statistics if the datum is reported as "No SARS-CoV2 detected".

SARS-CoV-2 infectious viral titer result will be imputed as follows:

- A value of 100 PFU/mL (half of the LOQ 200 PFU/mL) will be used to calculate descriptive statistics if the datum is reported as "< 200 PFU/mL" and the corresponding qualitative result is "Positive".

- A value of 50 PFU/mL (1/4 of the LOQ 200 PFU/mL) will be used to calculate descriptive statistics if the datum is reported as "< 200 PFU/mL" and the corresponding qualitative result is "Negative".

For baseline SARS-CoV-2 viral load, results of "No SARS-CoV2 detected", "Inconclusive", "<2228cp/mL SARSCoV2 detected" are considered as < LLOQ; numerical results are considered as ≥ LLOQ.

Numerical result of SARS-CoV-2 viral load and SARS-CoV-2 infectious viral titer from samples collected with less than specified volume of test solution will not be included in viral load or infectious viral titer analyses. The positive or negative result of these samples will not be impacted.

Any SARS-CoV-2 viral load and infectious viral titer samples collected on or after the day when the participants are receiving additional COVID-19 treatments (see Appendix 3) will be excluded from the viral load or infectious viral titer analysis.

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

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

Natural logarithm transformation will be used for analyzing concentrations in intensive PK samples from the PK Substudy. 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. Values that are 0 or characters will be excluded from the calculation of geometric means.

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

- 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 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 Section 4.2 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 virtual visit dates, the vital sign collection dates, the questionnaire collection dates, the laboratory collection dates, and the death date (if applicable, 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).

Baseline value is defined as the last value obtained on or prior to the first dose date 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

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 3	3	2	4*
Day 5	5	4*	7
Day 10	10	8	12
Day 15	15	13	22
Day 29	29	23	34

* If the nominal visit is a scheduled visit and the assessment is done on Day 4 (ie, Study Day = 4), assign to Day 3 or Day 5 analysis window based on the nominal visit label. If the nominal visit is an unscheduled visit or early discontinuation visit on Day 4, assign to Day 3 analysis window.

The analysis windows for SARS-CoV-2 mid-turbinate nasal swab are provided in Table 3-2.

Table 3-2. Analysis Visit Windows for SARS-CoV-2 Mid-turbinate Nasal Swab

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 3	3	2	4*
Day 5	5	4*	7
Day 10	10	8	12
Day 15	15	13	22

* If the nominal visit is a scheduled visit and the assessment is done on Day 4 (ie, Study Day = 4), assign to Day 3 or Day 5 analysis window based on the nominal visit label. If the nominal visit is an unscheduled visit or early discontinuation visit on Day 4, assign to Day 3 analysis window.

The analysis windows for hematology, chemistry, and coagulation laboratory tests are provided in Table 3-3.

Table 3-3. Analysis Visit Windows for Hematology, Chemistry, and Coagulation Laboratory Tests

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 3	3	2	4*
Day 5	5	4*	10
Day 15	15	11	22

* If the nominal visit is a scheduled visit and the assessment is done on Day 4 (ie, Study Day = 4), assign to Day 3 or Day 5 analysis window based on the nominal visit label. If the nominal visit is an unscheduled visit or early discontinuation visit on Day 4, assign to Day 3 analysis window.

The analysis windows for urine or serum pregnancy tests are provided in Table 3-4.

Table 3-4. Analysis Visit Windows for Urine or Serum Pregnancy Tests

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 15	15	2	22

The Symptoms of Infection with Coronavirus-19 (SIC) questionnaire will be completed daily from predose at Day 1 to Day 15 visit, then at Day 29 visit. Windows are not assigned and results will be summarized for each applicable Study Day through Day 15. For the Day 29 nominal visit, the analysis window is provided in Table 3-5.

Table 3-5. Analysis Visit Windows for the SIC Questionnaire

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 29	29	24	34

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 not require 1 value per 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 questionnaire data, the last nonmissing value on or prior to the first dosing date of study drug will be selected. If there are multiple records on or prior to the first dose date, the record prior to and closest to the first dose date and time will be used if available; otherwise the record after and closest to the first dose date and time will be used.

- For baseline data other than questionnaire, the last nonmissing value on or prior to the first dosing date of study drug will be selected, unless specified differently. If there are multiple records on the same day, the baseline value will be selected as follows:

    - For continuous data:

        - For SARS-CoV-2 viral load and SARS-CoV-2 infectious viral titer, 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 other continuous data, the average of the measurements will be taken.

    - For categorical data:

        - For SARS-CoV-2 positivity based on RT-qPCR, positivity based on infectious viral titer and Multiplex viral PCR, the worst severity (ie, a positive result, if available) will be selected.

        - For other categorical data, the lowest severity will be selected.

- For postbaseline values:
  - 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 SARS-CoV-2 viral load and SARS-CoV-2 infectious viral titer, 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 time to symptom alleviation, all records within the analysis visit window will be used.
    - For questionnaire data to be summarized, if there is more than 1 record on the selected day, the latest value will be selected.
    - For other parameters, if there is more than 1 record on the selected day, the average will be taken for continuous data and the worst severity will be taken for categorical data, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

Key study dates (ie, first participant screened, first participant randomized, last participant randomized, last participant last visit for the primary endpoint, and last participant last visit for the CSR) will be provided.

A summary of participant enrollment will be provided by treatment group for each investigator within a country, and overall using the All Randomized Analysis Set. The summary will present the number and percentage of participants enrolled. For each column, the denominator for the percentage calculation will be the total 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 enrolled participants. 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, if applicable.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of participant disposition will be provided by treatment group and overall. This summary will present the number of participants screened, the number of participants who met all eligibility criteria but were not randomized with reasons these participants were not randomized, the number of participants randomized, and the number of participants in each of the categories listed below:

- Safety Analysis Set
- FAS
- FAPS
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the number of participants in the Safety Analysis Set.
In addition, a flowchart will be provided to depict the disposition.

A by-participant listing of reasons for premature study drug or study discontinuation will be provided by participant ID number in ascending order.

4.2. Extent of Study Drug Exposure

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug and number of tablets taken will be summarized by treatment group for the Safety Analysis Set.

A by-participant listing of study drug administration and drug accountability will be provided separately by participant ID number (in ascending order).

