Shionogi

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A Phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of S-217622 in the prevention of symptomatic SARS-CoV-2 infection in household contacts of an individual with symptomatic COVID-19

16OCT2024
Statistical Analysis Plan

Version 3.0

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	Alanine Aminotransferase
ANCOVA	analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
CLC	central laboratory-confirmed
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease of 2019
CSR	clinical study report
CV	coefficient of variation
DSMB	Data Safety Monitoring Board
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Quality of Life Assessment
FAS	full analysis set
GEE	generalized estimating equations
GIQ	Global Impression Questionnaire
HEENT	head, ears, eyes, nose, throat
ICF	informed consent form
ICH	International Conference on Harmonisation
iid	Independent and Identically Distributed
INR	international normalized ratio
ITT	intent-to-treat
ITTBP	Intent-to-treat baseline positive
IWRS	interactive web response system
LAR	legally authorized representative
LLOD	Lower limit of detection
LLOQ	lower limit of quantitation
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mTSS	modified total symptoms score
NP	nasopharyngeal
NSP5	nonstructural protein 5
PP	per protocol
PT	preferred term
PVG	pharmacovigilance
QOL	quality of life
RMST	restricted mean survival time
RT-PCR	reverse transcriptase – polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

SOB	shortness of breath or difficulty breathing
SOC	System Organ Class
SD	standard deviation
TEAE	treatment-emergent adverse event
TSS	total symptoms score
TSSR	time to sustained symptoms resolution
ULN	upper limit of normal
VAS	Visual Analog Scale
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

STATISTICAL ANALYSIS PLAN REVISION HISTORY

Version	Date	Summary of Changes
Version 1.0	31OCT2023	Original version
Version 1.1	01OCT2023	Formatting changes required for FDA submission
Version 2.0	29FEB2024	Added clarification about symptoms diary baseline being Day 1 AM unless missing (section 4) Removed details about imputation of dates, made unnecessary due to data collection restrictions (section 4) Defined ITT baseline negative analysis population (section 4.3.5) Correction to surgical procedure history analysis description (not only on-study procedures; section 7) Clarification: accumulated dose reported for S-217622 arm only in exposure summary (7.2.1) Added condition to primary endpoint: symptoms onset and CLC positive RT-PCR test must occur within 10 days of one another to qualify as endpoint met (section 8.1) Described sensitivity analysis 3 (primary efficacy using interpolation/baseline-carried-forward algorithm for imputing missing symptoms; section 8.1.3.4) Section 8.2: For AUC methods, re-wrote sentence for clarity regarding selection of a single record if multiples are present at a timepoint, and specified that largest rather than the average of available measures would be used in AUC analysis. Section 8.2.1: Clarification that intercurrent events apply to this endpoint and will be handled as they are in the primary endpoint analysis Section 8.2.3: Clarified for endpoint of proportion of participants with CLC positive RT-PCR tests at each timepoint, that timepoints will include tests taken within protocol defined windows of scheduled visits. Section 8.2.4: Clarified that only date of RNA assessment and not time will be used in analysis of viral RNA AUC.

Version	Date	Summary of Changes
		Section 8.2.5 – 6: Stated that intercurrent events will be considered as part of these endpoints, as applicable (see details) Section 8.2.8: Added caveat that individual symptom onset must occur prior to Day 10 in order to align with the denominator of primary endpoint for previous section. Section 8.3.1: Per database modification #2, updated method of determination for SARS-CoV-2 relatedness of hospitalizations. Added requirement that only participants actually treated with S-217622 will provide data for EC_{50} analysis (section 8.3.2) Section 8.3.7: Updated language to align with objective as stated in protocol v4; identified index patients as a separate treatment group for display. Corrected omission of index patients from the analysis population. Clarified time window (through end of Day 28 window) for NSP5 sequence analysis exploratory objective (section 8.3.8) Added exploratory objective for viral/COVID-19 symptom rebound (section 8.3.12) Correction to SoA of staff-collected temperature for vital signs section 9.3 Removed notes in changes to planned analysis (section 13) about 15 vs. 28 day RMST discrepancy (it was corrected in protocol v4) and about choice of Study Day 10 vs. Day 10 visit window for primary endpoint
Version 2.1	19JUN2024	Baseline diary: Derivation now uses “Predose” records and missing baseline symptom(s) are imputed as 0. See Section 3.2.1 for details. (Sections 3.2.1 and 4) Analysis visits: Derivations were updated to incorporate protocol-defined visit windows. Additional rules for record selection when participants have more than one record within an analysis visit. (Section 4) Quantitative PCR results will be estimated as: • 0 log 10 copies/mL when Negative (LLOD) and

Version	Date	Summary of Changes
		• 2.27 - log10(2) when Positive (LLOQ <2.08). (Section 4) Analysis sets: • Index patient analysis set now excludes subjects with entrance criteria deviations. (Section 4.3.9) • mITT requires participants' associated index participant to not have inclusion/exclusion violations. (Section 4.3.4) • Household member survey analysis set accounts for household with multiple respondents. (Section 4.3.10) Missing data: Per the protocol, missing data will not be imputed. This SAP introduces caveats to the rule in Section 8.1 to allow for: • Implementation of the intercurrent events strategy in the case of hospitalizations and all-cause death related to SARS-CoV-2. (Section 8.1) • Sensitivity Analysis 3 now has additional detail regarding imputation of missing diary data. (Section 8.1.3.4) • Prior and concomitant medications now use imputation in order to categorize medications into the respective categories. (Section 4) • Subjects missing baseline diary data have baseline symptom(s) imputed as 0. (Section 4) Section 9.3.2.2 of the protocol states that the log-rank test in the Kaplan-Meier analyses used for secondary objectives will be stratified by geographic region. However, section 8.2 of this SAP has clarified that Kaplan-Meier analyses will be stratified by the time from index patient symptoms randomization factor, but pooled across geographic region to reduce the number of analytical strata. It is noted that analyses will be repeated within the Japan and North America geographic regions to allow for reporting within those particular strata. (Section 8.2) AUC will now be normalized for Day 10 in order to account for the protocol defined visit window. (Section 8.2.4)
Version 2.2	24JUL2024	Added clarification to 3.1 that randomization and treatment start date are the same date, to adhere to ITT trial principles. Section 4: Update to baseline diary entry definition; also, a general windowing algorithm now specifies (+) PCR tests and 'Yes' GIQ responses in step 2

Version	Date	Summary of Changes
		Section 4.3.1: Added note about universal exclusions due to certain protocol deviations Section 4.3.4: Added mITT population requirement that participants receive at least one dose of study treatment Section 4.3.5: Defined ITT baseline-positive analysis set as a pre-defined population for supplemental analysis. Removed ITT baseline negative analysis set as a pre-defined population; references now point to ITT analysis population instead Section 5.1: Screened patients removed from summary Section 5.2: Specified reporting on index patient deviations Section 7.2.2: Updated definition of study drug compliance Section 8.1.3.1: Previously unincorporated protocol v4 updates: Reporting through a Day 21 cutoff as a supplemental analysis, and removed the 'any symptoms' reporting. Moved sentence about imputed/assumed diary times from section 8.2 to where it was more appropriate. Added description of supplemental analyses of Day 10/15/21/28 endpoint in ITT baseline positive analysis set. Sections 8.2, 8.2.2, 8.2.12, and 8.2.13: For Kaplan-Meier analyses, deleted a general sentence in 8.2 describing event and censoring times, and added outcome-specific information in the descriptions of the corresponding secondary objective analysis. Section 8.2.6: Description of LOCF for symptoms on Day 10 if Day 10 diary entries are missing Section 8.2.7: participants only having onset from loss of taste and smell do not count toward the resolution objective; clarified subsequent resolutions will not be considered Section 8.3.5: Renamed section header to match analysis and added text for additional exploratory objective investigating the relationship between quantity of index patient viral RNA on Day 1 and incidence of primary endpoint in participants

Version	Date	Summary of Changes
		Section 8.3.9: Clarification of handling corresponding to analysis of one assessment per subject per timepoint after onset Section 9.1.1: Removed analysis of solicited AEs to align with protocol v5 and specified that Time to Sustained Symptoms Resolution will be presented as part of the safety analysis. Section 13: Noted the additional requirement of one dose of a study treatment for inclusion in the mITT analysis set. Described addition of ITT baseline positive analysis set to populations described in the protocol.
Version 2.3	30JUL2024	Table 1: Removed restriction on key secondary endpoint that participants needed a negative baseline SARS-CoV-2 test by local lab Removed requirement that participants have a negative baseline SARS-CoV-2 test by local lab for all efficacy analyses in the ITT analysis set Section 4: Removed notes on calculation of duration of symptoms that are no longer relevant. Also, a clarification that a PCR test value above the LoD but below the LLoQ is considered as a positive result for windowing Section 4.3: Noted subjects may be removed from analysis sets for GCP deviations. Section 4.3.5: added definition of baseline screening to ITT baseline positive set Section 7.1: Clarified that highest ATC level will be used if ATC level 4 is missing Section 8: Clarified that intercurrent events are counted as a primary endpoint occurrence and not just symptoms onset Section 8.1.3.1: Added new supplemental analyses of the primary endpoint without consideration of intercurrent events through Days 10, 15, 21, and 28. Reorganized the content in the supplemental analysis section for brevity

Version	Date	Summary of Changes
		Section 8.2.1: Specified an additional by-geography analysis of CLC-positive RT-PCR tests through Days 10, 15, 21, and 28 Sections 8.2.7-8.2.9: Clarification about handling of intercurrent events Sections 8.3.7 and 8.3.8: Removed analysis plans after the description of the objective, as gene sequence analysis will now be performed by the sponsor Section 8.3.11: Removed unconfirmed details for influenza coinfection exploratory analysis; noted that this analysis will occur after primary and secondary analyses have all been completed Section 8.3.12: Viral RNA rebound requires a minimum of 3.27 log10 copies/mL Section 8.3.12: Analysis populations updated for viral RNA and symptoms rebound endpoints
Version 3.0	16OCT2024	Sections 3.2.1, 3.2.2, 4: Specified that assessment time timestamp value will be used for symptoms diary data Section 4.2 and elsewhere throughout the document: Geographic regions will be pooled for inferential analyses unless otherwise stated Section 4.3: Handling of exclusions at sites with GCP violations Section 4.3.4: Updated mITT population inclusion criterion for COVID-19 positive index patient Section 4.3.6: Per protocol analysis population will be analysis by actual treatment groups Section 7: Removed description of prohibited medications display in data listing Section 8.1.3.1: Updated to describe newly added supplemental analyses, adjusting the symptoms onset threshold to <=24 hours, with and without intercurrent events, through Days 10, 15, 21, and 28

