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 Nonhospitalized Participants
Name of Test Drug:	Obeldesivir (ODV, GS-5245)
Study Number:	GS-US-611-6549
Protocol Version (Date):	Amendment 4: 12 December 2023
Analysis Type:	Primary Analysis and Final Analysis
Analysis Plan Version:	V1.0
Analysis Plan Date:	11 January 2024
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
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
ECG	electrocardiogram
ET	early termination
FAS	Full Analysis Set
FAPS	Full Analysis Positive Set
GCP	Good clinical practice
Hb	hemoglobin
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IXRS	interactive voice or web response system
LLT	lowest-level term
LLOQ	Lower limit of quantitation
LOD	Limit of detection
LOQ	limit of quantitation
MAV	medically attended visit
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
ODV	Obeldesivir, GS-5245
PT	preferred term
Q1, Q3	first quartile, third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SD	standard deviation
SE	Standard error
SI (units)	international system of units

SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the Primary analysis and the Final Analysis for Study GS-US-611-6549. The Primary analysis will be performed after all participants reach Day 29 or prematurely discontinue from the study. The Final Analysis will be performed after all participants have completed the study or prematurely discontinue from the study.

This SAP is based on the study protocol Amendment 4 dated 12 December 2023 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization for the primary analysis. Any critical changes (eg, changes related to the primary efficacy endpoint) made after the finalization of this SAP will be documented in the final clinical study report (CSR).

1.1. Study Objectives

Primary Objectives

- To evaluate the efficacy of GS-5245 in reducing the duration of COVID-19 symptoms
- To evaluate the safety and tolerability of GS-5245 administered in nonhospitalized participants with COVID-19

Secondary Objectives

- To assess the impact of GS-5245 on time to resolution of COVID-19 symptoms
- To evaluate the impact of GS-5245 on moderate relapse of COVID-19 symptoms
- 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 hospitalizations or all-cause death
- To evaluate the antiviral activity of GS-5245 on SARS-CoV-2 nasal swab viral load at Day 5
- To evaluate the effect of GS-5245 on duration of viral shedding
- To evaluate the effect of GS-5245 on viral rebound
- To evaluate the plasma PK of GS-441524 (metabolite of GS-5245)
- To evaluate the impact of GS-5245 on relapse of COVID-19 symptoms

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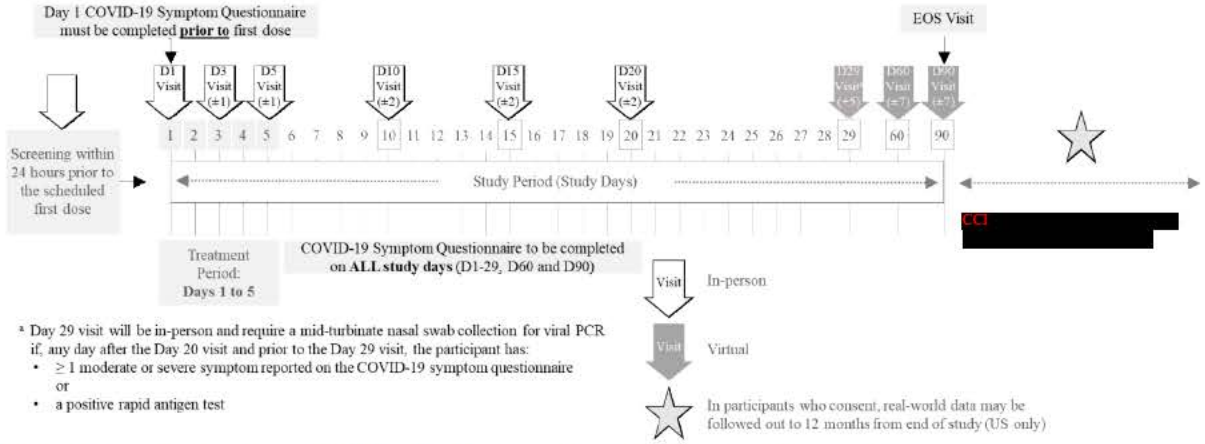
1.2. Study Design

This Phase 3 study is a global, randomized, double-blind, placebo-controlled study comparing the safety and efficacy of oral ODV with placebo in nonhospitalized participants, aged ≥ 12 to < 65 years, with COVID-19, without risk factors for progression to severe disease, regardless of vaccination status.

Randomization will be stratified by vaccination status (completed primary vaccination series: Yes or No).

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

Figure 1. Study Schema



COVID-19 = coronavirus disease 2019; D = Day; EOS = end of study; PCR = polymerase chain reaction

Approximately 1900 participants will be randomized into the study. Participants who meet randomization eligibility criteria will be randomized in a 1:1 ratio to ODV or placebo starting on Day 1.

The schedule of study procedures is presented in Appendix 1.

1.3. Sample Size and Power

A total sample size of approximately 1900 participants (assuming 90% are SARS-CoV-2 positive at baseline as confirmed by the central laboratory) provides approximately 87% power to detect a median difference of 2 days in time to alleviation of targeted symptoms, which is equal to a hazard ratio (HR) of 1.18 using a 2-sided significance level of 0.05 assuming the placebo group median time to symptom alleviation is 13 days. The estimate of median time to COVID-19 symptom alleviation is based on the EPIC-SR study.

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 interim analysis using the Lan-DeMets approach with O'Brien-Fleming type spending function).

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

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

2.1.1. DMC Analysis

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of the safety data in order to protect participant 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 are provided in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

A planned interim analysis of futility based upon the primary endpoint was conducted when approximately 50% of the planned participants reached Day 29 or prematurely discontinued from the study. The significance level for futility was determined using the O'Brien-Fleming approach. The DMC recommended the study to continue without any modifications.

2.2. Primary Analysis

The unblinded primary analysis of the primary endpoint will be conducted after all participants have completed the Day 29 assessments or discontinued from the study prematurely, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis. This analysis will serve as the primary analysis of the primary efficacy endpoint and key secondary efficacy endpoints.

2.3. 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.

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 ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the participant. The treatment group to which participants were randomized will be used in the listings. Age, sex at birth, race, ethnicity, and country 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. Participants included in each analysis set will be determined before the study blind is broken for analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

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

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

Good clinical practice (GCP) noncompliance observations were identified at 1 study center (Site 20189) that randomized 32 participants into this study. The observations were considered critical or major. Therefore, the 32 participants from Site 20189 will be excluded from the efficacy, safety, virology, and PK analyses; these participants will only be included in the All Randomized Analysis Set.

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 participants, except those from Site 20189, who (1) are randomized into the study and (2) have received at least 1 dose of study drug.