Total duration of exposure (in days) to study drug will be defined as last dosing date minus first dosing date plus 1. If the last study drug dosing date is missing for a participant, the last dose date is imputed as the earliest date from the following:

- Day 5 if the participant took 2 tablets on Day 1
- Day 6 if the participant took 1 tablet on Day 1
- Last study visit date

Study day for the imputed last dose day will not exceed Day 6.

4.2.2. Total Number of Tablets Administered

The total number of tablets administered will be summarized using descriptive statistics.

The presumed total number of tablets administered to a participant will be determined by the data collected on the drug accountability CRF using the following formula:

Total Number of Tablets Administered =

$$\left(\sum \text{No. of Tablets Dispensed}\right) - \left(\sum \text{No. of Tablets Returned}\right)$$

The maximum tablets administered is 10 tablets.

For missing number of tablets returned, imputation rules are described in programming specifications.

No formal statistical testing is planned.

A by-participant listing of study drug administration and drug accountability will be provided separately by participant ID number (in ascending order).

4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry but were enrolled in the study, will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of participants who did not meet at least 1 eligibility criterion and the number of participants who did not meet specific criteria by treatment group based on the All Randomized Analysis Set. A by-participant listing will be provided for all randomized participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

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 category (eg, eligibility criteria, informed consent) will be summarized by treatment group for the All Randomized Analysis Set. A by-participant listing will be provided for those participants with important protocol deviation.

4.4. Assessment of COVID-19 Impact

The study is in nonhospitalized participants with COVID-19; thus, no additional assessment of COVID-19 impact will be included.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (eg, age, age group [≥ 18 – < 65, ≥ 65 – < 75, ≥ 75 – < 85, ≥ 85 years], sex, race, and ethnicity) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of demographic data and baseline characteristics will be provided for the Safety Analysis Set and FAPS.

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 provided for the following subgroups corresponding to randomization strata: duration of symptoms at enrollment (≤ 3 days versus > 3 days); vaccination status (ever versus never)

A by-participant demographic listing, including the informed consent date, will be provided by participant ID number in ascending order.

5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables for the Safety Analysis Set and FAPS:

- Randomization strata: duration of symptoms at enrollment (≤ 3 days versus > 3 days); vaccination status (ever versus never)
- Duration of COVID-19 symptoms prior to first dose of study drug
- Duration from first positive SARS-CoV-2 diagnostic test to first dose of study drug
- Risk factors defined in the inclusion criteria
- Total number of risk factors
- Number of targeted COVID-19 symptoms at baseline measured via the SIC questionnaire
- Summary for each COVID-19 targeted symptom at baseline, where an answer “No” to the questions will be considered as 0 in the summary of severity rating

- Baseline seropositivity: overall positive, ie, anti-spike antibody positive or anti-nucleocapsid antibody positive, versus overall negative, ie, both anti-spike antibody and anti-nucleocapsid antibody negative

- Baseline respiratory viral coinfections: None; Yes subdivided into: Influenza A; Influenza B; respiratory syncytial virus (RSV)

- Baseline SARS-CoV-2 viral load (as a continuous variable, and a categorical variable with < 6 $\log_{10}$ copies/mL versus ≥ 6 $\log_{10}$ copies/mL)

- Baseline eGFR: Creatinine Clearance by Cockcroft-Gault: ≥ 90 mL/min, ≥ 60–< 90 mL/min, ≥ 30 – < 60 mL/min, < 30 mL/min

For categorical data, the 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 (except randomization strata) will be provided for the following subgroups corresponding to randomization strata: duration of symptoms at enrollment (≤ 3 days versus > 3 days); vaccination status (ever versus never).

A by-participant listing of other baseline characteristics will be provided by participant ID number in ascending order.

5.3. Medical History

Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed, or before the first dose of study drug 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 Medical Dictionary for Regulatory Activities (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. In addition, medical history will also be summarized by PT only, in descending order of total frequency.

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 proportion of COVID-19–related hospitalization or all-cause death by Day 29. The endpoint will be derived by combining the available all-cause death and COVID-19–related hospitalization reported by the site.

COVID-19–related hospitalization is defined as ≥ 24 hours of acute care for a reason related to COVID-19, in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with COVID-19. This includes specialized acute medical care units within an assisted living facility or nursing home. This does not include hospitalization for the purposes of public health and/or clinical study execution. The date and duration of hospital admission, and primary reason for hospitalization (including if the hospitalization is related to COVID-19) will be recorded.

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 29 between the 2 treatment groups is equal to 1.

Alternative hypothesis: The hazard ratio of COVID-19–related hospitalization or all-cause death by Day 29 between the 2 treatment groups is not equal to 1.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The FAPS will be used for the primary efficacy endpoint analysis.

The hazard ratio of COVID-19–related hospitalization or all-cause death by Day 29 between the 2 treatment groups will be estimated using a Cox proportional hazards model with the stratification factors (duration of symptoms and vaccination status) as covariates. The hazard ratio, p-value, 95% confidence interval (CI) for the hazard ratio from the Cox model, and proportion of COVID-19-related hospitalization or all-cause death at Day 29 from the Kaplan-Meier estimate will be provided. In addition, the p-value from stratified log rank test will be provided. If 5 events or fewer across both treatment groups are observed within 1 or more stratum, the primary endpoint will be evaluated in the same analysis described above without using the corresponding stratification factor(s) as covariates.

If a participant prematurely discontinues from the study prior to Day 29 and prior to COVID-19-related hospitalization and is alive by Day 29, or the hospitalization status is missing, the participant is censored at the Last Study Date or Day 29, whichever is earlier. If a participant prematurely discontinues from the study prior to Day 29 and prior to COVID-19-related hospitalization and then dies on or prior to Day 29, then date of the death and status will be used for the primary analysis for this participant. 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. Handling of intercurrent events is defined in Section 6.4.

The number and percentage of participants with COVID-19–related hospitalization or all-cause death by Day 29 will be summarized.

6.2. Secondary Endpoints

Key Secondary Efficacy Endpoints

The alpha-controlled secondary endpoints include the following:

- Proportion of participants with all-cause hospitalization by Day 29
- Proportion of participants with COVID-19–related MAVs or all-cause death by Day 29
- Proportion of participants with COVID-19–related MAVs by Day 29
- Proportion of participants with all-cause death by Day 29

Medically attended visits are defined as 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 professional.