Version	Date	Summary of Changes
		Section 8.1.4: Clarification of covariates included in GEE model Section 8.1.5: Handling of participants with no expected entries Section 8.2.1: Corrected inadvertent omission noting the geography randomization strata will not be included as a GEE model covariate for the analysis within geographic subgroup. Section 8.3.6: Specified three-level pooled geographic region variable will be used as covariate for consistency with other models Section 8.3.11: Analysis of influenza coinfection endpoint now performed by the sponsor Section 13: Per-protocol analysis using actual (rather than planned) treatments, handling of actual treatment assignment in safety analysis for subjects exposed to multiple IP kits, and use of the 3-level pooled geographic region variable as a model covariate, and GEE model covariates in the subgroup analysis are noted as changes from the planned analysis

1. INTRODUCTION

This document is the Statistical Analysis Plan (SAP), which describes the statistical methods that will be used to assess data collected in the SHIONOGI clinical trial protocol 2206T1331 ("A Phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of S-217622 in the prevention of symptomatic SARS-CoV-2 infection in household contacts of an individual with symptomatic COVID-19"; hereafter, referred to as "the protocol"). This SAP provides detail for all prespecified analyses included in protocol version 5, amendment 4, dated08 Jul 2024.

During the current SARS-CoV-2 outbreak, the number of confirmed cases has rapidly increased and, as of February 2023, there have been > 755 million confirmed cases and more than 6 million deaths attributed to COVID-19 globally, per the World Health Organization (WHO; see REFERENCES). Global efforts to evaluate novel antivirals and therapeutic interventions to treat COVID-19 have intensified. Therefore, there is an urgent public health need for rapid development of novel interventions.

S-217622 is being developed by SHIONOGI as a therapeutic agent to treat patients with SARS-CoV-2 infection, as well as household members who are at increased risk of infection due to exposure. S-217622 is an inhibitor of SARS-CoV-2 3CL protease, which cleaves the virus pp1a and pp1ab polyproteins at multiple junctions to generate a series of proteins critical for virus

replication and transcription, including RNA-dependent RNA polymerase, the helicase, and the 3CL protease itself. No close human analogs of the SARS-CoV-2 3CL proteases are known. The essential functional importance in virus replication cycle, together with the absence of closely related homologs in humans, make the 3CL protease an attractive antiviral drug target.

The current study is being conducted to evaluate the efficacy and safety of orally administered S-217622 in the prevention of symptomatic SARS-CoV-2 infection in household contacts of an individual with symptomatic COVID-19. It is a randomized, double-blind, multicenter, parallel-group, placebo-controlled comparative study in approximately 2200 study participants for 92 events. The total number of participants enrolled may be adjusted to achieve this number of events based on actual event rate. Participants are household contacts of another individual with symptomatic COVID-19 (referred to as the "index patient"), who are randomized in a 1:1 ratio to receive S-217622 or placebo.

The final analysis described in this SAP will be performed by the Biostatistics and Programming team at [redacted]. All analyses will be performed using the statistical software SAS version 9.4 or higher. International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use E3 and E9 Guidelines will be followed where applicable.

2. OBJECTIVES

2.1. Primary objective

The primary objective of this study is to compare S-217622 with placebo in the prevention of symptomatic SARS-CoV-2 infection through Day 10 in modified Intention-To-Treat population study participants (negative for confirmed infection at screening) who are household members of SARS-CoV-2-infected index patients. Hereafter in this SAP, confirmed SARS-CoV-2 infection is defined as a central laboratory-confirmed (CLC) positive Reverse-Transcriptase – Polymerase Chain Reaction (RT-PCR) test, unless otherwise stated. When present with COVID-19 symptoms onset, CLC positive RT-PCR tests collected on or before a participant's Day 10 visit (visit 4 in the schedule of assessments, shown in 15.1) will be considered as meeting the primary endpoint. Symptoms and onset of symptomatic COVID-19 are defined further in section 3.2.1.

2.2. Key secondary objective

The key secondary objective of this study is to compare S-217622 with placebo in the prevention of symptomatic SARS-CoV-2 infection through Day 10 in Intention-to-Treat population study participants who are household members of SARS-CoV-2-infected index patients, using the same definitions for SARS-CoV-2 infection and symptoms as the Primary Objective.

2.3. Secondary objectives

- To compare S-217622 with placebo in the prevention of SARS-CoV-2 infection in participants, defined as a CLC positive RT-PCR test.
- To compare S-217622 with placebo to determine if S-217622 reduces levels of SARS-CoV-2 in nasopharyngeal (NP) swabs in participants who test positive for SARS-CoV-2 through Day 10

- To compare S-217622 with placebo to evaluate how S-217622 affects COVID-19 symptoms resolution and improvement through Day 28 in participants who test positive (CLC positive RT-PCR) for SARS-CoV-2 through Day 10
- To compare S-217622 with placebo in reducing the number of hospitalizations and death in participants who test positive for SARS-CoV-2 infection (CLC positive RT-PCR test) during the study
- To confirm the pharmacokinetics of S-217622 in participants following multiple doses of S-217622 for 5 days
- To compare S-217622 with placebo and the effect on safety and tolerability in participants

2.4. Exploratory objectives

- To compare S-217622 with placebo in reducing the number of days of hospital and intensive care unit stay in participants who test positive for SARS-CoV-2 infection during the study
- To explore the association between the index patient's amount of viral RNA and the participant's CLC positive RT-PCR test
- To investigate the relation between the index patient's amount of SARS-CoV-2 viral RNA and the events of SARS-CoV-2 infection in household contacts
- To identify SARS-CoV-2 variants in NP swabs for participants who test positive for SARS-CoV-2 and for index patients corresponding to test-positive participants through Day 28
- To investigate treatment-emergent amino acid substitutions in protease Non-Structural Protein 5 (NSP5) and its cleavage site using NP swabs of participants who test positive for SARS-CoV-2 through Day 28
- To evaluate antiviral activity of S-217622 against SARS-CoV-2 clinical isolates derived from NP swabs of participants who have confirmed treatment-emergent amino acid substitutions in protease (NSP5) and its cleavage site through Day 28
- To compare S-217622 with placebo on the effect on Quality of Life (QOL) in participants
- To compare S-217622 with placebo on the effect on Global Impression Questionnaire (GIQ) in participants who test positive for SARS-CoV-2 infection during the study
- To investigate coinfection with influenza and SARS-CoV-2 using NP swabs of participants who test positive for SARS-CoV-2 through Day 28
- To investigate SARS-CoV-2 RNA and/or COVID-19 symptom rebound during the study

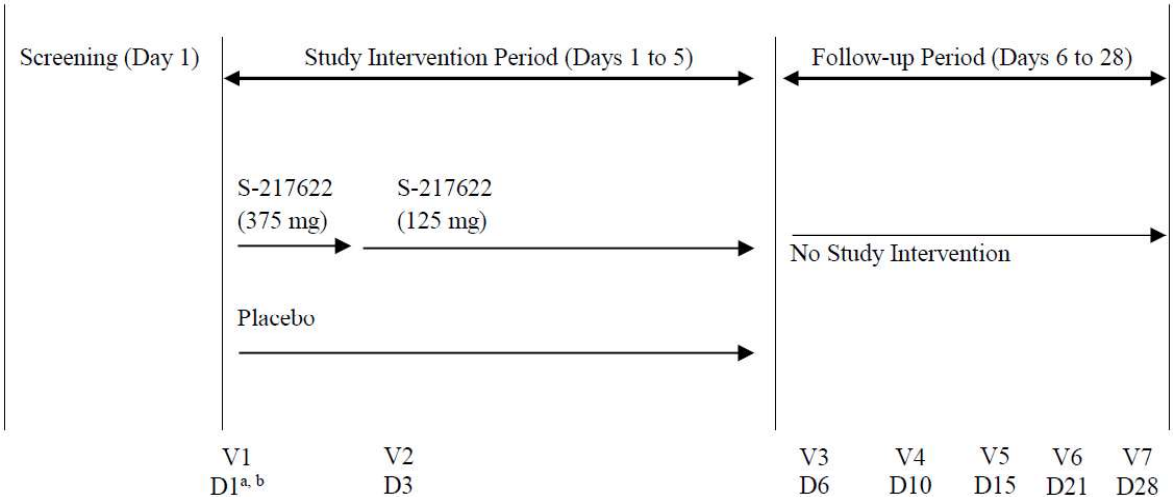
3. INVESTIGATIONAL PLAN

3.1. Overall study design and plan

This is a randomized, double-blind, multicenter, parallel-group, placebo-controlled comparative study in approximately 2200 participants (depending on the event rate) who are household members of symptomatic SARS-CoV-2-infected index patients. Participants are randomly assigned in a 1:1 ratio to receive study intervention (S-217622 or matching placebo). Participants will receive the study intervention from Days 1 to 5 in the form of three 125-mg tablets on Day 1, followed by one 125mg tablet daily on Days 2 to 5. Thereafter, participants will be followed for an additional 23 days (from Days 6 to 28) without additional study intervention. A final study

assessment is scheduled on Day 28. See the schematic in Figure 1 below and the schedule of assessments in Section 15.1 for more detail.

Figure 1. Study schematic



For the index patient, Visit 1, Day 1 will not necessarily be the same day as Visit 1, Day 1 for the participant(s). However, each participant must provide informed consent within 72 hours from onset of COVID-19 symptoms (see section 3.2.1) in the index patient, and ≤1 calendar day from the time the index patient provides consent. If a participant qualifies for the study, the study intervention will be administered immediately after randomization. For all particpants, the initiation of treatment is expected to occur on the same day they are randomized (Day 1 of the study).

3.2. Study endpoints

The study's primary, secondary, and exploratory objectives and their associated endpoints are displayed in Table 1. Further detail and definitions on terms used in the table are found in sections 3.2.1 to 3.2.4.