3.1.3. Full Analysis Positive Set

The Full Analysis Positive Set (FAPS) includes all participants, except those from Site 20189, who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3)

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 participants, except those from Site 20189, who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have a baseline SARS-CoV-2 viral load ≥ Lower limit of quantification (LLOQ). Refer to Section 3.4 for the definition of LLOQ.

3.1.5. Antigen Analysis Set

The Antigen Analysis Set includes all participants, except those from Site 20189, who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have at least 1 SARS-CoV-2 rapid antigen test positive from Day 1 to Day 5 and SARS-CoV-2 PCR positive at baseline per FAPS.

3.1.6. Safety Analysis Set

The Safety Analysis Set includes all participants, except those from Site 20189, who (1) are randomized into the study and (2) have received at least 1 dose of study drug.

3.1.7. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized participants, except those from Site 20189, who took at least 1 dose of study drug and have at least 1 nonmissing concentration value reported by the PK laboratory for GS-441524. This is the primary analysis set for all PK analyses.

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3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set, FAPS, Virology Analysis Set, or Antigen 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 the 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 vaccination status (completed primary vaccination series): Yes or No.

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

The primary efficacy endpoint will be evaluated using stratification factors as covariates or stratification variables for analyses, as specified in Section 6. In addition, observed imbalances between treatment groups in other baseline characteristics may be considered as covariates in sensitivity analyses of efficacy endpoints.

If 5 events or less across both treatment groups are observed within 1 or more stratum, efficacy analyses including stratification factors will be evaluated in the same analyses without using stratification factors.

3.4. Examination of Subject Subgroups

Subgrouping of participants based on randomization stratification factor will be explored for subgroup analyses. In addition, the primary and select secondary efficacy endpoint(s), and selected safety endpoints may be examined using the following subgroups:

- Age: ≥ 12 – < 18, ≥ 18 – < 65, ≥ 65 years
- Sex at birth: Male vs Female
- Race: (a) Asian, (b) Black, (c) White, (d) Other
- Ethnicity: Hispanic vs non-Hispanic
- Region: US vs ex-US
- Baseline SARS-CoV-2 viral load: < 6 $\log_{10}$ copies/mL vs ≥ 6 $\log_{10}$ copies/mL
- Baseline SARS-CoV-2 viral load: ≥ LLOQ vs < LLOQ. Baseline SARS-CoV-2 viral load result of 'No SARS-CoV2 detected', 'Inconclusive', '< 2228 cp/mL SARS-CoV2 detected' are considered <LLOQ; numerical results are considered as ≥ LLOQ. Participants for whom the baseline SARS-CoV-2 viral load sample was collected with less than specified volume of test solution will not be included for analysis.

- Baseline SARS-CoV-2 seropositivity: overall positive, defined as any one of the anti-spike antibody or anti-nucleocapsid antibody is positive, vs overall negative, defined as both anti-spike antibody and anti-nucleocapsid antibody negative if both results are available or 1 test result is negative if only 1 test result is available.

- BMI: < 25 kg/m^2 vs ≥ 25 kg/m^2

- Baseline eGFR: ≥ 90, ≥ 60 - < 90, ≥ 30 - < 60, < 30 regardless of unit. Creatinine Clearance by Cockcroft-Gault formula is used for participants ≥ 18 years old. Bedside-Schwartz formula is used for participants ≥ 12 and < 18 years old.

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 efficacy endpoint and key α-controlled secondary endpoints will be controlled using the Lan-DeMets approach with O'Brien-Fleming type spending function accompanying a gatekeeping testing strategy (ie, the primary efficacy endpoint will be tested first and the key α-controlled secondary endpoints will be tested in a sequential manner only if the primary efficacy endpoint is met).

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 COVID-19 questionnaire assessment date.

For missing last dosing date of study drug, imputation rules are described in Section 4.2. The handling of missing or incomplete dates for 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. No sensitivity analyses to evaluate the impact of outliers on efficacy or safety outcomes are planned. Unless specified otherwise, all data will be included in the analyses.

3.7. Data Handling Conventions and Transformations

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 First dose date will be used instead. If an enrolled participant was not dosed with any study drug, the randomization date will be used instead of the First dose 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 (1/2 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"

Numerical result of SARS-CoV-2 viral load and infectious viral titer results 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 2) 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 and PK parameters. Concentration values that are BLQ will be presented as "BLQ" in the concentration data listing and PK concentration summary tables. 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, questionnaire collection dates and 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

*If the nominal visit is a scheduled visit and the assessment is done on Day 4 (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	17
Day 20	20	18	23
Day 29	29	24	43

*If the nominal visit is a scheduled visit and the assessment is done on Day 4 (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*	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 (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 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

SARS-CoV-2 rapid antigen tests will be self-collected daily on all visit and non-visit days, up to Day 15, thereafter, on Days 17, 19, 21, 23, 25, 27, and 29. Windows are not assigned and results will be summarized for each applicable Study Day through Day 15. For assessment from Day 17 to Day 29 nominal visits, the analysis windows are provided in Table 3-5.

Table 3-5. Analysis Visit Windows for SARS-CoV-2 Rapid Antigen Test Collected after Day 15

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 17	17	16	17
Day 19	19	18	19
Day 21	21	20	21
Day 23	23	22	23
Day 25	25	24	25
Day 27	27	26	27
Day 29	29	28	43

The COVID-19 Symptom Questionnaire will be completed daily from predose at Day 1 to Day 29 visit, then at Day 60 and Day 90 visits. Windows are not assigned and results will be summarized for each applicable Study Day through Day 29. For the Day 60 and Day 90 nominal visits, the analysis windows are provided in Table 3-6.

The WPAI + CIQ:COVID-19 Questionnaire will be completed at Days 1, 10, 29, 60, and 90 and PROMIS-29 Questionnaire will be completed at Days 1, 29, 60, and 90. The analysis windows are provided in Table 3-6.

Table 3-6. Analysis Visit Windows for Questionnaires

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 10*	10	8	12
Day 29*	29	24	43
Day 60	60	53	67
Day 90	90	83	97

* for WPAI + CIQ:COVID-19 and PROMIS-29 questionnaires as applicable

The number of contacts in the household and how many tested positive for COVID-19 will be recorded on Day 15 visit. Study day 13 to 22 will be assigned to Day 15 analysis visit for household contact diagnosed with COVID-19.

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 questionnaires, 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) 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 and time to symptom resolution, all records within the analysis visit window will be used.
- For postbaseline questionnaire data (not for time to event endpoint), if there is more than 1 record on the selected day, the latest value will be selected.
- For time to antigen negativity and antigen rebound, all records within the analysis visit window will be used.
- 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

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

A summary of participant enrollment will be provided by treatment group for each investigator within a country or region, 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.