Other Secondary Efficacy Endpoints

- Time to COVID-19 symptom alleviation by Day 15
- Change from baseline (Day 1) in SARS-CoV-2 nasal swab viral load at Day 5

Symptom alleviation is defined as all targeted symptoms measured via the SIC questionnaire (Appendix 2) with a rating of 0, or at least 3 points decrease in rating from baseline, or an answer "No" to the question for at least 48 consecutive hours. A new version of the questionnaire that measures COVID-19 symptoms, COVID-19 Symptom Questionnaire, was introduced in protocol Amendment 1 but was not available to any participant by the time of stop of enrollment. Data for the COVID-19 Symptom Questionnaire were not collected.

Targeted symptoms are those listed below:

- Nasal congestion (stuffy nose)
- Runny nose
- Sore throat

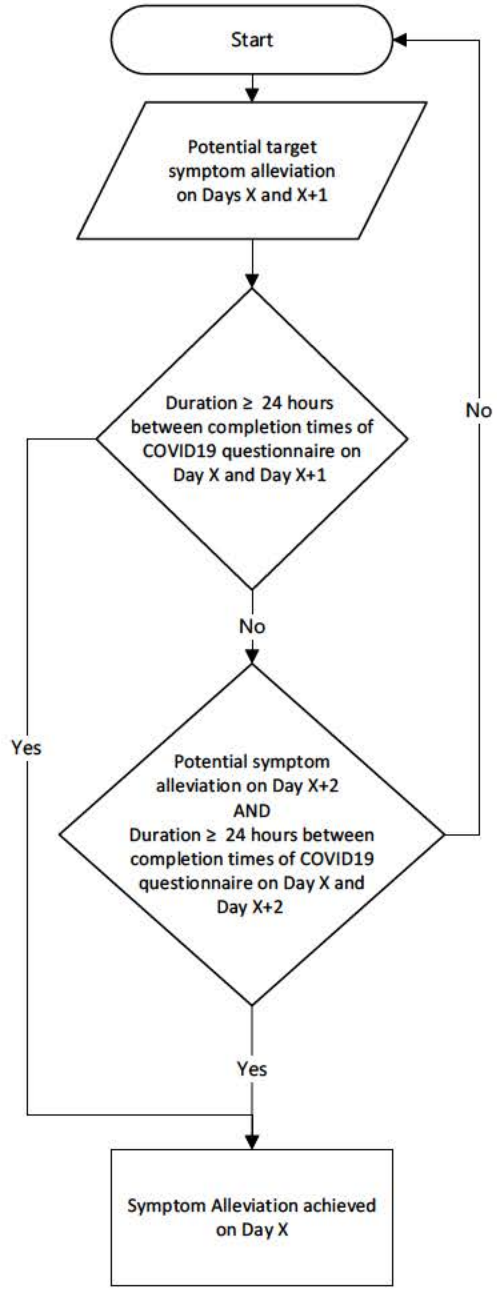
- Shortness of breath (difficulty breathing)
- Cough
- Feeling generally unwell (run down)
- Fatigue (tiredness)
- Physical weakness
- Feeling faint
- Muscle aches/pains
- Joint aches/pains
- Headache
- Chills
- Uncontrollable body shaking/shivering
- Fever

The first day of the 48 consecutive hours will be considered the symptom alleviation date. The date and time stamps at which participants complete the questionnaire each day are captured in electronic diary as "Form Saved Time" and will be used to determine whether the requirement of 48 continuous hours is satisfied.

A potential symptom alleviation is identified first and defined as all targeted symptoms with a rating of 0, or at least 3 points decrease in rating from baseline, or an answer "No" to the question, ie, without 48 consecutive hours confirmation. For participants with missing baseline symptoms data, all targeted symptoms need to have either a rating of 0 or an answer "No" to the question to be considered as potential symptom alleviation.

If there is any intercurrent event prior to Day 15 and prior to the time a participant achieves symptom alleviation, it will be handled per Section 6.4.

As the questionnaire recall time is the previous 24 hours, an additional consecutive 24 hour period is needed to achieve 48 consecutive hours of symptom alleviation. The duration for the second consecutive 24 hours is calculated as shown in the flowchart:



No missing day is allowed between first date and last date of potential symptom alleviation included in the calculation.

The date-time of the first potential alleviation will be considered as the date-time of symptom alleviation and will be used for the calculation of time to symptom alleviation. Otherwise, repeat the algorithm for the next potential symptom alleviation time.

Details and examples of algorithm for symptom alleviation are provided in Appendix 3.

6.2.1. Analysis of Secondary Efficacy Endpoints

The FAPS will be the primary analysis set for key secondary efficacy endpoints and time to COVID-19 symptom alleviation. The Virology Analysis Set will be the primary analysis set for SARS-CoV-2 nasal swab viral load.

The key secondary endpoints will be tested in the following sequential order using a gatekeeping approach:

1. Proportion of participants with all-cause hospitalization by Day 29
2. Proportion of participants with COVID-19–related MAVs or all-cause death by Day 29
3. Proportion of participants with COVID-19–related MAVs by Day 29
4. Proportion of participants with all-cause death by Day 29

The proportion of participants with all-cause hospitalization by Day 29, COVID-19–related MAVs or all-cause death by Day 29, COVID-19 related MAVs by Day 29, and all-cause death by Day 29 will be analyzed in a similar manner to the primary endpoint.

All-cause death by Day 29 will also be compared between the 2 treatment groups using the Fisher's exact test. If a participant prematurely discontinues from the study prior to Day 29 and the death status is missing, the participant will not be included in the analysis.

The Kaplan-Meier product limit method will be used to estimate, and stratified log-rank test will be used to compare the 2 treatment groups for the time to COVID-19 symptom alleviation by Day 15. In addition, a Cox proportional hazards regression model with the stratification factors as covariates will be used to estimate the hazard ratio and its 2-sided 95% CI.