Table 1. Objectives and endpoints

Objective	Endpoint(s)
Primary	
To compare S-217622 with placebo in the prevention of symptomatic SARS-CoV-2 infection in participants with a negative screening SARS-CoV-2 infection who are household members of SARS-CoV-2-infected patients through Day 10 (using the mITT population)	Proportion of participants in the mITT population with a negative screening SARS-CoV-2 infection[1] who are infected with SARS-CoV-2[1] and have COVID-19 symptoms onset through Day 10
Key Secondary	
To compare S-217622 with placebo in the prevention of symptomatic SARS-CoV-2	Proportion of participants in the ITT population who are infected with SARS-

Objective	Endpoint(s)
infection in participants with a negative screening SARS-CoV-2 infection who are household members of SARS-CoV-2-infected index patients through Day 10 (using the ITT population)	CoV-2[1] and have symptoms onset through Day 10
Secondary	
To compare S-217622 with placebo in the prevention of SARS-CoV-2 infection in participants[1]	Proportion of participants who are infected with SARS-CoV-2[1] through Days 10, 15, 21, and 28 regardless of occurrence of COVID-19 symptoms
To compare S-217622 with placebo to determine if S-217622 reduces levels of SARS-CoV-2 in NP swabs in participants who test positive for SARS-CoV-2 through Day 10	SARS-CoV-2 viral RNA endpoints : • Time to the first CLC positive RT-PCR result • Proportion of participants with CLC positive RT-PCR result at each timepoint • Area under the curve (AUC) of change in amount of SARS-CoV-2 viral RNA
To compare S-217622 with placebo to evaluate how S-217622 affects COVID-19 symptoms resolution and improvement through Day 28 in participants who test positive[1]for SARS-CoV-2 through Day 10	•Proportion of participants who are infected with SARS-CoV-2[1]and have no COVID-19 symptoms onset through Day 10 • Proportion of participants who are infected with SARS-CoV-2[1] have no COVID-19 symptoms through Day 10 • Proportion of participants with sustained resolution of all COVID-19 symptoms through Day 28 • Proportion of participants with sustained resolution of the 5 key COVID-19 symptoms (nasal congestion or runny nose, sore throat, cough, fever, and fatigue) through Day 28 • Proportion of participants with sustained resolution of each COVID-19 symptom through Day 28 • Change in total score of COVID-19 symptoms at each timepoint

Objective	Endpoint(s)
	• Change in total score of the 5 key COVID-19 symptoms at each timepoint • Time from first confirmed SARS-CoV-2[1] until at least 1 COVID-19 symptom through Day 28 • Time from first confirmed SARS-CoV-2[1]until COVID-19 symptoms onset through Day 28 • AUC of the daily total symptom score associated with COVID-19 over time from the COVID symptoms onset through Day 28 • AUC of the daily total symptom score for the 5 key COVID-19 symptoms over time from onset of the 5 key COVID-19 symptoms through Day 28
To compare S-217622 with placebo in reducing the number of hospitalizations and death in participants who test positive for SARS-CoV-2 infection during the study	Proportion of participants with hospitalization or death from any cause through Day 28
To confirm the pharmacokinetics of S-217622 in participants following multiple doses of S-217622 for 5 days	Plasma concentration of S-217622 at Visits 2, 3, and Event-driven Visit
To compare S-217622 with placebo and the effect on safety and tolerability in participants	Number and proportion of participants with Treatment-Emergent Adverse Events (TEAEs), deaths, other serious TEAEs, and TEAEs leading to discontinuation of study intervention
Exploratory	
To compare S-217622 with placebo in reducing the number of days of hospital and intensive care unit stay in participants who test positive for SARS-CoV-2 infection during the study	Number of days of hospital and intensive care unit stay in participants with SARS-CoV-2-related hospitalization through Day 28 as reported by the sites
To explore the association between index patient's viral RNA and the participant's CLC positive RT-PCR test	Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the CLC positive RT-PCR reported cases in the household

Objective	Endpoint(s)
To investigate the relation between the index patient's amount of SARS-CoV-2 infection in household contacts	Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the incidence of SARS-CoV-2 cases within their household contacts
To identify SARS-CoV-2 variants in NP swabs for participants who test positive for SARS-CoV-2 and for index patients corresponding to test-positive participants through Day 28	SARS-CoV-2 variant based on NP swab spike gene sequence
To investigate treatment-emergent amino acid substitutions in protease (NSP5) and its cleavage site using NP swabs of participants who test positive for SARS-CoV-2 through Day 28	Treatment-emergent amino acid substitutions based on NP swab NSP5 and its cleavage site gene sequence
To evaluate antiviral activity of S-217622 against SARS-CoV-2 clinical isolates derived from NP swabs of participants who have confirmed treatment-emergent amino acid substitutions in protease (NSP5) and its cleavage site through Day 28	Phenotypic assay (EC_{50}[2]) of S-217622 against SARS-CoV-2 clinical isolates derived from the NP swabs that have confirmed treatment-emergent amino acid substitutions in protease (NSP5) and its cleavage site
To compare S-217622 with placebo on the effect on QOL in participants	• Change from baseline in QOL as measured by the EuroQol 5 Dimensions 5 Levels Quality of Life (EQ-5D-5L) instrument • Proportion of participants who achieve baseline or better health through Day 28
To compare S-217622 with placebo on the effect on Global Impression Questionnaire in participants who test positive for SARS-CoV-2 infection[1] during the study	• Change from baseline in Global Impression Questionnaire • Proportion of participants who achieve baseline or better health through Day 28 in Global Impression Questionnaire
To investigate coinfection with influenza and SARS-CoV-2[1] using NP swabs of participants who test positive for SARS-CoV-2 through Day 28	Proportion of participants who are coinfected with influenza and SARS-CoV-2
To investigate SARS-CoV-2 RNA and/or COVID-19 symptom rebound during the study	• Proportion of participants who have viral RNA rebound from Day 6 up to Day 28 • Proportion of participants who have COVID-19 symptomatic rebound after the sustained resolution of COVID-19 through Day 28

[1] As determined by Central laboratory-confirmed positive RT-PCR test
[2] EC_{50} = Effective concentration required to produce 50% of the maximal response

3.2.1. COVID-19 symptoms onset

COVID-19 symptoms onset is defined as the occurrence (or worsening [increasing a symptom score from baseline] in the case of preexisting COVID 19-like symptoms) of ≥ 1 of the 14 specified COVID-19 symptoms for at least 48 hours.

The 14 specified COVID-19 symptoms are (1) fever* (defined as body temperature ≥ 38.0ºC per tympanic or rectal thermometer or ≥ 37.5° C per axillary, oral, or forehead/temporal thermometer; see Section 8.2.3) (2) shortness of breath or difficulty breathing, (3) cough*, (4) sore throat*, (5) nasal congestion or runny nose*, (6) chills, (7) fatigue*, (8) body or muscle pain or aches, (9) headache, (10) nausea, (11) vomiting, (12) diarrhea, (13) change in sense of taste, and (14) change in sense of smell.

Symptoms denoted with the asterisk (*) symbol are considered the 5 key symptoms of COVID-19, and are used in the analysis of several secondary objectives. The DAIDS Grading scale will apply to the derivation of fever.

Symptoms are assessed by site staff at baseline. Also, participants are expected to record symptoms twice per day in a diary entry. Each diary entry should record the participant's body temperature (if more than 1 is provided, only the maximum should be used), as well as the participant's perceived severity (None, Mild, Moderate, or Severe) of each symptom. If **all** non-missing diary entries for any of the 14 listed symptoms have a rating of "Mild", "Moderate", or "Severe" (or worse severity compared to that participant's baseline for pre-existing symptoms) over a period of ≥48 hours as determined by the diary entry (assessment time) timestamps, the criteria for symptoms onset will be met, even if data is missing for one or more of the entries within that time frame. See the appendix in section 15.7 for further illustration of symptoms onset qualification. It is noted that five consecutive diary entries is expected to occur over a 48-hour period on average, but without a difference of at least 48 hours between the first and last timestamps, five entries showing a new or worsening symptom is not considered sufficient to meet the symptoms onset definition. Onset will be considered as having occurred at the assessment time of the first diary entry indicating a greater-than-baseline symptom severity for a symptom that continues for ≥48 hours.

Nasal congestion or runny nose, sore throat, cough, fever, and fatigue are collectively referred to in the protocol and in this SAP as the five "key" symptoms of COVID-19. Several of this study's secondary objectives assess the incidence, duration, and/or resolution of this subset of key symptoms, irrespective of the presence of other symptoms.

3.2.2. Sustained symptoms resolution

Sustained symptoms resolution is considered to have occurred at the time of the first of at least 2 consecutive days (≥48 hours, as measured by symptoms diary assessment time timestamps) with complete resolution of all COVID-19 symptoms (or improvement to baseline for study participants with pre-COVID-19 symptoms). The same rules for handling missing symptoms diary entries used in determination of symptoms onset will apply to symptoms resolution as well (see appendix in section 15.7): if all non-missing diary entries show a baseline level of symptoms for a ≥48 hour-interval, sustained resolution will be considered to have occurred regardless of any intermediate

missing data). The Time to Sustained Symptoms Resolution (TSSR) is defined as the time from COVID-19 symptoms onset (defined in Section 3.2.1) until sustained symptoms resolution. Note that per the protocol, for study participants with pre-COVID-19 symptoms, improvement to baseline is considered complete resolution for all symptoms (except for loss of smell and taste). Furthermore, note that because the symptom(s) with first reported onset dates and symptom(s) with latest resolution dates may differ, a participant's TSSR may be greater than the maximum duration for any of the individual symptoms reported by a participant. Time to symptoms resolution will be calculated as:

(assessment time of the first symptoms diary entry of a ≥48-hour interval with baseline-level COVID-19 symptoms) – (time of symptoms onset, as determined by the symptoms diary assessment time for first entry in the ≥48-hour interval of symptoms))., For analysis purposes this may be expressed in half day increments based on the number of expected symptoms diary entries from symptoms onset to resolution.

Loss of smell and loss of taste are not considered in the calculation of TSSR. If a COVID-19 symptom other than loss of taste or smell is still present on Day 28 without resolution, the participant will not be included for descriptive summaries of TSSR. See section 8.1.1 for a description of handling of missing symptoms data.