The number and percentage of participants enrolled by randomized stratum will be summarized using stratum assignment based on the clinical database. The denominator will be the number of participants in the All Randomized Analysis Set. A listing of participants with discrepancies between IXRS and the clinical database 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 for all screened participants. This summary will include the number of participants screened, screen failure participants who were not randomized, participants who met all eligibility criteria and were not randomized with reasons participants not randomized, participants randomized, participants randomized but never treated, participants from Site 20189, participants in the Safety Analysis Set, participants in the FAS, and participants in the FAPS.

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

- Completed study drug as recorded on the Study Drug Completion form
- Did not complete study drug with reasons for premature discontinuation of study drug as recorded on the Study Drug Completion form
- Continuing study up to the data cut date
- Completed study
- Did not complete the study with reasons for premature discontinuation of study as recorded on the Study Completion form

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 percentages of participants in each category will be the number of participants in the Safety Analysis Set. In addition, a flowchart will be provided to depict the disposition.

A data listing of reasons for premature study drug/study discontinuation will be provided.

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 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, the last dose date is imputed as the earliest date from the following. Study day for the imputed last dose day will not exceed Day 6.

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

4.2.2. Total Number of Tablets Administered

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 and maximum tablets administered is 10 tablets:

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

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

4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry but who were enrolled in the study, will be summarized. 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 listing will be

provided for all randomized participants who violated at least 1 inclusion or exclusion criterion. The listing will include the criteria not met.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations and the total number of important protocol deviations by deviation category (eg, eligibility criteria, informed consent) will be summarized by treatment group for the All Randomized Analysis Set, the analysis will be repeated for the FAPS. A by-participant listing will be provided for those participants with important protocol deviations.

4.4. Assessment of COVID-19 Impact

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

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic data (eg, sex, race, race category, ethnicity, age, and age group [≥ 12 - < 18, ≥ 18 - < 65, ≥ 65 years) and baseline characteristics (eg, BMI [kg/m^2]) will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of participants for categorical data. The summaries of demographic data and baseline participant 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 produced for the following subgroups: completed primary vaccination series (Yes or No) and region: (US vs ex-US).

A by-participant demographic listing will be provided.

5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for the Safety Analysis Set and FAPS:

- Randomization stratum: completed primary vaccination series (Yes or No)
- 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
- Number of targeted COVID-19 symptoms at baseline
- Count and percentage of category for each COVID-19 symptom at baseline
    - None, Mild, Moderate, and Severe for targeted symptoms and Nausea;
    - No vomit/diarrhea, 1-2 times, 3-4 times, 5 or more times for Vomit and Diarrhea;
    - The same as usual, Less than usual, No sense for Sense of smell and sense of taste
- Total scores of targeted COVID-19 symptoms at baseline, where 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe
- Baseline COVID-19 vaccination status: Ever vs Never

  - Baseline seropositivity: overall positive, defined as any one of the anti-spike antibody positive or anti-nucleocapsid antibody is positive, vs overall negative, defined as both anti-spike antibody and anti-nucleocapsid antibody negative if both results are available or 1 test result is negative if only 1 test result is available.

- 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 < 6 $\log_{10}$ copies/mL vs ≥ 6 $\log_{10}$ copies/mL)

- Baseline eGFR: ≥ 90, ≥ 60 - < 90, ≥ 30 - < 60, < 30 regardless of unit. Creatinine Clearance by Cockcroft-Gault formula is used for participants ≥ 18 years old. Bedside-Schwartz formula is used for participants ≥ 12 and < 18 years old.

For categorical data, the CMH test (general association statistic for nominal data and row mean scores for ordinal data) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

Similar summaries will be produced for the following subgroups: completed primary vaccination series (Yes or No).

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

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary endpoint is the time (days) to COVID-19 symptom alleviation by Day 29 on the targeted symptoms measured via the COVID-19 symptom questionnaire. Symptom alleviation is defined as follows: all targeted symptoms scored moderate or severe at baseline are scored as mild or none for at least 48 consecutive hours and all targeted symptoms scored mild or none at baseline are scored as none for at least 48 consecutive hours; the first day of the 48 consecutive hours will be considered the symptom alleviation date.

Targeted symptoms are those listed below:

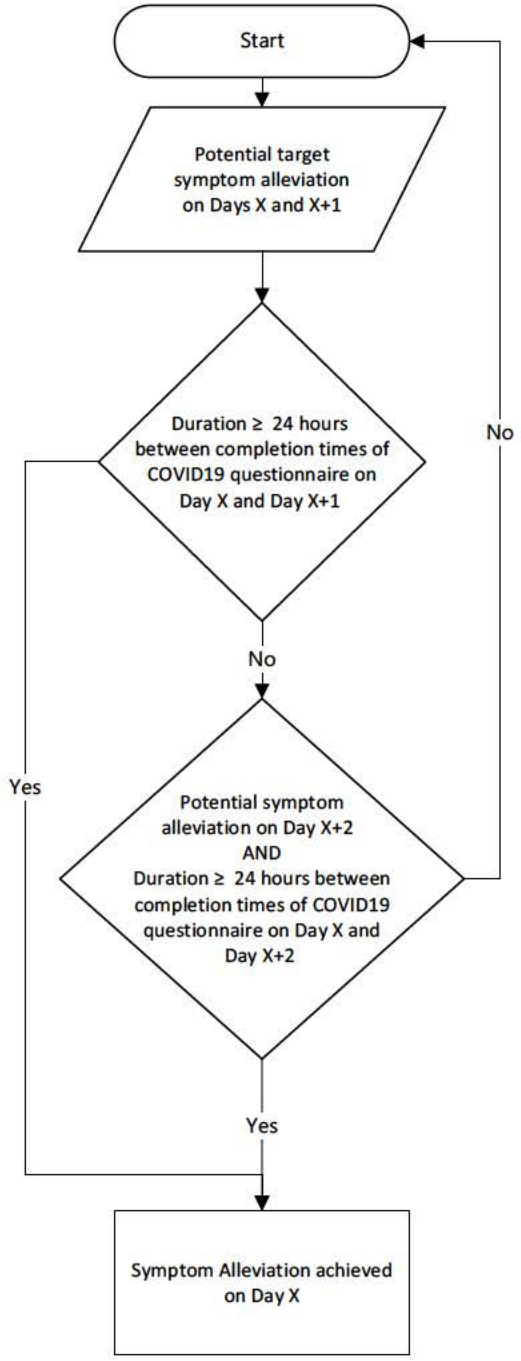
- Stuffy or runny nose
- Sore throat
- Shortness of breath (difficulty breathing)
- Cough
- Low energy or tiredness
- Muscle or body aches
- Headache
- Chills or shivering
- Feeling hot or feverish

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 scored moderate or severe at baseline are scored as mild or none and all targeted symptoms scored mild or none at baseline are scored as none, ie, without 48 consecutive hours confirmation. For participants with missing baseline symptoms data, all targeted symptoms need to be scored as none to be considered as potential symptom alleviation.