Change from baseline in SARS-CoV-2 nasal swab viral load to each visit including Day 5 will be compared between the 2 treatment groups using a mixed-effects model repeated measures (MMRM) approach. Additionally, change in SARS-CoV-2 viral load from baseline at each postbaseline analysis visit will be provided. Descriptive statistics will be provided by treatment group as follows: (1) Baseline values, (2) Values at each postbaseline analysis visit, (3) Change from baseline at each postbaseline analysis visit. CCI [redacted]

CCI [redacted]

CCI [redacted]

6.4. Intercurrent Events

Handling of intercurrent events for the efficacy endpoints related to hospitalization, MAVs, death, symptom alleviation, SARS-CoV-2 viral load, or SARS-CoV-2 infectious viral titer are shown in Table 6-1. Intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurement of an endpoint. An event (eg, use of rescue medication) that occurs after an endpoint of interest (eg, hospitalization) is not considered as an intercurrent event.

Table 6-1. Handling of Intercurrent Events

Endpoint	Intercurrent event	Strategy	Description
Proportion of COVID-19–related hospitalization or all-cause death by Day 29 Proportion of participants with all-cause hospitalization by Day 29	Discontinue randomized treatment prior to endpoint (due to AE, lack of efficacy, investigator's discretion, noncompliance with study drug, protocol violation, participant decision, lost to follow-up)	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)
Proportion of participants with COVID-19–related MAVs or all-cause death by Day 29 Proportion of participants with COVID-19–related MAVs by Day 29 Proportion of participants with all-cause death by Day 29	Use of rescue medication	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)

Endpoint	Intercurrent event	Strategy	Description
Time to COVID-19 symptom alleviation by Day 15	Hospitalization for the treatment of COVID-19 or all-cause death	Composite policy	Hospitalization for the treatment of COVID-19 or all-cause death means never achieve symptom alleviation (censored at Day 14)
	Discontinue randomized treatment prior to symptom alleviation (due to AE, lack of efficacy, investigator's discretion, noncompliance with study drug, protocol violation, participant decision, lost to follow-up)	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)
	Use of rescue medication	Composite policy	Use of rescue medication means never achieve symptom alleviation (censor at Day 14)
Proportion of participants with negative SARS-CoV-2 nasal swab viral load at Days 3, 5, 10, 15 Proportion of participants with negative SARS-CoV-2 nasal swab infectious viral titer at Days 3, 5, 10, 15	Hospitalization for the treatment of COVID-19 or all-cause death	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)
	Discontinue randomized treatment prior to endpoint (due to AE, lack of efficacy, investigator's discretion, noncompliance with study drug, protocol violation, participant decision, lost to follow-up)	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)
	Use of rescue medication	Composite policy	Use of rescue medication means never achieve negativity

AE = adverse event; COVID-19 = coronavirus disease 2019; MAVs = medically attended visits

6.5. Changes From Protocol-Specified Efficacy Analyses

An interim analysis of safety, futility and efficacy was planned in the protocol using the O'Brien-Fleming approach when 50% (1150 participants) of planned participants completed the Day 29 assessment or prematurely discontinued from the study. The second DMC meeting was to include review of the interim analysis results. Due to early stopping of enrollment of this study, the planned interim analysis was not conducted. The second and any following DMC meeting were not held.

The primary analysis set for efficacy analyses was specified as the FAS in the protocol, but will be the FAPS per FDA feedback.

The secondary endpoints of all-cause hospitalization by Day 29 and COVID-19–related MAVs by Day 29 were to be analyzed using a competing risk analysis approach, with death as the competing risk as described in the protocol. Competing risk analysis approach will not be used due to very low event rate for deaths.

Sensitivity analyses for the primary endpoint that were specified in the protocol will not be conducted.

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The questionnaires to assess the impact on work productivity, activities of daily living, and functionality, WPAI + CIQ: COVID-19 and PROMIS-29, were not available to any participants by the time of stop of enrollment. Data for these questionnaires were not collected and statistical analysis will not be conducted.

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. SOC, high-level group term (HLGT), high-level term (HLT), PT, and lowest-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 categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

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 Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

Incidence of treatment-emergent adverse events (TEAEs) and laboratory abnormalities, and incidence of SAEs, and AEs leading to study drug discontinuation are secondary safety endpoints of this study.

7.1.5.1. Definition of 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 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 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.

7.1.6. 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, HLT (if applicable), PT, and treatment group. For other AE categories described below, summaries will be provided by SOC, PT, and treatment group:

- Grade 3 or higher TEAEs
- All treatment-emergent treatment-related AEs
- Grade 3 or higher treatment-emergent treatment-related AEs
- All treatment-emergent SAEs
- All treatment-emergent treatment-related SAEs
- All treatment-emergent AEs leading to premature discontinuation from study drug

TEAE and treatment-related TEAE will be summarized by SOC, 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 will be provided by treatment group. All treatment-emergent deaths observed in the study will also be included in this summary. Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of 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, Grade 3 or higher TEAEs, treatment-emergent treatment-related AEs, Grade 3 or higher treatment-emergent treatment-related AEs, and treatment-emergent SAEs, will be summarized by PT only, in descending order of total frequency.

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

- All AEs, indicating whether the event is treatment emergent
- Treatment-related AEs
- All AEs with severity of Grade 3 or higher
- All SAEs
- All Deaths
- Treatment-related SAEs
- All AEs leading to premature discontinuation of study drug

7.1.7. Additional Analysis of Adverse Events

The following categories of AEs will be summarized by treatment group:

- Renal dysfunction: Acute renal failure Standard MedDRA Query (SMQ) (broad)
- Hepatic findings: Liver toxicity KUR list

The number and percentage of participants who experienced any of the above events will be summarized for each treatment group by category and PT.

TEAEs will also be summarized for the subgroups for safety endpoints (ie, age, sex at birth, race, region, BMI and baseline eGFR) defined in Section 3.4.

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. SARS-CoV-2 viral load result of "Inconclusive" will not be included in numeric summary. Hemolyzed test results will not be included in the analysis, but they will be listed in by-participant laboratory listings.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, serum chemistry, and coagulation 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.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for selected laboratory tests in Hematocrit, Hemoglobin, Absolute Neutrophil Count, Absolute Lymphocyte Count, Platelet Count, White Blood Cells, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Total bilirubin, Serum Creatinine, eGFR: Creatinine Clearance by Cockcroft-Gault, and International Normalized Ratio (INR) as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date 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.