3.2.3. Total symptoms score

Total symptom score (TSS) is defined as the sum of scores for all 14 targeted symptoms (each individual symptom score is 0 = none, 1 = mild, 2 = moderate, and 3 = severe). See section 3.2.1 for details on how severity grades are assigned to fever based on recorded temperatures. Loss of taste or smell is included in the TSS, but is scored differently, with 0 points assigned to a rating of 'same as usual', 1 point to a rating of 'less than usual', and 2 points for 'no sense'. Therefore, observed scores will range from values of 0 to a maximum possible 40 points. Because the TSS is calculated without regard to a participant's baseline symptoms, a participant's raw TSS may be greater than 0 after resolution of symptoms as defined above. Prior to symptoms onset (defined in 3.2.1), TSS values will be set to 0 regardless of any baseline symptoms reported. Similarly, all TSS values will be set to 0 after *sustained* resolution (defined above) is achieved.

3.2.4. Hospitalization

Hospitalization is defined as ≥ 24 hours of acute care (in a hospital or similar acute care facility, including emergency rooms or urgent care clinics), with duration calculated between the start and discharge times recorded on the Hospitalization and Acute Care electronic case report form (eCRF). When admission and/or discharge times are unavailable, a difference of 1 or more days between first event start and last event end date will be used for calculating duration.

When hospitalization is evaluated as an intercurrent event, the date of hospitalization will be compared with the date of the event, and times will not be considered.

3.3. Study interventions

The study intervention will consist of three 125-mg tablets of either S-217622 or matching placebo on Day 1, followed by 1 125-mg S-217622 or placebo tablet per day for Days 2 to 5,

according to the participant's randomized assignment. See the schedule of assessments in Section 15.1 for further detail.

3.4. Dose adjustment/modifications

Per the protocol, dose modifications are not permitted.

4. GENERAL STATISTICAL CONSIDERATIONS

All study data will be presented in by-participant listings unless otherwise stated. Data from participants excluded from an analysis will be included in the applicable data listings, but not included in the calculation of summary statistics for that analysis set. In tables, listings, or figures for which there are no data points that meet the reporting criteria, "No data available to report" will be displayed.

Descriptive summaries of continuous variables will include number of participants (N), the arithmetic mean (Mean), standard deviation (SD), minimum, median, and maximum. For discrete variables, summary statistics will be calculated for the number and proportion of participants in each category. All percentages will be rounded to one decimal place. The number and percentage will be presented in the form XX (XX.X), where the percentage is displayed in parentheses.

Unless otherwise stated, mean, median, standard deviation, and percentiles will be displayed to one level of precision greater than the data collected. For the summary statistics of all numerical variables, minimum and maximum will be displayed to the same level of precision as reported.

Summaries presented by visit will only present the visits at which a presented parameter was planned to be collected, per the schedule of assessments (see Sections 15.1 and 15.2). Listings of data collected at study visits will include all such data, regardless of whether it was planned to be collected during that visit.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. Any numerical summary statistics that have e.g. a denominator value of zero will be displayed as "---". Display of a frequency of 100% will be displayed as 'XX (100). The denominator for all percentages will be the number of participants in the treatment group within the analysis set of interest, unless otherwise specified.

The symptoms e-diary will be used to establish a participant's baseline for COVID-19 symptoms. Baseline symptoms will be derived using the participant's diary responses from the entry with the last (assessment time) timestamp prior to the first dose (among both Predose and Postdose forms). If a participant does not have any records prior to the first dose, baseline symptoms will be derived using the first of any post-dose diary entries from Day 1 that are recorded on a Predose form. If a participant does not have any symptoms diary records that are either (1) prior to the first dose or (2) on Day 1 from the Predose form, then baseline symptoms will be imputed as 0/"None", based on protocol-required inclusion criteria. For purposes of assessing symptom duration or resolution, baseline is defined as onset of COVID-19 symptoms (see section 3.2.1 for details); e.g. the first day a participant who has no symptoms at baseline reports a symptom with 'Mild', 'Moderate', or 'Severe' severity in their symptoms diary. For all other purposes, baseline will be

defined as the latest non-missing value prior to, or on, the date of the first dose of study intervention (S-217622 or placebo).

All participant COVID-19 symptoms indicated in diary entries will be displayed in a listing.

Change from baseline will be calculated for numeric parameters as (result at post-baseline-visit – baseline value). The change from baseline will only be calculated if the post-baseline visit value and baseline value are both available, and will otherwise be considered missing and not imputed, except for specific exceptions mentioned elsewhere in the SAP.

The study day prior to treatment initiation will be calculated as (event date – treatment start date). After treatment initiation, the study day will be calculated as (event date – treatment start date + 1), such that treatment initiation begins on Day 1. The protocol-defined schedule of assessments shown in section 15.1 defines acceptable time windows for the seven expected visits for study participants. For purposes of assigning timepoints to study data, the analysis visit for records will be derived based on the study day of occurrence relative to these protocol-defined windows, with two noted exceptions: study Day 2 will be considered within the window for Visit 2, and study Day 12 will be considered within the window for Visit 5.

For serology, hematology, and blood chemistry test results, values below the Lower Limit of Quantitation (LLOQ) will be treated as missing values. For quantitative PCR tests, values below the Lower Limit of Detection (LLOD) will be set to zero log 10 copies/mL. while values between the LLOD and LLOQ will be treated as positive tests and set to 2.27 - log10(2).

For analyses requiring one observation per participant per scheduled timepoint, the following selection algorithm will be used to flag records for inclusion when multiple records meet criteria:

(1) Records with missing values are excluded. If only a single record has a non-missing result or if only a single record with a missing result is present, it is selected by default.
(2) For PCR tests, preferentially consider any records with positive results (including less than LLOQ but detected) over records with negative or inconclusive results. For GIQ records, preferentially consider affirmative/'Yes' responses over other or missing responses.
(3) If multiple records still meet criteria, consider only those occurring on the date with the minimum difference from the protocol-defined target date.
(4) If multiple records have the minimum difference with the target date, select the record with the lowest SDTM domain sequence number or analysis sequence number as applicable.

All analyses and tabulation of listings will be performed using SAS version 9.4 (or higher). Unless otherwise stated, statistical testing will be 2-sided with a significance level of 0.05.

No imputation of missing lab test, adverse event, or medical history date values will be performed. Entry of missing or partial date data is not permitted for Adverse Events or PCR tests in this study. Partial medication dates are permitted and are imputed to categorize as prior or concomitant (see below).

Missing and partial start and stop dates:

For the purpose of inclusion in prior and/or concomitant medication, incomplete start and stop dates will be imputed as follows:

Missing start dates (where UK and UKN indicate unknown or missing day or month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study intervention, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study intervention month and year and the end date (after any imputation) is on or after the first dose of study intervention, then assume the date of the first dose of study intervention. If the month and year are the same as the first dose of study intervention month and year and the event end date (after any imputation) is prior to the first dose of study intervention, then assume the event end date for the start date.
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of the first dose of study intervention, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study intervention year and the event end date (after any imputation) is on or after the first dose of study intervention, then assume the date of the first dose of study intervention. If the year is the same as the first dose of study intervention and the event end date (after any imputation) is prior to the first dose of study intervention, then assume the event end date for the start date.

Missing stop dates (where UK and UKN indicate unknown or missing day or month respectively):

- UK-MMM-YYYY: Assume the last day of the month
- DD-UKN-YYYY/UK-UKN-YYYY: Assume DD-DEC-YYYY/31-DEC-YYYY

Imputation of dates will be used for analysis purposes only. All listings will show dates as collected without imputation.

4.1. Sample size

Based on the assumptions, enrollment in the study will remain open until 92 events (ie, the number of participants with a negative screening SARS-CoV-2 infection [central laboratory-confirmed negative RT-PCR test] who are infected with SARS-CoV-2 [central laboratory-confirmed positive RT-PCR test] and have COVID-19 symptoms onset through Day 10) are achieved. Assuming 7.0% of placebo-treated participants and 3.5% of S-217622–treated participants have an event, it is estimated that approximately 2200 participants will need to be randomized to achieve this number of events. However, the total number of participants enrolled may be adjusted to achieve this number of events. For example, if the event rate is as low as 5.90% and 2.95%, respectively, it is estimated that approximately 2600 participants will need to be randomized to achieve this number of events. (See Section 8.1.1 and REFERENCES below).

4.2. Randomization, stratification, and blinding

All participants determined to be eligible by screening will be centrally and randomly assigned to the S-217622 group or to the placebo group at a ratio of 1:1 using an interactive web response system (IWRS). Stratified randomization methods will be applied to the study, and the randomization of participants will be stratified by time from symptom onset in the index patient to time of enrollment of study participant (< 48 hours, ≥ 48 hours) and geographic region (North America, South America, Europe, Africa, Asia excluding Japan, and Japan). Note that for purposes of obtaining convergence in inferential analyses, the four lowest-enrolling geographical strata will be combined into a "Rest of World" level. In this SAP, this three-level geographic region variable is referred to as "pooled geographic region".

This is a double-blind study in which participants/investigators are blinded to study intervention. In addition, given possible decreases in high-density lipoprotein cholesterol with S-217622 dosing, results from this safety lab test will not be reported to the sites until after database lock. Details on blinding and procedures for breaking the blind are available in Section 6.3 of the protocol.

4.3. Analysis sets

The analysis sets define the groups of patients that will be analyzed and presented in the tables, listings, and figures that are described in this SAP. Each of these may also be referred to as analysis populations, e.g. the Safety analysis population, as the terms 'analysis set' and 'analysis population' are used interchangeably in this SAP. Patients will be listed along with their inclusion or exclusion in each of the analysis sets defined in this section.

A total of 10 analysis sets are to be used in the study:

- All screened analysis set
- Enrolled analysis set
- Intention-to-treat (ITT) analysis set
- Modified Intention-to-treat (mITT) analysis set
- Intention-to-treat baseline positive (ITTBP) analysis set
- Per protocol analysis set
- Safety analysis set
- PK analysis set
- Index patient analysis set
- Household member survey analysis set

Analysis sets may exclude participants from sites with non-compliance to Good Clinical Practice (GCP). For this study, such exclusions will be managed through protocol deviations.

4.3.1. All screened analysis set

The screened population consisted of all index patients and participants who complete screening for entry into the study, regardless of whether they are ultimately enrolled. Individuals with universally exclusionary deviations (e.g. due to lack of informed consent or scientific misconduct) will not be considered as part of the All screened analysis set. The All screened analysis Set will be used for tables and listings reporting on participant disposition, and for

combined listings in which index patients and participants have the same data collected (baseline symptoms assessed by the site, PCR test results).