If there is any intercurrent event prior to Day 29 and 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 the symptom alleviation are provided in Appendix 2.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

Null hypothesis: There is no difference in time to COVID-19 symptom alleviation by Day 29 between the 2 treatment groups.

Alternative hypothesis: There is a difference in time to COVID-19 symptom alleviation by Day 29 between the 2 treatment groups.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The median time to symptom alleviation and its 95% confidence interval (CI) will be estimated by treatment group using the Kaplan-Meier method. A stratified log-rank test with stratification factor included will be used to compare the treatment difference in time to COVID-19 symptom alleviation.

For participants with symptom alleviation by Day 29 (event), time to COVID-19 symptom alleviation is calculated as symptom alleviation date/time minus the first dose date/time (expressed as days with 8 decimal places). In the analysis output, 1 decimal place in days will be used for display purposes. For participants who complete Day 29 of the study or discontinue from the study before Day 29 without symptom alleviation (censored) and without intercurrent events, the time will be calculated as the last date/time on which the symptom alleviation is assessed by Day 29 minus the first dose date/time or Day 28, whichever occurs first.

Handling of intercurrent events is defined in Section 6.4.

The proportion of participants with symptom alleviation using Kaplan-Meier estimates will be provided in tables and plots by treatment.

In addition, a Cox proportional hazards regression model will be used to estimate the HR and its 2-sided 95% CI. Randomization stratification factor will be included as a covariate in the Cox proportional hazards model.

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

6.1.4. Secondary Analyses of the Primary Efficacy Endpoint

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

- A sensitivity analysis using a competing risk analysis approach, with intercurrent events (death or COVID-19–related hospitalization) as the competing risk, if there are sufficient intercurrent events.

- Missing symptom alleviation status imputed using multiple imputation assuming missing at random.

- Depending on the percentage of participants with other concomitant respiratory viral coinfection(s) at baseline, a sensitivity analysis may be conducted using the respiratory viral coinfection status (yes/no) at baseline as an additional stratification factor in the stratified log-rank test and as an additional covariate in the Cox proportional hazards model.

- Restricted mean time to symptom alleviation for each treatment group will be provided.

6.2. Secondary Endpoints

Key Secondary Efficacy Endpoints:

The alpha-controlled secondary endpoints include the following:

- Time to COVID-19 symptom resolution by Day 29.

COVID-19 symptom resolution is defined as all targeted symptoms scored as none for at least 48 consecutive hours. The first day of the 48 consecutive hours will be considered the date of symptom resolution. The time to COVID-19 symptom resolution is the time (expressed as days with 8 decimal places) from the first dose date/time to the date/time of symptom resolution.

- Proportion of participants with moderate relapse of COVID-19 symptoms by Day 29.

COVID-19 symptom relapse is defined as the first day of at least 2 consecutive diary entries (regardless of missing entries in between) where there is any symptom (regardless of severity) after achieving short symptom recovery, or if a participant is hospitalized for COVID-19 or dies after achieving short symptom recovery. Short symptom recovery is defined as the first day of at least 2 consecutive diary entries (regardless of missing entries in between) where all targeted symptoms are absent. If a hospitalization for COVID-19 or death event occurs prior to the short recovery day, this participant is considered as not having short symptom recovery for 28 days.

COVID-19 moderate symptom relapse is defined as having at least 1 symptom being moderate or severe OR at least 2 mild symptoms OR a hospitalization for COVID-19 or death, observed on a day during COVID-19 symptom relapse (first day of symptom relapse to Day 28).

- Proportion of participants with COVID-19–related MAVs or 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. The nature and cause of the visit should be identified.

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

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 trial execution. The date and duration (if there is 1 day difference between the start date and end date) of hospital admission, and primary reason for hospitalization (including if the hospitalization is related to COVID-19) will be recorded.

Other secondary efficacy endpoints include:

- Change from baseline in SARS-CoV-2 nasal swab viral load at Day 5
- Time to antigen negativity
    - Antigen negativity is defined as 2 consecutive negative SARS-CoV-2 rapid antigen test (regardless if there is missing data in between), or negative test at last available sample for participants who completed or discontinued from the study after at least 1 positive antigen test. Antigen negativity through Day 29 will be derived using rapid antigen test data included for analysis as defined in Table 3-5.
    - The time to antigen negativity is defined (in days) as the number of days to the first date of 2 consecutive dates achieving a negative result:

      First date of 2 consecutive dates achieving negative result – First dose date +1.

    Participants without a negative antigen test will be censored at the last non-missing antigen test date.
- Proportion of participants with viral antigen rebound through Day 29
    - Viral antigen rebound is defined as any positive SARS-CoV-2 rapid antigen test after antigen negativity
- Proportion of participants with relapse of COVID-19 symptoms by Day 29

6.2.1. Analysis of Secondary Endpoints

The FAPS will be the primary analysis set for secondary endpoints. The Virology Analysis Set will be the primary analysis set for SARS-CoV-2 endpoints. The Antigen Analysis Set will be the primary analysis for antigen related endpoints.

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

- Time to COVID-19 symptom resolution by Day 29.
- Proportion of participants with moderate relapse of COVID-19 symptoms by Day 29.
- The proportion of participants with COVID-19–related MAVs or all-cause death by Day 29.
- Proportion of participants with COVID-19–related hospitalization or all-cause death by Day 29.

The time to COVID-19 symptom resolution will be analyzed in a similar manner to the primary endpoint using the FAPS.

Proportion of participants with moderate relapse of COVID-19 symptoms by Day 29 will be estimated with 95% CIs including participants in the FAPS who have achieved short symptom recovery and compared between treatment groups using the Fisher's exact test.

The proportion of participants with MAVs or all-cause death by Day 29 in the FAPS will be summarized using Kaplan-Meier estimates and compared between treatment groups using the log-rank test. Similar analysis methods will be used for the proportion of participants with COVID-19–related hospitalization or all-cause death by Day 29.

Change from baseline in SARS-CoV-2 nasal swab viral load to each visit including Day 5 will be compared between treatment groups using a mixed-effects model repeated measures (MMRM) approach. The analysis will be repeated in subgroups based on baseline viral load (< 6 $\log_{10}$ copies/mL, ≥ 6 $\log_{10}$ copies/mL).