Median (Q1, Q3) change from baseline values for selected laboratory tests listed above will be plotted using a line plot by treatment group and each postbaseline visit.

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 to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. 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 all laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by participant ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades and abnormal flags displayed.

For the INR of prothrombin time and activated partial thromboplastin time (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 participant 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 participant is not taking an oral anticoagulant, which is a conservative approach that may lead to over-reporting of abnormalities for INR and aPTT.

Abnormalities in coagulation parameters will be included for INR and aPTT.

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:

- AST: (a) > 3 times of the ULN; (b) > 5 × ULN; (c) > 10 × ULN; (d) > 20 × ULN
- ALT: (a) > 3 × ULN; (b) > 5 × ULN; (c) > 10 × ULN; (d) > 20 × ULN
- AST or ALT: (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
- AST or ALT > 3 × ULN and total bilirubin: (a) > 1.5 × ULN; (b) > 2 × ULN
- AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. 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 who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date.

Listings of liver-related laboratory tests will be provided.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for vital signs (including heart rate, respiratory rate, temperature, oxygen saturation, and blood pressure) as follows:

- Baseline value
- Values at each postbaseline analysis window visit
- Change from baseline at each postbaseline analysis window visit

A baseline value will be defined as the last available value collected on or prior to the date 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 body weight, BMI, and vital signs will be provided by participant 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.

7.4.1. Prior Medications

Prior medications are defined as any medications with a start date prior to the first dosing date of study drug, regardless of when the stop date is. If a partial start date is entered, the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be considered as prior medications.

Prior medications will not be summarized.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a participant took study drug. Day 1 to Day 29 medications are defined as medications taken from Day 1 to Day 29. Use of concomitant medications and Day 1 to Day 29 medications will be summarized separately 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. COVID-19 rescue medications (see Appendix 3) taken postbaseline will be listed and summarized if there are sufficient data.

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. Day 1 to Day 29 medications will follow the same logic of concomitant medications using Day 29 instead of last dosing date of study drug. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All reported medications will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

7.5. Other Safety Measures

A by-participant listing of participant pregnancies during the study will be provided by participant ID number. No additional safety measures are specified in the protocol.

7.6. Changes From Protocol-Specified Safety Analyses

Treatment-emergent AEs were defined in the protocol as 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. In this SAP, any AEs leading to premature discontinuation of study drug are added in addition to the protocol definition of TEAEs.

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

8. PHARMACOKINETIC ANALYSES

8.1. PK Sample Collection

Sparse PK blood samples will be collected during an in-person visit for all participants.

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8.2. PK Analyses Related to Intensive PK Sampling

Concentrations of GS-441524 in plasma will be determined using validated bioanalytical assays. Due to limited number of participants with intensive PK data, PK parameters will not be determined in participants in the PK Substudy Analysis Set for this study. Summary of PK parameters will not be provided.

Individual participant concentration data for GS-441524 will be listed and summarized using descriptive statistics by treatment. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, geometric mean, 5th percentile, 95th percentile, Q1, and Q3) will be presented for individual participant concentration data by time point.

Individual concentration data listings and summaries will include all participants with concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower LOQ for postdose time points.

The following tables will be provided for each analyte by treatment:

- Individual participant concentration data and summary statistics

The following figures may be provided for each analyte by treatment:

- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

Individual, mean, and median postdose concentration values that are ≤ LOQ will not be displayed in the figures and remaining points connected.

PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age will be provided in listings.

8.3. PK Analyses Related to Sparse PK Sampling

Individual participant concentration data from participants in the PK Analysis Set for GS-441524 will be listed and summarized using descriptive statistics. PK concentration data from samples out of window will be listed but will not be included in the summary statistics.
Summary statistics (n, mean, SD, %CV, median, min, max, 5^{th} percentile, 95^{th} percentile, Q1, Q3, geometric mean, %CV, and 95% CI for geometric mean) will be presented by day and by nominal time point.

Sparse and intensive PK sampling data from this study may be combined with data from other studies in a meta-population analysis using mixed-effect modeling techniques. Details of the population PK analysis will be provided in a separate document prepared by the PK scientist.

8.4. Changes From Protocol-Specified PK Analyses

PK parameters will not be determined for this study. Summary and listing of PK parameters for GS-441524, as specified in the protocol, will not be provided.

9. REFERENCES

Ferdinands JM, Rao S, Dixon BE, Mitchell PK, DeSilva MB, Irving SA, et al. Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19-Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance - VISION Network, 10 States, August 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022;71 (7):255-63.

Pfizer Inc. Pfizer Reports Additional Data on PAXLOVID™Supporting Upcoming New Drug Application Submission to U.S. FDA [Press Release]. 2022:

Thompson MG, Natarajan K, Irving SA, Rowley EA, Griggs EP, Gaglani M, et al. Effectiveness of a Third Dose of mRNA Vaccines Against COVID-19-Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance - VISION Network, 10 States, August 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022;71 (4):139-45.

10. SOFTWARE

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

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

East® 6.5. Cytel, Waltham, MA, USA.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision
Draft Version 1.0 (13 Nov 2023)		Original Version	
Version 1.0 (22 Jan 2024)	3.8.3	Addition of selection of baseline for SARS-CoV-2 data	Align with selection of analysis record for postbaseline
	6.1.3	Updated primary analysis of the primary efficacy endpoint	Provide additional analysis of the primary efficacy endpoint
	6.4	Addition of handling of intercurrent events for the SARS-CoV-2 related efficacy endpoints	Clarify the impact of intercurrent events on SARS-CoV-2 related efficacy endpoints and the corresponding handling rules
	7.1.6	Revised section with removal of sections 7.1.6.1 and 7.1.6.2	Update to clarify the summaries of AE incidence by severity
	8.2	Removal of sections 8.2.1 and 8.2.2, and any analyses of PK parameters	Update to clarify that PK parameters will not be determined or analyzed for this study