4.3.2. Enrolled analysis set

The enrolled population consists of all participants who sign the informed consent form, complete screening requirements, and have met all eligibility requirements. Also, consented and eligible subjects who are associated with index patients who are later removed from the analysis due to a study deviation will be excluded from the enrolled analysis set.

4.3.3. Intention-to-treat analysis set

The Intention-to-Treat (ITT) population is defined as all participants randomly assigned to a study intervention. The ITT analysis set will be used for the analysis of disposition, demographic and other standard summaries and listings.

4.3.4. Modified intention-to-treat analysis set

The Modified intention-to-treat (mITT) population consists of all participants randomly assigned to a study intervention who:

1) also have a negative screening for SARS-CoV-2 infection confirmed by RT-PCR (central laboratory) collected from a sample prior to the first dose of randomized treatment (Visit 1) ; and,
2) are associated with index patients with a positive RT-PCR result for COVID-19 from the central lab at the Day 1 Screening visit
3) Have had at least one dose of either S-217622 or placebo

To be included in the mITT subset, participants are required to have at least one dose of a study treatment, but will be analyzed according to the assigned (randomized) study intervention. Note that the requirement of a *confirmed* negative test implies that this population represents a subset of the ITT analysis set who have first had a negative screening result at a local lab. The mITT analysis set will be used for evaluation of the study's primary efficacy objective, and for all secondary objectives other than the key secondary objective.

4.3.5. Intention-to-treat baseline positive analysis set

The Intention-to-treat baseline positive (ITTBP) analysis set is defined as the subset of ITT analysis set participants with a positive baseline screening result for SARS-CoV-2, with the test sample collected on or before the date of randomization) assessed by RT-PCR at the central lab. The ITTBP analysis set will be used in supplemental analysis of the primary outcome, as described below in section 8.1.3.1, and for analysis of spike gene and NSP5 sequences for exploratory analysis.

4.3.6. Per protocol (PP) Analysis Set

The per protocol set includes all participants in the mITT population without any exclusionary major protocol deviations (see Section 5.2 for additional details). Participants in the per-protocol analysis set will be analyzed according to the actual treatment intervention they receive.

4.3.7. Safety Analysis Set

The Safety analysis population is defined as all participants randomly assigned to a study intervention who also received at least one dose of the study intervention. Participants will be analyzed with the S-217622 arm if they received any doses of the active treatment, while participants in the placebo group for the safety analysis set will have received placebo for all doses.

4.3.8. Pharmacokinetic analysis set

The Pharmacokinetic (PK) population includes all participants who receive at least 1 dose of S-217622 and have at least 1 evaluable concentration of S-217622 in plasma. This population will be used for the concentration listing and graphical presentations.

4.3.9. Index patient analysis set

The Index patient analysis population is defined as all index patients who have met all eligibility requirements and who have themselves or by a legally authorized representative (LAR) provided informed consent, and who are associated with one or more participants who are randomized to receive a study intervention (i.e., participants in the ITT Analysis Set), and who do not have any exclusionary deviations. This analysis set is not defined in the protocol, but will be used for summaries specific to index patients for demographics and exploratory objectives.

4.3.10. Household member survey analysis set

The Household Member Survey population is defined as the subset of randomized participants who are designated respondents to the household member survey for residents of their dwelling. Membership in this analysis set is determined by the response to the Day 1 Household Member Survey question “Is the following participant the one answering the questionnaire on behalf of the household?”. This analysis set is not protocol-defined, but will be used in the exploratory objective to characterize the association between index patient viral RNA levels and household SARS-CoV-2 secondary attack rates (see Section 8.3.5). According to section 8.1.4 of protocol, only one participant per household will provide responses to the survey. However, if the questionnaire is completed by multiple participants within the same household, only the member who answered the question most recently (with the latest date time) will be counted in the Household member survey analysis set.

5. SUBJECT DISPOSITION

5.1. Disposition

The number and percentage of participants who are currently on study intervention, who completed the study intervention, who discontinued the study intervention, who are on follow-up period and who were withdrawn from the study will be summarized for the ITT Analysis Set. In addition, reasons for withdrawal from the study will be summarized by treatment group:

- Failure to meet eligibility criteria (screen failure)
- AE
- Protocol deviation
- Withdrawal by subject

- Lost to follow up [for reasons not related to COVID-19]
- Pregnancy
- Death
- COVID-19 reason other than AE
- Lost to follow up due to COVID-19 reasons
- Sponsor decision due to COVID-19 reasons
- Sponsor decision due to other than COVID-19 reasons
- Other

The number of participants included in each analysis population will be presented. Participant disposition will be presented in a listing for the All Screened analysis set.

Index patient disposition will be minimally described in terms of numbers and percentages screened and enrolled, and numbers of associated participants randomized. Index patient disposition summary will be performed in the All Screened analysis set.

5.2. Protocol Deviations

All protocol deviations will be assessed on an ongoing basis and categorized as Significant/Not Significant, and as Major or otherwise, based on the classification given in the deviation rules document.

Significant protocol deviations are those that:

- affect primary efficacy and/or safety assessments (as applicable)
- affect the safety or mental integrity of a participant
- affect the scientific value of the project

Major protocol deviations are defined as deviations that lead to exclusion from the per-protocol analysis set. Major deviations are a subset of significant deviations. Significant protocol deviations will be summarized by the counts and percentages of participants with deviations by category and treatment group in the ITT Analysis Set and separately in the index patient analysis set. Additional detail provided by study sites about protocol deviations in the ITT and Index Patient populations, and whether the deviation was considered a significant and/or major deviation, will be displayed in listings.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

Demographics will be summarized by study intervention using descriptive statistics in both the mITT and Safety Analysis Sets. For each analysis population, demographics and baseline characteristics will be summarized by treatment group. The summary will include the following demographic variables:

- Age (years)
- Age category (<18, 18 to 64, or ≥ 65)
- Sex (Male or Female)

- Fertility Status (Childbearing Potential, Premenarchal, Postmenopausal, Surgically Sterile, or Not Applicable)
- Race (White, African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Height and weight (collected during the physical examination at Screening; see Section 9.4) and BMI (calculated as [weight]/[height^2], with respective units kg and meters) will also be summarized with the demographic variables. The randomization factors of participant enrollment time from index patient symptom onset (< 48 hours, ≥ 48 hours) and geographic region (North America, South America, Europe, Japan, Asia excluding Japan, and Africa) will be obtained from IWRS and will also be summarized with demographic data. Pooled geographic region will also be described by treatment group. Baseline characteristics of participants in the ITT analysis population will be presented in a listing. A separate listing of demographic variables and COVID-19-specific treatments for the index patient analysis set will also be provided. The number and percentages of participants randomized by country and site will be summarized in the ITT analysis set overall and by treatment group.

6.2. Baseline disease characteristics

No aggregate summary of baseline disease characteristics will be performed, as participants must test negative for COVID-19 by RT-PCR on Day 1 for eligibility in the mITT cohort. However, all RT-PCR screening results will be presented in a data listing. Symptoms of COVID-19 pre-existing at baseline will be assessed by study staff on Day 1. The number and frequency of staff-assessed pre-existing COVID-19 symptoms will be summarized in the ITT analysis set. Additionally, pre-existing COVID-19 symptoms will be displayed in a data listing for participants and for index patients.

6.3. Medical history

Medical history terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher. The number and percentage of participants with any medical history will be summarized and for each System Organ Class (SOC) and Preferred Term (PT) using the Safety Analysis Set. Targeted medical history relating to COVID-19 symptoms or risk which are specifically solicited on the medical history eCRF will be summarized in a table by study intervention group. All medical history data will be presented in a listing for the ITT analysis set**.**

6.4. Tobacco history

Participants' history of tobacco use will be collected on the Smoking History eCRF. Number and percentages of participants reporting current, previous, or no history of use of cigarettes, cigars, tobacco pipes, e-cigarettes, and other types of tobacco will be presented in a summary table, along with a descriptive summary of uses per day of each. Smoking history will be displayed in a listing for the ITT analysis set.

6.5. Inclusion and exclusion criteria

For inclusion in the study, participants must be household members of a qualifying index patient with symptomatic COVID-19. Refer to Section 5.1 of the protocol for a comprehensive list of inclusion criteria for index patients and participants.

Details on exclusion criteria are in Section 5.2 of the protocol.

Per Consolidated Standards of Reporting Trials (CONSORT) requirements, a minimum level of information (demographics, eligibility criteria violations, and other commentary from investigators) will be captured for reporting on participants who fail screening. A listing will display whether the participants who were screened met and/or did not meet the inclusion and exclusion criteria.

7. STUDY INTERVENTIONS AND MEDICATIONS

The World Health Organization Drug Dictionary (WHODD) version MARCH 2023 or later will be used to code prior and concomitant medications.

For purposes of this analysis, a prior medication is defined as any medication for which the start date (imputed or otherwise) occurs before the first administration of the study intervention. This includes all medications started prior to enrollment that continue while the participant is enrolled. A concomitant medication is defined as any therapy, other than study intervention, with a start date occurring on or after the date of the first dose of the study intervention until the participant's Day 28 visit or exit from the study (whichever occurs first).

For inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed (see Section 4 for details). If it cannot be determined whether the start date of a medication is prior to the administration of the study intervention, it will be assumed that the medication was received prior to the administration of the study intervention (i.e., it will be assumed by default a medication is a prior medication). If it cannot be determined whether the stop date of a medication is after administration of study drug, it will be assumed that the medication was taken concomitantly.

Sensitive CYP3A substrates (e.g. alfentanil, cyclosporine, sirolimus, tacrolimus, and terfenadine), corticosteroids other than prednisolone, other treatments with potential for DDI with S-217622 (paxlovid, hydroxychloroquine, ivermectin), strong CYP3A inducers, methotrexate, digoxin, and high-dose rosuvastatin are prohibited during the study intervention period (Day 1 to Day 5). Additionally, some of the aforementioned medication types may be prohibited up to 28 days prior to the first dose of study intervention and/or 10 days after the last dose of study intervention (see protocol Section 6.8.1 for further details).

All prior and concomitant medications will be displayed in a combined data listing. All planned analysis of prior and concomitant medications will be performed in both the Safety Analysis Set and mITT Set.