The Kaplan-Meier product limit method will be used to estimate and log-rank test will be used to compare treatment groups for the time to antigen negativity through Day 29. Count and percentage of participants with viral antigen rebound through Day 29 will be summarized among those who achieve antigen negativity by treatment group and compared between treatment groups using the Fisher's exact test.

Proportion of participants with relapse of COVID-19 symptoms will be estimated with 95% CIs and compared between treatment groups using the Fisher's exact test, including participants in the FAPS who have achieved short symptom recovery.

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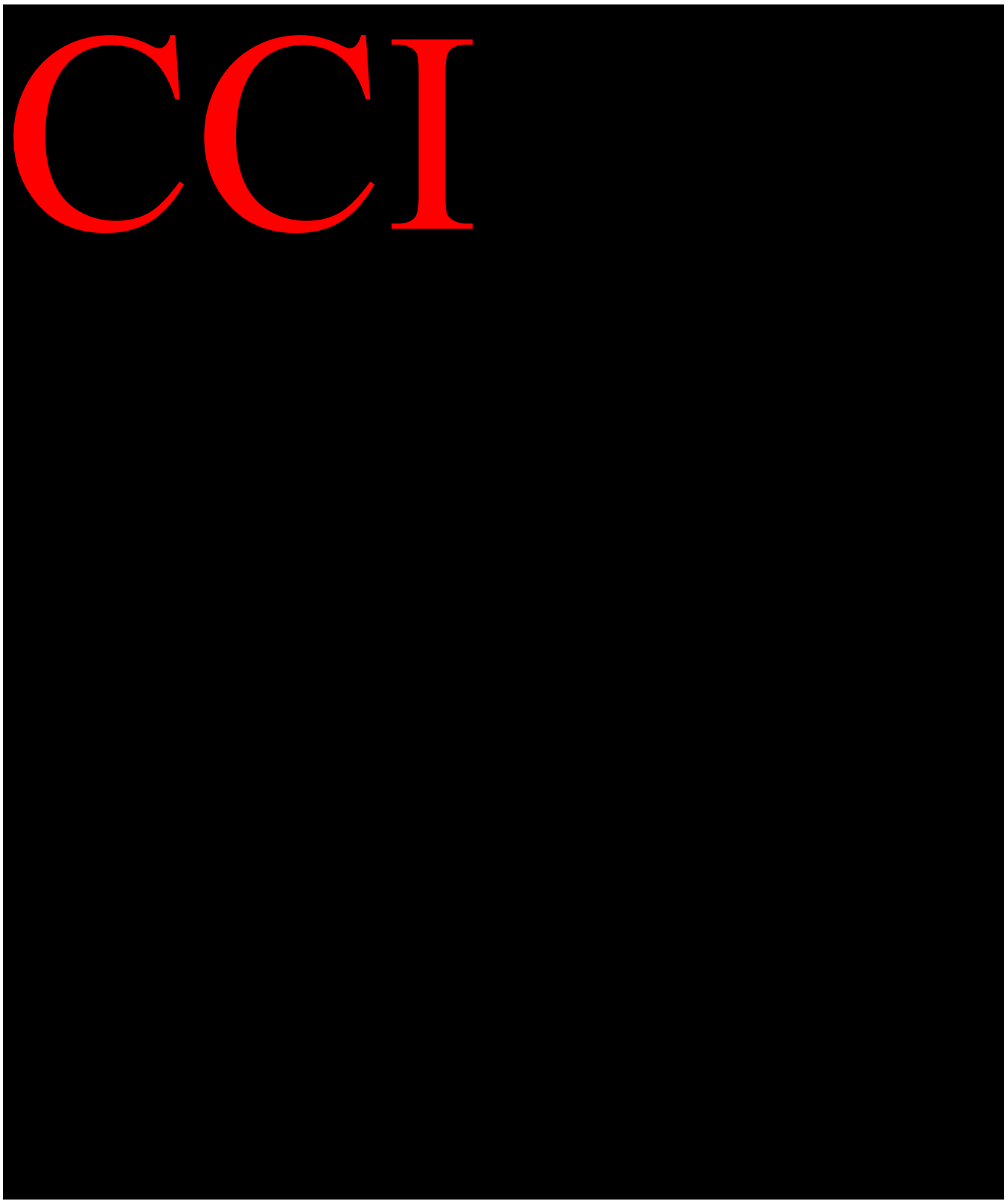
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6.4. Intercurrent Events

Handling of intercurrent events for the primary endpoint and secondary efficacy endpoints are shown in Table 6-1. Intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements of an endpoint. An event (eg. use of rescue medication) that occurs after an endpoint of interest (eg. symptom alleviation) is not considered as an intercurrent event.

Table 6-1. Handling of Intercurrent Events

Endpoint	Intercurrent event	Strategy	Description
Time to COVID-19 symptom alleviation by Day 29 Time to COVID-19 symptom resolution by Day 29	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/resolution (censored at Day 28)
	Discontinue randomized treatment prior to symptom alleviation/resolution (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/resolution (censor at Day 28)
Proportion of participants with moderate relapse of COVID-19 symptoms by Day 29 Proportion of participants with relapse of COVID-19 symptoms by Day 29	Hospitalization for the treatment of COVID-19 or all-cause death after short symptom recovery	Composite policy	Hospitalization for the treatment of COVID-19 or all-cause death means moderate relapse/relapse
	Discontinue randomized treatment after short symptom recovery (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 after short symptom recovery	Composite policy	Use of rescue medication means moderate relapse/relapse
Proportion of COVID-19–related hospitalization or all-cause death by Day 29 Proportion of participants with COVID-19-related MAVs or all-cause death 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)
	Use of rescue medication	Treatment policy	Ignore the occurrence of intercurrent events (use observed outcome)

Endpoint	Intercurrent event	Strategy	Description
Time to antigen negativity	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 antigen negativity (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 antigen negativity (censor at Day 28)
Proportion of participants with viral antigen rebound	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 antigen rebound (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 after antigen negativity	Composite policy	Use of rescue medication means antigen rebound

AE = adverse event; COVID-19 = coronavirus disease 2019

6.5. Changes From Protocol-Specified Efficacy Analyses

An interim analysis of futility and efficacy was planned in the protocol using the O'Brien-Fleming approach when 50% of planned participants completed the Day 29 assessment, or prematurely discontinued from the study. The assessment of stopping the study for efficacy was not conducted and the interim analysis assessed futility only.

Participants from Site 20189 with GCP noncompliance observations will be excluded from efficacy, safety, virology, and PK analyses.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and 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 left as "missing" for data listings.

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

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

7.1.5.1. Definition of Treatment-Emergent Adverse Events

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

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

7.1.5.2. Incomplete Dates

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

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

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

7.1.6. 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, High lever term (HLT), PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group:

- Grade 3 or higher treatment-emergent AEs
- 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

Treatment-emergent AE and treatment related TEAE will be summarized by system organ class, PT, Severity, and treatment group.