12. APPENDICES

Appendix 1. Schedule of Assessments

Study Visit	Screening[a]	Baseline/ Day 1[a, b]	Day 3[b]	Day 5[b]	Day 10	Day 15[b]	Day 29	Early Discontinuation Visit[b]
Visit Window			± 1 day[c]		± 2 days		+ 5 days	
Visit Type	In Person[d]		In Person[d] or Virtual[e]	In Person[d]	In Person[d] or Virtual[e]			In Person[d]
Written informed consent	X							
Medical history[f]	X							
Document SARS-CoV-2 infection	X							
Complete physical examination[g]	X	X		X				X
Symptom-directed physical examination			X			X		
Height and weight	X							
Vital signs[h]	X	X	X	X	X	X	X	X
Screening ALT, bilirubin, serum creatinine, and CL_{cr}/eGFR[i]	X							
Chemistry, coagulation, and hematology panels[j]		X	X	X		X		X
Urine or serum pregnancy tests[k]	X	X				X		X
Mid-turbinate nasal swab[l]		X	X	X	X	X		X
SARS-CoV-2 serology		X						
CCI								
CCI								
MAV information/oxygen supplementation requirement[o]		X	X	X	X	X	X	X

Study Visit	Screening[a]	Baseline/ Day 1[a, b]	Day 3[b]	Day 5[b]	Day 10	Day 15[b]	Day 29	Early Discontinuation Visit[b]
Visit Window			± 1 day[c]		± 2 days		+ 5 days	
Visit Type	In Person[d]		In Person[d] or Virtual[e]	In Person[d]	In Person[d] or Virtual[e]			In Person[d]
COVID-19 Symptom Questionnaire[p]		X	X	X	X	X	X	X
PROMIS-29		X				X	X	X
WPAI + CIQ: COVID19		X				X	X	X
Study drug dispensation		X						
Study drug dosing (GS-5245 or placebo)		X	X	X				
Study drug bottle return[q]				X	X	X	X	X
Adverse events and concomitant medications	X	X	X	X	X	X	X	X

ALT = alanine aminotransferase; CL_{cr} = creatinine clearance; COVID-19 = coronavirus disease 2019; ED = early discontinuation; eGFR = estimated glomerular filtration rate; MAV = medically attended visit; PCR = polymerase chain reaction; PK = pharmacokinetic(s); PROMIS-29 = Patient-Reported Outcomes Measurement Information System-29; RT-qPCR = reverse transcriptase-quantitative polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WPAI + CIQ:COVID19 = Work Productivity and Activity Impairment + Classroom Impairment Questions: COVID-19 Infection

a Screening window is within 48 hours of the Day 1 visit. Day 1 visit may occur on the same day as screening. If the Day 1 and screening visits are the same day, do not repeat physical exam and vital signs.

b Laboratory tests for safety will be performed on Days 1 and 5, on Days 3 and 15 when an in-person visit is conducted, and at early discontinuation.

c Day 3 and Day 5 visits should be conducted on separate calendar days.

d In-person is defined as a visit at a medical facility or elsewhere by a health care provider (where permitted).

e Virtual visit is defined as an interaction with a health care professional using telephone or online-based interaction (eg, telehealth, webcast, video conferencing).

f Medical history will include the date of first COVID-19 symptoms, overall COVID-19 symptoms, all COVID-19 vaccinations prior to screening, exposure source, demographics, baseline characteristics, allergies, and all other medical history.

g 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. For participants with compensated cirrhosis, a complete physical exam must also include a clinical assessment of ascites (absent, slight, or moderate) and a clinical assessment of hepatic encephalopathy (Absent, Grade I, Grade II, Grade III, or Grade IV), as described in Section 6.3.2.1 of the protocol. Urogenital and reproductive examination should only be completed if clinically indicated.

h Vital signs include heart rate, respiratory rate, temperature, oxygen saturation, and blood pressure. Vital signs are collected at in-person visits only.

i **Screening:** Serum ALT, bilirubin, serum creatinine, and CL_{cr}/eGFR assessments at screening (prior to dosing) are not required unless deemed necessary by the investigator to confirm eligibility, using a local laboratory. See Appendix 11.4 of the protocol for country-specific requirements.

j All required baseline laboratory assessments should be collected prior to first study drug dose.

k At screening, a urine pregnancy test will be performed at the local laboratory for participants assigned female at birth and of childbearing potential. On Day 1, Day 15, and ED visits, these participants will have a serum pregnancy test performed via the central laboratory for in-person visits or a urine pregnancy test for virtual visits. At screening, a follicle-stimulating hormone test is required to confirm the postmenopausal state in participants younger than 54 years, who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure, as described in Appendix 11.3 of the protocol.

l A mid-turbinate nasal swab will be collected at in-person visits and used for SARS-CoV-2 RT-qPCR, potential multiplex viral PCR, potential infectious viral titer assessment, and potential resistance testing. The nasal swab must be collected by clinic/study personnel in person. For virtual visits on Days 3, 10, or 15 no samples will be collected.

[redacted]

o 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 professional. The nature and cause of the visit should be identified. Medically attended visit information and oxygen supplementation information should be collected through Day 29.

p The COVID-19 symptom questionnaire should be completed daily (at approximately the same time each day) from predose (prior to first dose on Day 1) through Day 15, and on Day 29. If a participant discontinues from the study early, the participant should complete this questionnaire during the early discontinuation visit.

q Study drug bottle should be returned by the participant on Day 5, if the participant has already completed both doses of study drug. If the participant has study drug at the end of the Day 5 visit, the participant may return the study drug bottle on Day 10. If the Day 10 visit is virtual, drug accountability should be performed virtually and the participant will be instructed on returning the study drug bottle.

Appendix 2. Patient Reported Outcomes

CONFIDENTIAL: SIC Version 2.0
May 29, 2020

Symptoms of Infection with Coronavirus-19 (SIC)

The following questions ask about symptoms people with coronavirus-19 infection may experience. Answer each question carefully by choosing 'Yes' if you have experienced the symptom or 'No' if you have not experienced the symptom in the last 24 hours. If you choose 'yes', select the rating that best matches your experience.