Surgical procedure history will be captured on the Surgical or Medical Procedures eCRF. Data from this form (procedure description, date , reason or indication, and associated AEs or medical history) will be presented in a data listing in the Safety Analysis Set.

7.1. Prior and concomitant medications

See Section 4 for details regarding missing dates.

7.1.1. Prior medications

Prior COVID-19 vaccination history (any vs. none) and type(s) of COVID-19 vaccinations received will be collected separately from other medications and summarized by treatment group. All other prior medications will be summarized by treatment group and by Anatomical Therapeutic Chemical (ATC) level 4 (or highest available level) and Preferred Term. ATC and Preferred Terms (PTs) will be displayed in order of decreasing frequency within the overall study, and then alphabetically. Participants will only be counted once per ATC and once per Preferred Term if they report multiple medications within the same ATC or Preferred Term.

7.1.2. Concomitant medications

Concomitant medications will be summarized by treatment group and by ATC level 4 (or highest available level) and PT. ATC and PTs will be displayed in order of decreasing frequency within the overall study, and then alphabetically. Participants will only be counted once per ATC and once per PT if they report multiple medications within the same ATC or PT.

7.2. Study interventions

7.2.1. Extent of exposure

The study intervention consists of 3 orally administered 125 mg tablets (either S-217622 or matching placebo) on Day 1, followed by 1 additional 125-mg tablet on each of the next 4 days (Days 2 to 5). Participants will self-administer doses on Days 2 to 5. The second dose should occur between 16 and 32 hours after the initial dose, and the remaining doses are recommended to recur every 24 ± 2 hours thereafter. There will be no dose modifications in this study.

Because this is a study for an acute condition with a treatment administered only 5 times over 5 days, participant compliance will be assessed (see Section 7.2.2) but no further analysis of the extent of exposure will be performed.

7.2.2. Study intervention compliance and modifications

Doses will be skipped if more than 12 hours late. Participants are instructed to return any remaining tablets to the investigational site at the end of 5 days. A summary of the number of completed doses and percentage of participants with completed doses will be presented by day and treatment group for the both the mITT and the Safety Analysis Sets. Accumulated dosages over the entire treatment period will be presented for the S-217622 actual treatment arm only. Additionally, the number and percentage of subjects from the ITT analysis set who had at least 1 tablet of study intervention administered will be displayed by treatment group. Dose administration data captured on the Study Drug Administration eCRF (including intervention start and stop times, and reasons for missed doses and dose delays) for participants in the ITT Analysis Set will be provided in a data listing. For each participant, compliance will be calculated as follows:

Compliance (%) = (Actual total number of tablets / Expected total number of tablets) x 100

The expected total number of tablets is as follows:

- For participants who have not stopped study intervention by Day 5, the expected total number of tablets is 7 (3 for Day 1 + 1 for each day on treatment from Day 2 to Day 5).
- For participants who have died or stopped study intervention before Day 5, the expected total number of tablets equals 3 (for Day 1), plus 1 for each day up to and including the day of death or discontinuation of study intervention.

8. EFFICACY ANALYSIS

The primary objective of this study is to compare S-217622 with placebo in the prevention of symptomatic SARS-CoV-2 infection in modified Intention-to-Treat population participants who are household members of SARS-CoV-2-infected index patients. The null hypothesis to be tested is that the risk for incident symptomatic COVID-19 over 10 days in participants assigned to treatment with S-217622 (R_1) is the same compared to the risk for incident symptomatic COVID-19 over 10 days in participants who were assigned to treatment with a matching placebo (R_0). The null hypothesis will be weighed against the alternative hypothesis that the risk for symptomatic COVID-19 over 10 days is not the same in participants assigned to the S-217622 group versus participants in the placebo group. This can also be expressed as:

H_0: $R_1/R_0 = 1$
H_a: $R_1/R_0 \neq 1$

This two-sided hypothesis test will be performed using a GEE approach for a Poisson regression model with a robust variance estimator and modified for binary data. If the p-value for the model's regression coefficient of interest is less than the predefined type I error rate of 0.05, the null hypothesis will be rejected in favor of the alternative. See Section 8.1 for further detail about the analysis of the primary endpoint (estimand, intercurrent events, etc.). Several supplementary and sensitivity analyses (see section 8.1.3) and subgroup analyses (8.1.4) are planned to further inform this hypothesis test.

The study's key secondary objective is defined similarly to the primary objective (CLC positive RT-PCR test at or before the Day 10 visit with symptoms onset on or before Day 10), but will be performed in the ITT population instead of the mITT population, and will only be performed conditionally upon rejection of the null hypothesis for the primary objective. The supplementary and sensitivity analyses described in section 8.1.3 will also be conditionally performed for the key secondary objective).

All other secondary objectives also address the efficacy of S-217622 as a treatment for SARS-CoV-2. These include comparisons between treatment groups for the following:

- Risk ratios for any (symptomatic or asymptomatic) COVID-19 at Days 10, 15, and 28
- Time to first CLC positive RT-PCR results
- Proportion of participants with CLC positive RT-PCR results at each timepoint
- AUC of change in SARS-CoV-2 viral RNA from baseline
- Risk for asymptomatic COVID-19

- Proportion of participants infected with SARS-CoV-2 without symptoms onset through Day 10
- Proportion of participants with asymptomatic SARS-CoV-2 infection through Day 10
- Proportion of participants sustained resolution of all COVID-19 symptoms through Day 28
- Proportion of participants sustained resolution of the 5 key COVID-19 symptoms through Day 28
- Proportion of participants with sustained resolution of each COVID-19 symptom through Day 28
- COVID-19 symptoms score at each timepoint
- COVID-19 symptoms score at each timepoint, considering only the 5 key symptoms
- Time from first confirmed SARS-CoV-2 infection until the first reported COVID-19 symptom through Day 28
- Time from first confirmed SARS-CoV-2 infection until first onset of COVID-19 symptoms through Day 28
- AUC of the daily total COVID-19 symptoms score over time through Day 28
- AUC of the daily total COVID-19 symptoms score over time through Day 28, considering only the 5 key symptoms
- Proportion of participants with hospitalization or death from any cause through Day 28

Details about the analysis of secondary endpoints are further elaborated in Section 8.2.

Exploratory endpoints for the efficacy analysis include, but are not limited to:

- Days of hospital and intensive care unit stay in participants with SARS-CoV-2-related hospitalization through Day 28
- S-217622 antiviral activity
- Change from baseline in EQ-5D-5L scores
- Proportion of participants reporting baseline-equivalent or better health at Day 28
- Proportion of participants with viral RNA and/or COVID-19 symptoms rebound

Additional specification of exploratory analyses can be found in Section 8.3 of this document.

See 8.1.4 for details regarding subgroup analyses. For convenience, exploratory objectives are considered with efficacy analyses in this SAP, regardless of whether they are technically measures of antiviral activity against SARS-CoV-2 from S-217622 vs. placebo. Descriptive summaries of all primary, secondary, and exploratory endpoints will be displayed by treatment group and presented in listings.

Note that COVID-19 symptoms used in determination of the primary endpoint and several secondary objectives are rated by participants as ‘Mild’, ‘Moderate’, or ‘Severe’. A summary of COVID-19 symptoms by symptom type, and study day will be provided with the efficacy tables for reference. For supplementary, subgroup, and secondary objectives, risk ratios will only be evaluated if at least five events are observed in at least one treatment group.

8.1. Primary efficacy endpoint

Table 2 shows the primary estimand and related information regarding the primary endpoint.

Table 2: Primary estimand

Primary estimand	The occurrence of infection with SARS-CoV-2 (CLC positive RT-PCR test) and COVID-19 symptom(s) through Day 10 regardless of adherence to study intervention
Analysis population	mITT population
Handling of intercurrent events	Expected and potential intercurrent events: a. Withdrawal of study intervention due to use of rescue or prohibited medication before occurrence of the event for the primary endpoint b. Death or hospitalization from any cause before occurrence of the event for the primary endpoint c. Withdrawal from the study before occurrence of the event for the primary endpoint Treatment policy strategy will be used to evaluate treatment effects irrespective of intercurrent events (e.g. irrespective of whether a participant received the complete dose(s) of an agent/placebo, rescue or prohibited medication). For participants with intercurrent events "a", the participants should continue participating in the study. Where possible, data for the participants will be collected after participants' withdrawal and will be used for primary analysis. For participants with "b" or "c", the participant will be assumed to have been infected with SARS-CoV-2 with symptoms at the time of death, hospitalization, or withdrawal.
Primary endpoint	Proportion of participants who are infected with SARS-CoV-2 (CLC positive RT-PCR test) and have COVID-19 symptoms onset through Day 10

Summary measure	Risk ratio of proportion of participants who are infected with SARS-CoV-2 (CLC positive RT-PCR test) and have COVID-19 symptoms onset through Day 10 between S-217622 and placebo

The primary endpoint for the study is defined as the proportion of participants who are infected with SARS-CoV-2 (CLC positive RT-PCR test) and have COVID-19 symptoms onset through Day 10. This requires that both of the following criteria are met:

- CLC RT-PCR positive test for SARS-CoV-2 between first study intervention administration and the Day 10 visit (through Day 11 due to the protocol defined window).
- Onset of COVID-19 symptoms (see 3.2.1) between first study intervention administration and Day 10 (including Day 10), as noted in the participant symptoms diary.

The beginning of symptoms onset must be within 10 calendar days of a CLC positive RT-PCR test in order for the primary endpoint to be considered met.

For the primary estimand, participants experiencing the intercurrent events of hospitalization, death, or withdrawal from the study will be considered as having a CLC positive RT-PCR test with symptoms onset on the date of the intercurrent event. For participants hospitalized, the event should have started by Day 10 and lasted ≥48 hours to be considered as a CLC positive RT-PCR test with symptom onset.