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

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

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

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

- All AEs
- Treatment-Related AEs
- AEs with severity of Grade 3 or higher
- SAEs
- Treatment-Related SAEs
- Deaths
- 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 each treatment group by PT for following subgroups defined in Section 3.4: Age, Baseline eGFR, Sex, Race, Region, and BMI.

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, or all available data at the time of the database snapshot. The analysis will be based on values reported in conventional units. When values are below or above the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7. SARS-CoV-2 viral load result of "Inconclusive" will not be included in numeric summary.

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.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for selected laboratory tests (Hemoglobin, Hematocrit, Absolute Neutrophil Count, Absolute Lymphocyte Count, Platelet Count, White Blood Cells, ALT, AST, Total bilirubin, Serum Creatinine, eGFR (Creatinine Clearance by Cockcroft-Gault for participants ≥ 18 years old; Bedside-Schwartz for participants ≥ 12 and < 18 years old), 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 for participants who have permanently discontinued study drug, or the last available date in the database snapshot for other participants. 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.

For the international normalized ratio (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:

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

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

Listings of liver-related laboratory tests will be provided.

7.3. Body Weight and Vital Signs

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

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

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, 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.

A summary of prior medications will not be provided.

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 medication 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 2) 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. 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 logics of concomitant medication 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 are 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 the SAP, any AEs leading to premature discontinuation of study drug are added in addition to the protocol definition of TEAEs. There are no other deviations from the protocol-specified safety analyses.

Participants from Site 20189 with GCP noncompliance observations will be excluded from efficacy, safety, virology, and PK analyses.

8. PHARMACOKINETIC (PK) ANALYSES

PK analyses will be included in the SAP for the final analysis of the study.

8.1. PK Sample Collection

Pharmacokinetic assessments will be conducted in all participants during an in-person visit.

Approximately 30 participants at participating sites will have intensive PK samples collected. For participants in the optional intensive PK substudy, sparse PK samples will not be collected on the days of intensive PK sampling.

- Sparse PK assessments
  - Day 1: 0.75 hours postdose and 2 hours postdose
  - Day 3: predose [within 1 hour before dosing] and 0.75 hours postdose
  - Day 5: predose [within 1 hour before dosing] and 0.75 hours postdose

    Note: ± 20% time window will be applied for all postdose time points. On Days 1, 3, and 5, 1 of the 2 doses must be administered during the in-person visit. If a visit occurs on Day 6, PK samples should not be collected.

- Intensive PK assessments

  Day 1 (first dose) and/or Day 5 visit (morning or evening dose) at 0.25, 0.5, 0.75, 1.5, 3, and 4 hours postdose; At Day 5 visit, an additional sample will be collected predose (within 1.0 hour before dosing).

  Note: ± 20% time window will be applied for all postdose time points. On Days 1 and 5, 1 of the 2 doses must be administered during the in-person visit. If a visit occurs on Day 6, PK samples should not be collected.

8.2. PK Analyses Related to Intensive PK Sampling

Pharmacokinetic parameters will be determined for participants in the PK Substudy Analysis Set. Concentrations of GS-441524 in plasma will be determined using validated bioanalytical assays.

8.2.1. Estimation of PK Parameters

Pharmacokinetic parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear up log down rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0. Pre-dose concentration values on Day 5 will also be used as 12-hours postdose values to allow for AUCtau estimation.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{tau}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.2.2. PK Parameters

Pharmacokinetic parameters will be generated for all subjects in the PK Substudy Analysis Set. The analytes and parameters presented in Table 8-1 will be used to evaluate the PK objectives of the study. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-1. Pharmacokinetic Parameters for Analyte

Analyte	Parameters
GS-441524	AUC_{tau}, C_{tau}, and C_{max}

Individual participant concentration data and individual participant PK parameters 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 both individual participant concentration data by time point and individual participant PK parameters by treatment. Moreover, the geometric mean, %CV for the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values will be presented for individual participant PK parameter data.

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.

Individual PK parameter data listings and summaries will include all participants for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of participants with nonmissing data for that PK parameter.

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

- Individual participant concentration data and summary statistics
- Individual participant plasma PK parameters and summary statistics
- Individual participant plasma PK parameters and summary statistics by baseline Creatinine clearance categories.

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.

Pharmacokinetic 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. Summary statistics (n, mean, SD, coefficient of variation [%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.

9. REFERENCES

HealthMeasures, National Institutes of Health (NIH). PROMIS Adult Profile Scoring Manual. Available at: https://www.healthmeasures.net/images/PROMIS/manuals/Scoring_Manuals_/PROMIS_Adult_Profile_Scoring_Manual.pdf. Accessed: 09 June 2023. Last Updated: 10 September. 2021:

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 (14 Nov 2023)		Original version	
Version 1.0 (11 Jan 2024)	6.5	Remove text of change in FAPS and Virology analysis set and remove reorder of key secondary endpoints.	The changes are included in protocol amendment 4
	1.3	The futility stopping boundary and study power were revised	To align with primary efficacy analysis set clarification
	3.8.3	Addition of selection of baseline for SARS-CoV-2 data	Align with selection of analysis record for postbaseline
	3.1.7, 3.1.8, 8	Addition of PK analysis sets and PK analyses for final analysis	Update to include analysis for the final analysis
	6.3	Addition of analyses for SARS-CoV-2 infectious viral titer and subgroup analysis by lineage for final analysis	Update to include analysis for the final analysis

12. APPENDICES

Appendix 1. SCHEDULE OF ASSESSMENTS

Study Visit	Screening[a, b]	Baseline Day 1[a]	Day 3	Day 5	Day 10	Day 15	Day 20	Day 29	Day 60	EOS Day 90	Early Discontinuation Visit
Visit Window			**± 1 day[c]**		**± 2 days**			**+ 5 days**	**± 7 days**		
Visit Type	**In Person[d]**							**In Person[e] or Virtual[f]**	**Virtual[f]**		**In Person[d]**
Written informed consent (and assent as applicable)	X										
CCI											
Medical history[h]	X										
Document SARS-CoV-2 infection	X										
Complete physical examination[i]	X	X		X							X
Symptom-directed physical examination			X			X					
Height and weight	X										
Vital signs[j]	X	X	X	X	X	X					X
COVID-19 Symptom Questionnaire[k]		X	X	X	X	X	X	X	X	X	X
WPAI + CIQ:COVID19		X			X			X	X	X	X
PROMIS-29		X						X	X	X	X
Household contacts[l]						X					
Chemistry, coagulation, and hematology panels[m]		X	X	X	X	X					X
Urine or serum pregnancy tests[n]	X	X				X					X
SARS-CoV-2 rapid antigen test[o]		X	X	X	X	X		X			X