In the last 24 hours, have you experienced…	
Feeling generally unwell (run down) ☐ **Yes** ☐ **No** If yes, →	How severe was this **feeling (generally unwell or run down)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Fatigue (tiredness) ☐ **Yes** ☐ **No** If yes, →	How severe was your **fatigue (tiredness)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Physical weakness ☐ **Yes** ☐ **No** If yes, →	How severe was your feeling of **physical weakness** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Cough ☐ **Yes** ☐ **No** If yes, →	How severe was your **cough** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Shortness of breath (difficulty breathing) ☐ **Yes** ☐ **No** If yes, →	How severe was your **shortness of breath (difficulty breathing)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Sore throat ☐ **Yes** ☐ **No** If yes, →	How severe was your **sore throat** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Nasal congestion (stuffy nose) ☐ **Yes** ☐ **No** If yes, →	How severe was your **nasal congestion (stuffy nose)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Wheezing (whistling sound while breathing) ☐ **Yes** ☐ **No** If yes, →	How severe was your **wheezing (whistling sound while breathing)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible

1

SIC Version 1.0 *May 29 2020*

In the last 24 hours, have you experienced…	
Runny nose ☐ **Yes** ☐ **No** If yes, →	How severe was your **runny nose** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Sneezing ☐ **Yes** ☐ **No** If yes, →	How severe was your **sneezing** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Chest congestion (mucus in chest) ☐ **Yes** ☐ **No** If yes, →	How severe was your **chest congestion (mucus in chest)** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Chest pain/ pressure/tightness ☐ **Yes** ☐ **No** If yes, →	How severe was your **chest pain/pressure/tightness** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Muscle aches/pains ☐ **Yes** ☐ **No** If yes, →	How severe were your **muscle aches or pains** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Joint aches/pains ☐ **Yes** ☐ **No** If yes, →	How severe were the **aches or pains in your joints** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Headache ☐ **Yes** ☐ **No** If yes, →	How severe was your **headache** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Feeling faint ☐ **Yes** ☐ **No** If yes, →	How severe was your **feeling of faintness** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Problems thinking clearly/brain fog ☐ **Yes** ☐ **No** If yes, →	How severe were your **problems thinking clearly/brain fog** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible

2

SIC Version 1.0 *May 29 2020*

In the last 24 hours, have you experienced…	
Chills ☐ **Yes** ☐ **No** If yes, →	How severe were your **chills** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Skin rash ☐ **Yes** ☐ **No** If yes, →	How severe was your **skin rash** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Eye irritation/discharge ☐ **Yes** ☐ **No** If yes, →	How severe was your **eye irritation/discharge** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Diarrhea ☐ **Yes** ☐ **No** If yes, →	How severe was your **diarrhea** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Vomiting ☐ **Yes** ☐ **No** If yes, →	How severe was your **vomiting** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Nausea ☐ **Yes** ☐ **No** If yes, →	How severe was your **nausea** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Abdominal/stomach pain ☐ **Yes** ☐ **No** If yes, →	How severe was your **abdominal/stomach pain** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible
Loss of appetite ☐ **Yes** ☐ **No** If yes, →	How severe was your **loss of appetite** in the last 24 hours? ☐ 0 None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible

In the last 24 hours, have you experienced…	
Fever ☐ **Yes** ☐ **No** If yes, →	What was your **highest temperature** in the last 24 hours? ____ °F

3

In the last 24 hours, have you experienced…
Uncontrollable body shaking/shivering ☐ Yes ☐ No
Decreased sense of smell ☐ Yes ☐ No
Decreased sense of taste ☐ Yes ☐ No
Red or bruised looking feet or toes ☐ Yes ☐ No

4

Appendix 3. Programming Specifications

1) Symptom alleviation and time to symptom alleviation

SIC questionnaire is shown in Appendix 2.

1. Targeted symptoms are those listed below. Only targeted symptoms will be evaluated in deriving of the secondary endpoint in time to COVID-19 symptom alleviation by Day 15.

- Nasal congestion (stuffy nose)
- Runny nose
- Sore throat
- Shortness of breath (difficulty breathing)
- Cough
- Feeling generally unwell (run down)
- Fatigue (tiredness)
- Physical weakness
- Feeling faint
- Muscle aches/pains
- Joint aches/pains
- Headache
- Chills
- Uncontrollable body shaking/shivering
- Fever

2. Alleviation of all targeted symptoms:

- Symptom with a rating of 0 at postbaseline
- Symptom with a nonmissing rating at baseline has a decrease of at least 3 points in rating at postbaseline
- Symptom with an answer “No” to the question at postbaseline

and

- for 48 consecutive hours (SAS datetime format dd:hh:mm:ss will be used for the duration)
  - A potential symptom alleviation is identified first without 48 consecutive hours confirmation. Participants with missing baseline symptoms data, all targeted symptoms need to have a rating of 0 or an answer "No" to the question for symptom alleviation.
  - Since the questionnaire recall time is over the last 24 hours, an additional consecutive 24 hours is needed to achieve consecutive 48 hours symptom alleviation, the reference start time of the second 24 hours is the assessment time of the first potential symptom alleviation.
  - No missing assessment is allowed between the first date and the last date of potential symptom alleviation included in the calculation.
  - The last day potentially able to meet the definition of alleviation is Day 14.

Examples of counting additional 24 consecutive hours:

Example		Study Day										Day and time of symptom alleviation	
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**			
1	Time		18:00	9:00	10:00								Day 3 9:00 to Day 4 10:00 ≥ 24 hrs
	PSA		N	Y	Y	Y	Y	Y	Y	Y	Y	Day 3 9:00	
2	Time			9:00	10:00								Day 3 9:00 to Day 4 10:00 ≥ 24 hrs, Missing symptoms on Day 2 has no impact.
	PSA		.	Y	Y	Y	Y	Y	Y	Y	Y	Day 3 9:00	
3	Time		18:00	9:00	8:00	8:30							Day 3 9:00 to Day 4 8:00 <24 hrs, so check for next day Day 3 9:00 to Day 5 8:30 ≥ 24 hrs
	PSA		N	Y	Y	Y	Y	Y	Y	Y	Y	Day 3 9:00	
4	Time		18:00	9:00	8:00	8:30	10:00	10:00					Day 3 9:00 to Day 4 8:00 <24 hrs, so check for next day Day 5 is not a PSA so need to check later date
	PSA		N	Y	Y	N	Y	Y	Y	Y	Y	Day 6 10:00	

Example	Study Day											Day and time of symptom alleviation	
		1	2	3	4	5	6	7	8	9			
5	Time		18:00	9:00	.	9:00	10:00	10:00					no missing data is allowed within consecutive 24 hrs, need to restart the clock; Day 5 9:00 – Day 6 10:00 ≥24 hrs
	PSA		N	Y	.	Y	Y	Y	Y	Y	Y	Day 5 9:00	
6	Time		18:00	8:00	8:00	8:30	10:00	10:00					Day 3 8:00 to Day 4 8:00 ≥ 24 hrs, symptom alleviation achieved even if symptoms reported on Day 5
	PSA		N	Y	Y	N	Y	Y	Y	Y	Y	Day 3 8:00	
7	Time		18:00	9:00	8:00	9:00	10:00	10:00	8:00				Censored at Day 8 8:00 if prematurely discontinued from study after Day 8
	PSA		N	N	N	N	N	N	N				

PSA – potential symptom alleviation; Y – Yes; N – No; Yellow – symptom alleviation ≥ 48 hours; Tan – symptom alleviation < 48 hours

Note: If a participant answered "No" to the question for all symptoms at baseline, alleviation status will not be derived, and the participant is excluded from the analysis.