8.1.1. Primary analysis

The main estimation for the primary analysis (risk ratio between treatments for symptomatic COVID-19 through Day 10) will be performed using a GEE approach applied via a Poisson regression model. The model's response variable is the primary endpoint (see Section 8.1), and it contains terms for the study intervention (S-217622 or placebo), the index patient onset randomization stratification factor (described in Section 4.2), and pooled geographic region as independent variables. An exchangeable structure will be assumed for the covariance matrix to account for correlation between participants from the same household. A sandwich estimator will be used for robust inference. Participant, study intervention, time from index participant symptoms, and pooled geographic region will be treated as class variables. The main estimation of interest will be of the (exponentiated) coefficient for the treatment effect of S-217622 relative to placebo. If convergence of the GEE model is not observed due to low numbers of events within a covariate stratum (either time from index patient onset or pooled geographic region), a reduced model with the study treatment group as the only predictor variable will be used to estimate the risk ratio. If the reduced model still does not converge due to sparse data within strata, a null result will be reported. Should the GEE Poisson regression model fail to converge for reasons other than lack of events (or non-events), the model from the sensitivity analysis described in section 8.1.3.3 will be used for the estimation of the primary endpoint. The risk ratio and 95% confidence interval (CI) for S-217622 relative to placebo will be presented along with the p-value corresponding to the coefficient from the GEE model. Estimation will be performed using PROC GENMOD in SAS 9.4 or higher, with a Poisson distribution specified in the model statement and a log link function. These results will be presented alongside a summary of the

number and proportion of participants experiencing the primary endpoint by treatment group, and the corresponding 95% Clopper-Pearson confidence intervals.

The primary efficacy analysis will be performed in the mITT Analysis Set.

8.1.2. Key secondary analysis

For the key secondary analysis of the primary endpoint, the same analysis as that of the primary analysis will be conducted in participants from the ITT population. The fixed-sequence procedure will be applied for the multiplicity adjustment in the primary analysis and the key secondary analysis of the primary endpoint. In the fixed-sequence method of type I error control, the key secondary analysis will be performed only if the statistical test for the null hypothesis is that the risk ratio is 1 shows statistically significant at the 2-sided significance level of 0.05.

8.1.3. Supplemental and sensitivity analyses

A total of 41 supplemental and three sensitivity analyses of the primary endpoint and key secondary endpoint are planned. The purpose of the supplemental analyses is to assess to what degree results of the primary analysis of interest are affected by (1) handling of intercurrent events and missing data, (2) the length of follow-up period for which participants are at risk for the primary endpoint, (3) the 48-hour threshold for symptoms in the definition of COVID-19 onset, and (4) subjects with major protocol deviations. Meanwhile, the aim of the three sensitivity analyses is to demonstrate robustness of the conclusion with respect to the choice of statistical methods used to test the hypothesis of interest.

8.1.3.1. Supplemental analyses

To appraise the practical significance of intercurrent events, protocol deviations, and endpoint and/or population definitions, supplemental analyses will be performed as variations on the primary efficacy analysis:

- Excluding participants with intercurrent events due to withdrawal from the study intervention due to use of rescue or prohibited medication, as indicated by investigators on the Discontinuation of Study Intervention CRF, prior to meeting the primary efficacy endpoint
- Excluding participants with intercurrent events due to hospitalization or death by Day 10 prior to meeting the primary efficacy endpoint
- Excluding participants with intercurrent events due to early exit from the study by Day 10 prior to meeting the primary efficacy endpoint
- In the per-protocol population
- Through Days 15, 21, and 28 rather than through Day 10
- In the ITT baseline positive analysis set through Days 10, 15, 21, and 28
- Without considering intercurrent events through Days 10, 15, 21, and 28
- When the threshold for COVID-19 symptoms onset is decreased to symptoms for ≥24 hours instead of ≥48 hours (for one or more symptoms), both with and without considering intercurrent events through Day 10, 15, 21, and 28

Note that in supplemental analyses, intercurrent events will be evaluated using dates only, and times will not be considered.

Each of the aforementioned supplemental analyses will be performed in both the mITT analysis set, and in the ITT analysis set (except the per-protocol supplemental analysis). The same methods will be used as for the primary efficacy analysis described in Section 8.1.1, and results will be presented in the same manner.

8.1.3.2. Sensitivity analysis 1

A planned sensitivity analysis of the primary endpoint is to evaluate both the absolute and relative differences in risk of the primary endpoint between participants assigned to S-217622 and placebo will be performed in the mITT Analysis Set. This analysis will be stratified by the two randomization factors (time from index participant symptoms to participant enrollment of < 48 vs ≥ 48 hours; geographic region of North America, South America, Africa, Japan, or Asia excluding Japan). A Mantel-Haenszel test will be used to obtain stratum-adjusted proportions, and the stratum-specific relative risks and 95% CIs will be reported. The 95% confidence interval of the common difference in proportions of participants who met the primary endpoint between treatment groups will also be estimated.

This sensitivity analysis will be performed in both the mITT analysis set and repeated for the key secondary endpoint in the ITT analysis set.

8.1.3.3. Sensitivity analysis 2

A second planned sensitivity analysis for the primary hypothesis test will be performed to assess the degree to which conclusions are affected by the specification of the Poisson model used in calculation of the relative risks between assigned treatments. A Poisson regression model modified according to the methods of Zou et al (see REFERENCES) will be used to assess the relative risk of the primary endpoint in the same way as the model described in section 8.1.1. As with the GEE model used in the main estimation of interest, this model will contain terms for the study intervention (S-217622 or placebo) and randomization stratification factors for time from index patient onset (described in Section 4.2) and pooled geographic region as independent variables. It does not contain a household-level random effect, but a robust error variance will be estimated by adding a random effect with an unstructured covariance matrix for the participant.

This sensitivity analysis will be performed in both the mITT analysis set and repeated for the key secondary endpoint in the ITT analysis set. If the model does not converge, this sensitivity analysis will not be performed.

8.1.3.4. Sensitivity analysis 3

The final planned sensitivity analysis for the primary objective will be performed to assess assumptions related to missing symptoms diary data. For this sensitivity analysis, the regression model and methods will be identical to that of the primary endpoint, except that symptoms onset will be determined after symptoms diary data has been imputed by interpolation or baseline-carried-forward when missing, according to the following algorithm:

- If a diary entry is missing (for a symptom or in total) but was reported by the participant in diary entries one day prior to, and after the missing data, the average numeric severity

(0 = 'None', 1 = 'Mild', etc.) of the nearest of those entries before and after the missing datapoint will be assigned.
- If the average is not an integer it will be rounded toward the participant's baseline value for that symptom.
- If non-missing diary data for a symptom is unavailable before or after a missing symptom value, then baseline severity for that symptom will be used in place of the missing value.

For example, a participant reports mild shortness of breath or difficulty breathing on Days 2 and 4, but he is missing diary data on Day 3. He would be considered mildly symptomatic on Day 3. Meanwhile, consider a participant who reports cough on Day 3. She then does not complete diary data for the remainder of enrollment. Her remaining entries for cough would be treated as if she had provided a rating of "None" for Days 4 to 28, as "None" was her baseline level for that symptom.

For this analysis, temperature records from missing entries will be imputed as described above. Fever severity for missing entries will be calculated from imputed temperatures.

Interpolated data will not be used in the interpolation of subsequent datapoints. This means that a series of 3 or more missing entries will result in at least one of the values being assigned a baseline level of symptoms.

If the symptoms diary time is unavailable, a participant's first diary entry of a day will be assumed to occur at a local time of 6:00 hours (6 AM), while the second diary entry of a day will be assumed to happen at a local time of 18:00 hours.

This sensitivity analysis will be performed in both the mITT analysis set and repeated for the key secondary endpoint in the ITT analysis set.

8.1.4. Subgroup analysis

The primary efficacy analysis will be repeated within 6 predefined subgroups:

- By participant age: (Under 18, 18 to 64, ≥ 65)
- By treatment that the index patient received (any COVID-19 treatment or symptoms alleviation only/no treatment)
- By upper respiratory symptoms in the index patient at baseline (present or absent)
- By time from onset of COVID-19 symptoms in the index patient to participant randomization (≥48 hours or <48 hours)
- By presence of high-risk factors (present or absent) for severe COVID-19

Treatment given to the index patient will be assigned categories that are determined by the sponsor. The subgroup based on time from COVID-19 symptoms onset in the index patient will be assigned based on the randomization factor (see Section 4.2) For determination of whether index patient had upper respiratory symptoms at baseline, responses for 'Cough' and 'Nasal congestion or runny nose' questions on the Index Patient COVID-19 Symptom Questionnaire eCRF will be used.

The subgroup for severe COVID-19 high-risk factors is participants who have any of the following criteria:

- Age ≥ 65 years
- Age ≥ 18 and any of:
    - BMI > 29.5 kg/m^2
    - Cardiovascular disease requiring daily prescribed therapy or congenital heart disease
    - Chronic lung disease
    - Chronic kidney disease
    - Chronic liver disease
    - Down syndrome
    - Sickle cell disease
    - Immunocompromising conditions
    - Dementia or other neurological conditions
    - Cystic fibrosis
    - Diabetes (type 1 or type 2)
    - Smoking, current or former
    - History of stroke or cerebrovascular disease
    - Other specified medical history that is deemed a significant COVID-19 risk by investigators (contingent on sponsor review)

Each subgroup will be analyzed separately. Subgroup analysis for these predefined categories will not be displayed for categories with ≤ 5 participants. In contrast to the primary efficacy analysis, the GEE model used in all subgroup analyses will not contain covariates for time from index patient onset (<48 hours, >=48 hours) or pooled geographic region; instead only planned treatment group will be included as a predictor variable (i.e., the reduced model described in section 8.1.1 to handle non-convergence will be used). All subgroup analyses will be performed in the mITT Analysis Set.

8.1.5. Symptoms diary compliance

Because symptoms diary data is critical in determining the occurrence of the primary and key secondary endpoint, participants' symptoms diary compliance will be summarized by treatment group and overall. Compliance will be calculated at the participant level as:

[number of morning and evening symptoms diary entries (with at least one symptom completed)] / (number of morning and evening symptoms diary entries expected).

Any entry with nonmissing responses for one or more of the symptoms listed in section 3.2.1 (except for fever) will be considered as having been submitted. Two symptoms diary entries are expected per day from Day 1 to Day 28, except when the participant exits the study prior to Day 28. For early exits between Day 2 and Day 28, only one entry will be expected on the study end date. No diary entries are expected for participants who discontinue treatment on the same day as randomization, before taking the first dose of the study treatment and before completing the first pre-dose diary entry under staff supervision. These participants with no expected entries will be

excluded from the analysis. Any symptoms diary data captured after Day 28 will not be included in compliance calculations.