Study Visit	Screening[a, b]	Baseline Day 1[a]	Day 3	Day 5	Day 10	Day 15	Day 20	Day 29	Day 60	EOS Day 90	Early Discontinuation Visit
Visit Window			**± 1 day[c]**		**± 2 days**			**+ 5 days**	**± 7 days**		
Visit Type	**In Person[d]**							**In Person[e] or Virtual[f]**	**Virtual[f]**		**In Person[d]**
Mid-turbinate nasal swab[p]		X	X	X	X	X	X	X			X
SARS-CoV-2 serology		X									
Sparse PK[q]		X	X	X							
CCI											
MAV information/oxygen supplementation requirement[s]		X	X	X	X	X	X	X	X	X	X
Study drug dispensation		X									
Study drug dosing (ODV or placebo)[t]		X	X	X							
Study drug bottle return[u]				X	X						X
Adverse events and concomitant medications	X	X	X	X	X	X	X	X	X	X	X

COVID-19 = coronavirus disease 2019; EOS = end of study; MAV = medically attended visit; PK = pharmacokinetic(s); PROMIS-29 = Patient-Reported Outcomes Measurement Information System-29; 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 24 hours of the Day 1 visit. The Day 1 visit may occur on the same day as screening. If screening and the Day 1 visit are the same day, do not repeat physical examination and vital signs.

b Local screening laboratory tests including serum creatinine, creatinine clearance/estimated glomerular filtration rate, alanine aminotransferase, and bilirubin assessments at screening (prior to randomization) are not required unless deemed necessary by the investigator to confirm eligibility. Testing for influenza is also not required at screening.

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

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

e Day 29 visit will be an in-person visit and require a nasal swab collection, only if any day after the Day 20 visit and prior to the Day 29 visit the participant has ≥ 1 moderate or severe symptom reported on the COVID-19 symptom questionnaire or has a positive rapid antigen test.

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

g Long COVID-19 sequelae will be assessed using linked data between clinical study participant and real-world data (RWD).

h Medical history will include the date of first COVID-19 symptoms, overall COVID-19 symptoms, all COVID-19 vaccinations prior to screening, prior COVID-19 illness (including positive test type, month, and year), demographics, baseline characteristics, allergies, and all other relevant medical history.

i A complete physical examination must include source documentation of general appearance and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; and neurological. Urogenital and reproductive examination should only be completed if clinically indicated.

j Vital signs include heart rate, respiratory rate, temperature, oxygen saturation, and blood pressure.

k The COVID-19 Symptom Questionnaire will be completed daily (at approximately the same time each day) from predose to Day 29 visit, then at Day 60 and Day 90 visits.

l The number of contacts in the household and how many tested positive for COVID-19 to be recorded.

m Baseline laboratory assessments should be collected prior to first study drug dose.

n 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 early discontinuation/unscheduled visits, these participants will have a serum pregnancy test via central laboratory. 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 11.4.

o Rapid antigen tests will be self-collected daily on all visit and non-visit days, up to Day 15, thereafter, on Days 17, 19, 21, 23, 25, 27, and 29.

p The samples will be used for SARS-CoV-2 reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR), potential infectious viral titer assessment, and potential resistance testing. Multiplex viral PCR will only be performed at Baseline/Day 1 visit.

q Sparse PK samples will be collected at Day 1 visit (0.75 hours postdose and 2 hours postdose), Day 3 visit (predose [within 1 hour before dosing] and 0.75 hours postdose), and Day 5 visit (predose [within 1 hour before dosing] and 0.75 hours postdose); ± 20% time window will be applied for all postdose time points. On Days 1, 3, and 5, one of the 2 doses must be administered during the in-person visit. If a visit occurs on Day 6, PK samples should not be collected.

r CCI [redacted]

s 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 EOS/Day 90 visit.

t Study drug dosing is twice daily for 5 days.

u Study drug bottle should be returned by the participant on Day 5, if the participant has already completed all doses of study drug. If the participant has study drug remaining by the conclusion of the Day 5 visit, the participant must return the study drug bottle on the Day 10 visit.

Appendix 2. PROGRAMMING SPECIFICATIONS

1) Symptom alleviation and time to symptom alleviation, COVID-19 symptom questionnaire is shown in Appendix 3.

   1. Targeted symptoms are those listed below, only targeted symptoms will be evaluated in deriving of the primary endpoint.

      - Stuffy or runny nose
      - Sore throat
      - Shortness of breath (difficulty breathing)
      - Cough
      - Low energy or tiredness
      - Muscle or body aches
      - Headache
      - Chills or shivering
      - Feeling hot or feverish

   2. Alleviation of all targeted symptoms:

      ■ Symptom scored as Moderate or Severe at baseline is scored as None or Mild at postbaseline

      ■ Symptom scored as Mild at baseline is scored as None at postbaseline

      ■ Symptom scored as None or missing at baseline is scored as None 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 and defined as all targeted symptoms scored moderate or severe at baseline are scored as mild or none and all targeted symptoms scored mild or none at baseline are scored as none, i.e. without 48 consecutive hours confirmation. Participants with missing baseline symptoms data, all targeted symptoms need to be scored as none 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 28.

Examples of counting additional 24 consecutive hours:

Example		Study Day 1	2	3	4	5	6	7	8	9	...	Day and time of symptom alleviation	
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	
5	Time		18:00	9:00	.	9:00	10:00	10:00					no missing 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
	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's all symptoms are None at baseline, alleviation status will not be derived and the participant is excluded from the analysis.

If a participant's baseline symptoms are Mild or higher and symptoms from Day 2 and later are all missing, the participant is considered as censored at 23:59 on Day 1.

If a participant has no COVID-19 symptom questionnaire data reported from Day 1 to Day 29, the participant is excluded from the analysis.

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 29, 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 29 of the study without symptom alleviation, time to symptom alleviation will be censored at Day 28

Date and Time of Day 28 COVID-19 questionnaire assessment - Date and time of first dose

Use Day 28 23:59 if no Day 28 COVID-19 questionnaire assessment

- For participants who discontinue from the study before Day 29 without symptom alleviation, time to symptom alleviation will be censored at last COVID-19 questionnaire assessment

  Date and Time of last COVID-19 questionnaire assessment - Date and time of first dose.

- For participants with missing time of first dose, missing time is imputed using time of COVID-19 questionnaire assessment on the first dose date or 12:00 whichever occurs first

5. 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 #20)

  Date and Time of Day 28 COVID-19 questionnaire assessment - Date and time of first dose.