If a participant had nonmissing results for symptoms at baseline and symptoms for Day 2 and later are all missing, the participant is considered as censored at 23:59 on Day 1.

If a participant has no SIC questionnaire data reported from Day 1 to Day 15, the participant is excluded from the analysis.

For all participants in ADEFF, the symptom alleviation status will be set to "Not Achieved Alleviation" with corresponding numeric value 0 at baseline, although symptom alleviation is not evaluated at baseline.

3. Time to alleviation of symptoms (unit = day, keep 8 decimals from date/time calculation in dataset, use 1 decimal place for TFLs)

   - For participants with symptom alleviation by Day 15, use the first event of participant level alleviation status equals Yes,

     Date and Time of alleviation – Date and time of first dose.

   - For participants who complete Day 15 of the study without symptom alleviation, time to symptom alleviation will be censored at Day 14,

Date and time of Day 14 SIC questionnaire assessment – Date and time of first dose.

Use Day 14 23:59 if no Day 14 SIC questionnaire assessment.

- For participants who have nonmissing results for symptoms for at least 1 day after Day 1 and discontinue from the study before Day 15 without symptom alleviation, time to symptom alleviation will be censored at the last SIC questionnaire assessment,

  Date and time of last SIC questionnaire assessment – Date and time of first dose.

- For participants with missing time of first dose, missing time is imputed using the time of SIC questionnaire assessment on the first dose date or 12:00 whichever occurs first.

4. Additional censoring rules due to Intercurrent event:

   Hospitalization for the treatment of COVID-19 or all-cause death or Use of rescue medication (see definition in #2)

   Date and Time of Day 14 SIC questionnaire assessment – Date and time of first dose.

   Use Day 14 23:59 if no Day 14 SIC questionnaire assessment.

2) COVID-19 Rescue Medications

Details of COVID-19 rescue medications are provided in the table below.

Drug Class	Dictionary Level	Prohibited PREF Codes	Prohibited Ingredient, PREF, and/or ATC Decodes
Bamlanivimab and Etesevimab	PREF	15665101001	BAMLANIVIMAB;ETESEVIMAB
Bamlanivimab	PREF	15343501001	BAMLANIVIMAB
Bamlanivimab	PREF	15665101001	BAMLANIVIMAB;ETESEVIMAB
Casirivimab and Imdevimab	PREF	15585401001	CASIRIVIMAB;IMDEVIMAB
Cilgavimab and Tixagevimab	PREF	15616901001	CILGAVIMAB;TIXAGEVIMAB
Molnupiravir	PREF	15326101001	MOLNUPIRAVIR
Nirmatrelvir and Ritonavir	PREF	15892101001	NIRMATRELVIR;RITONAVIR
Remdesivir	PREF	14269001001	REMDESIVIR
Sotrovimab	PREF	15464401001	SOTROVIMAB
Bebtelovimab	PREF	16033001001	BEBTELOVIMAB
Ensitrelvir	PREF	16350701001	ENSITRELVIR
Ensitrelvir	PREF	16350702001	ENSITRELVIR FUMARIC ACID

ATC = anatomical therapeutic chemical; PREF = preferred

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

3) Population, denominator, and numerator for efficacy endpoints summaries of proportion

Endpoint / Summary	Population / Denominator	Numerator
Proportion of COVID-19–related hospitalization or all cause death by Day 29 Proportion of participants with all-cause hospitalization by Day 29 Proportion of participants with COVID-19-related MAVs or all-cause death by Day 29 Proportion of participants with COVID-19-related MAVs by Day 29 Proportion of participants with all-cause death by Day 29	FAPS Based on KM estimate, no explicit denominator used	Total number of events by selected visits Note: Proportions from KM estimate differ from proportion calculated directly from number of event and participants at risk
Proportion of participants with negative SARS-CoV-2 nasal swab viral load at Days 3, 5, 10, and 15	Participants in the Virology analysis set who had SARS-CoV-2 nasal swab collected and nonmissing result of viral load reported at selected visits	Number of participants with negative SARS-CoV-2 nasal swab viral load
Proportion of participants with negative SARS-CoV-2 infectious viral titer at Days 3, 5, 10, and 15	Participants in the Virology analysis set who had SARS-CoV-2 nasal swab collected and nonmissing result of SARS-CoV-2 infectious viral titer reported at selected visits	Number of participants with negative SARS-CoV-2 infectious viral titer

4) Definition of Hospitalization

MAVs type of Emergency Room, non-ICU Hospitalization, ICU Hospitalization, and Hospitalization (unknown ward) could meet criteria for hospitalization if one of the following conditions is met:

- If the duration of the MAV is greater than 24 hours.
- If the duration is missing and end date of the MAV is 1 day after the start date.

Time to hospitalization is calculated as Start date of Hospitalization – First dose date + 1.

5) SARS-CoV-2 positive at baseline

SARS-CoV-2 positive at baseline is defined as test result from central lab.

- Cepheid's Xpert Xpress CoV-2/Flu/RSV plus (Multiplex) test result is positive for SARS-CoV-2 or

- SARS-CoV-2 RT-qPCR test result is numerical viral load result or "<2228cp/mL SARSCoV2 detected", regardless the sample was collected with less than specified volume of test solution.

GS-US-611-6273-Final Analysis-SAP-v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	24-Jan-2024 01:01:34
PPD	Global Development Lead (GDL) eSigned	24-Jan-2024 17:55:34