  Use Day 28 23:59 if no Day 28 COVID-19 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 participants with COVID-19 symptom alleviation Proportion of participants with COVID-19 symptom resolution Proportion of participants with COVID-19 related MAVs or all-cause death by Day 29 Proportion of participants with COVID-19 related hospitalization or 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 moderate relapse of COVID-19 symptoms by Day 29	Participants in the FAPS who have achieved short symptom recovery by Day 29	Number of participants with moderate relapse of COVID-19 symptoms by Day 29
Proportion of participants with relapse of COVID-19 symptoms by Day 29	Participants in the FAPS who have achieved short symptom recovery by Day 28	Number of participants with relapse of COVID-19 symptoms by Day 29
Proportion of participants with symptoms at Days 60 and 90	Participants in the FAPS who completed Days 60 or 90 COVID-19 questionnaire	Number of participants with any symptoms at Days 60 or 90

Endpoint/Summary	Population /Denominator	Numerator
Proportion of participants with viral antigen rebound	Participants in the Antigen Analysis set who had antigen negativity at any postbaseline visit through Day 28	Number of participants with viral antigen rebound (antigen test positive after antigen negativity)
Proportion of participants with negative SARS-CoV-2 nasal swab viral load at Days 3, 5, 10, 15, 20, and 29	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, 15, 20, and 29	Participants in the Virology analysis set who had 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) Use of rescue medication for relapse of COVID-19 symptoms and moderate relapse of COVID-19 symptoms by Day 29

In addition to hospitalization or death, use of rescue medication is considered as an intercurrent event and handled as follows for symptom relapse:

If a participant takes rescue medication prior to the short recovery day, this participant is considered as not having short symptom recovery for 28 days.

If a participant takes rescue medication after achieving short symptom recovery, this participant is considered to have symptom relapse and moderate symptom relapse on the day of taking rescue medication.

5) Definition of Hospitalization

MAV 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.

6) 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.

Appendix 3. PATIENT REPORTED OUTCOMES

COVID-19 Symptom Questionnaire

1.What was the severity of your **stuffy or runny nose** at its worst over the last **24 hours**? • None • Mild • Moderate • Severe
2.What was the severity of your **sore throat** at its worst over the last **24 hours**? • None • Mild • Moderate • Severe
3.What was the severity of your s**hortness of breath (difficulty breathing)** at its worst over the last **24 hours**? • None • Mild • Moderate • Severe
4.What was the severity of your **cough** at its worst over the last **24 hours?** • None • Mild • Moderate • Severe
5.What was the severity of your **low energy or tiredness** at its worst over the last **24 hours**? • None • Mild • Moderate • Severe
6.What was the severity of your **muscle or body aches** at its worst over the last **24 hours**? • None • Mild • Moderate • Severe
7.What was the severity of your **headache** at its worst over the last **24 hours?**

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COVID-19 Symptom Questionnaire

• None • Mild • Moderate • Severe
8.What was the severity of your **chills or shivering** at its worst over the last **24 hours**? • None • Mild • Moderate • Severe
9. What was the severity of your **feeling hot or feverish** at its worst over the last **24 hours**? • None • Mild • Moderate • Severe
10. What was the severity of your **nausea (feeling like you wanted to throw up)** at its worst over the last **24 hours**? • None • Mild • Moderate • Severe
11. How many times did you **vomit (throw up)** in the last **24 hours**? • I did not vomit at all • 1–2 times • 3–4 times • 5 or more times
12. How many times did you have **diarrhea (loose or watery stools)** in the last **24 hours**? • I did not have diarrhea at all • 1–2 times • 3–4 times • 5 or more times
13. Rate your sense of **smell** in the last **24 hours.** • My sense of smell is THE SAME AS usual • My sense of smell is LESS THAN usual • I have NO sense of smell

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COVID-19 Symptom Questionnaire

14. Rate your sense of **taste** in the last **24 hours.** • My sense of taste is THE SAME AS usual • My sense of taste is LESS THAN usual • I have NO sense of taste

Work Productivity and Activity Impairment Questionnaire
plus Classroom Impairment Questions:
COVID-19 Infection Specific V2.0 (WPAI+CIQ:COVID19 Infection)

The following questions ask about the effect of your COVID-19 Infection on your ability to work, attend classes, and perform regular daily activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO _____ YES

If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your COVID-19 Infection? *Include hours you missed on sick days, times you went in late, left early, etc., because of your COVID-19 Infection. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____ HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your COVID-19 Infection affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your COVID-19 Infection affected your work only a little, choose a low number. Choose a high number if your COVID-19 Infection affected your work a great deal.

Consider only how much your COVID-19 Infection affected productivity while you were working.

My COVID-19 Infection had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	My COVID-19 Infection completely prevented me from working

6. Do you currently attend classes in an academic setting (middle school, high school, college, graduate school, additional course work, etc.)? _____ NO _____ YES

   If NO, check "NO" and skip to question 10.

7. During the past seven days, how many hours did you miss from class or school because of problems associated with your COVID-19 Infection? *Do not include time you missed to participate in this study.*

   _____ HOURS

8. During the past seven days, how many hours did you actually attend class or school?

   _____ HOURS *(If "0", skip to question 10.)*

9. During the past seven days, how much did your COVID-19 Infection affect your productivity while in school or attending classes in an academic setting?

   Think about days your attention span was limited, you had trouble with comprehension or days in which you could not take tests as effectively as usual. If your COVID-19 Infection affected your productivity at school or in class only a little, choose a low number. Choose a high number if your COVID-19 Infection affected your productivity at school or in class a great deal.

   Consider only how much your COVID-19 Infection affected productivity while in school or attending classes.

My COVID-19 Infection had no effect on my class work	0	1	2	3	4	5	6	7	8	9	10	My COVID-19 Infection completely prevented me from doing my class work

10. During the past seven days, how much did your COVID-19 Infection affect your ability to do your regular daily activities, other than work at a job or attending classes?

    By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your COVID-19 infection affected your activities only a little, choose a low number. Choose a high number if your COVID-19 Infection affected your activities a great deal.

    Consider only how much your COVID-19 Infection affected your ability to do your regular daily activities, other than work at a job or attending classes.

My COVID-19 Infection had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	My COVID-19 Infection completely prevented me from doing my daily activities

Adapted from: Reilly MC, Tanner A, Meltzer EO: Work, classroom and activity impairment instruments: validation studies in allergic rhinitis. Clin Drug Invest 1996; 11(5):278-288.

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Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41	How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Pain Intensity **In the past 7 days…**											
Global07	How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	12-Jan-2024 15:40:32
PPD	Global Development Lead (GDL) eSigned	13-Jan-2024 02:39:17