8.2. Secondary efficacy endpoints

All analyses of secondary objectives are performed twice: first in the mITT Analysis Set, and then repeated in the ITT set.

The objectives in Sections 8.2.2, 8.2.12, and 8.2.13 are time-to-event analyses. All will use Kaplan-Meier methods, with standard errors approximated using Greenwood's formula. All analyses will be stratified by the time from index patient symptom onset to time of enrollment randomization factor, as described in Section 4.2, but will be analyzed across all geographic regions, and then analyzed separately for North America and for Japan. Restricted mean survival time (RMST) and the corresponding 95% CIs will be estimated by treatment group. For calculation of RMST, all event or censoring times that occur after the risk window (depending on the objective) will be censored at the applicable limit. The difference in RMST between S-217622 125 mg and placebo and its 95% CI will be calculated, and a log-rank test will be performed with two-sided $\alpha = 0.05$. Results will be displayed in Kaplan-Meier plots by study intervention and the time from onset randomization factor.

Objectives in Sections 8.2.4, 8.2.14, and 8.2.15 have endpoints that are AUCs of viral RNA change, TSS change, and TSS change for the five key symptoms, respectively. For all AUC secondary objectives, AUC will be calculated by the trapezoidal method. This approach assumes a linear change between consecutive measures, creating a trapezoid between each change in the outcome measure with its base on the x-axis (with length of the base as the time between measurements), and heights of the right and left sides determined by changes from baseline in the outcome of interest. Note that for symptoms outcomes, diary data is expected twice per day, and (for participants with no missing entries) the base of each trapezoid will have a length of 0.5 days. Missing data will not be imputed for AUC objectives, but per the approach outlined in Section 4, values below the Lower Limit of Detection will be set to 1 for outcomes plotted on a log scale or 0 for outcomes on a linear scale. If a participant has more than one observation for a measurement from the same timepoint, the largest of the assessments at the timepoint will be used to calculate the height. Participants without at least 3 data points in an AUC analysis will be excluded, as will any participants with missing values for the final (Days 10 or 28, as applicable) outcome assessment.

8.2.1. Symptomatic or asymptomatic COVID-19 through Days 10, 15, 21, and 28

The secondary endpoint "Proportion of participants who are infected with SARS-CoV-2 (CLC positive RT-PCR test) through Days 10, 15, 21, and 28 regardless of occurrence of COVID-19 symptoms" is defined similarly to the primary efficacy endpoint, but does not require that a participant have COVID-19 symptoms, only a CLC positive RT-PCR test at any point through the end of the corresponding visit window. This endpoint will be analyzed and presented in the same manner as the primary efficacy endpoint (including handling of intercurrent events; see Section 8.1.1), and repeated for the outcomes of CLC positive RT-PCR tests through Day 15, Day 21, and through Day 28.

Additionally, the analysis for this endpoint through Days 10, 15, 21, and 28 will be repeated separately within pre-specified subgroups based on pooled geographic region. The geographic subgroup analysis of CLC-positive RT-PCR test rates through Days 10, 15, 21, and 28 will be performed in both the mITT and ITT analysis sets. Note that the pooled geographic region randomization stratum will not be included as a GEE model covariate for the analysis within geographic subgroup.

8.2.2. Time to the first CLC Positive RT-PCR result

This secondary endpoint is defined as the time from the start of the study intervention to the first confirmation of a CLC positive RT-PCR result through the Day 28 visit (Day 31 per the protocol defined window). This objective will be analyzed using the Kaplan-Meier methods for time-to-event endpoints described in Section 8.2. Time 0 is defined as the time of the first administration of the study intervention. Event-free participants will be censored at the last date and time of a RT-PCR test on or before the end of the Day 28 visit window (Day 31) as recorded on an eCRF. As an analysis separate from the times to first CLC positive RT-PCR tests that are displayed in the Kaplan-Meier plots, for consistency with other secondary objective analyses (see 8.2.3), the cumulative event rates at the end of the Day 3, 6, 10, 15, 21, and 28 visit windows (and their corresponding 95% confidence intervals) will be reported. Intercurrent events will not be considered for this endpoint. The analysis will be performed for all geographic regions combined and will be repeated for participants in the Japan and North America regions separately.

8.2.3. Proportion of participants with CLC Positive RT-PCR result at each timepoint

This secondary endpoint is defined as the proportion of study participants with a CLC RT-PCR positive test result occurring within the visit window of each scheduled timepoint. Frequency and proportion of participants testing positive, as well as exact 95% Clopper-Pearson confidence intervals will be reported. The common relative risk between treatments for a positive RT-PCR test within the window of any scheduled timepoint over the 28 day study period will be estimated using a Mantel-Haenszel test using time from index symptom onset to participant enrollment and geographic region (i.e., the randomization strata) as stratification factors. Intercurrent events will not be considered for this endpoint.

8.2.4. Area Under the Curve of change in amount of SARS-CoV-2 viral RNA

This secondary endpoint is defined as the AUC of change from baseline in amount of SARS-CoV-2 viral RNA. Change in viral RNA will be assessed on a $\log_{10}$ scale and evaluated from the Screening Day 1 visit until the Day 10 visit. The trapezoidal method described in Section 8.2 above will be used to calculate each participant's AUC of change in amount of viral RNA from baseline (which should be zero in all mITT participants; hence, this will be equivalent to the AUC for absolute amount of viral RNA as well). Additionally, AUC data will be normalized by dividing by the number of days multiplied by 10. Intercurrent events are not applicable to the analysis of this objective.

An analysis of covariance (ANCOVA) model will be applied to perform pairwise comparison of the AUC between the S-217622 and placebo groups. Randomization factors and study day will be used as covariates in the ANCOVA model. In addition, the summary statistics will be calculated by treatment group.

8.2.5. COVID-19 through Day 10 without symptoms onset

This endpoint is defined as the proportion of study participants who are infected with SARS-CoV-2 by CLC RT-PCR positive test and have no COVID-19 symptoms onset (≥1 symptom for ≥48 hours) through Day 10 after administration of study intervention; that is, participants may have no symptoms, or may have any number of new or worsening symptoms that all have a maximum duration of <48 hours. This is defined and analyzed similarly to the primary efficacy endpoint and will be presented in the same manner (see Section 8.1.1). The same intercurrent events handling methods used with respect to the primary endpoint will also apply to this endpoint, with the modification that a participant will be assumed to have been infected with SARS-CoV-2 without (rather than with) symptoms on the date of death, hospitalization, or withdrawal.

8.2.6. SARS-CoV-2 infection with no COVID-19 symptoms on Day 10

This secondary efficacy endpoint is defined as the proportion of participants who meet all of the following criteria:

- Incident SARS-CoV-2 infection between first study intervention administration and Day 10 visit, as confirmed by CLC positive RT-PCR test
- No negative RT-PCR test between (1) the day of the first positive test and (2) Day 10 visit after the first study intervention
- No COVID-19 symptoms occurrence on Day 10 (or if Day 10 is missing, no symptoms recorded on the most recent diary entry prior to Day 10)

In other words, this objective is to estimate the point prevalence of asymptomatic COVID on Day 10. If Day 10 symptoms data is missing, symptoms will be imputed from the participants' most recent completed diary entry prior to Day 10 using Last Observation Carried Forward (LOCF). The objective will be assessed using same methods as the primary efficacy endpoint. Intercurrent events prior to or on Day 10 will be counted as an asymptomatic infection on Day 10.

8.2.7. Proportion of participants with sustained resolution of COVID-19 symptoms through Day 28

Sustained symptoms resolution is defined as ≥48 hours with each symptom having an equal or lower symptom score relative to that symptom's baseline value, as described in Section 3.2.2. Time to sustained symptoms resolution is defined as the time from first COVID-19 symptom onset until the first timestamp in the period of ≥48 hours with complete resolution of COVID-19 symptoms. The proportion of participants who meet the 2 following criteria is the outcome of interest for this objective:

- Experience the primary efficacy endpoint (including due to intercurrent events b or c)
- Have a sustained resolution of the first episode of symptoms meeting the criteria for onset on or before Day 28

Participants who experience the primary efficacy endpoint will be included in the denominator, unless the only symptoms meeting criteria for onset were loss of taste or loss of smell. The

analysis will be performed using same methods as the primary efficacy endpoint. Intercurrent events after the primary endpoint is met will not be considered for this secondary endpoint.

8.2.8. Proportion of participants with sustained resolution of each COVID-19 symptom through Day 28

The proportion of participants with sustained resolution (defined as ≥48 hours with an equal or lower symptom score relative to that symptom's baseline value) of each symptom will be evaluated at Day 28. For this objective, the study day of sustained resolution will be calculated as described in Section 3.2.2, but for each of the participant-reported symptoms separately (excluding loss of taste or smell). For each symptom, the denominator will be participants who meet the primary endpoint and report onset of the specific symptom with duration >=48 hours on or prior to study Day 10. The numerator of the proportion will be the number of participants in the denominator who had a symptom-specific resolution start date prior to Day 28. Analysis of this objective will be performed using the same methods as the primary efficacy objective, except that covariates (time from index patient onset, pooled geographic region) will not be included in the model due to anticipated data sparsity. Intercurrent events occurring after the primary endpoint is met will not be considered for this endpoint.

8.2.9. Proportion of participants with sustained resolution of key COVID-19 symptoms through Day 28

For this secondary objective, the definition of sustained symptoms resolution in section 3.2.2 will be modified such that only the 5 key symptoms of COVID-19 (nasal congestion or runny nose, sore throat, cough, fever, and fatigue) are used in the calculation. Using the modified symptoms resolution definition based on the key COVID-19 symptoms only, the same analysis will be performed as described in Section 8.2.8 (i.e., the same methods will be used as for the symptoms resolution definition that is based on all symptoms except for loss of taste and smell). Only mITT or ITT participants who experience the primary endpoint will be included in this analysis; however, in addition, this analysis will be limited to the subset of participants who report at least one of the 5 key COVID-19 symptoms over a 48 hour period. In other words, participants who otherwise meet the criteria for the primary endpoint without experiencing ≥1 key symptom for 48 hours will not be included. Intercurrent events occurring after the primary endpoint is met will not be considered for this endpoint.

8.2.10. Change in total score of COVID-19 symptoms at each timepoint

This secondary endpoint is defined as the change from baseline (at onset of symptoms, defined in Section 3.2.1) in TSS at each scheduled timepoint, with TSS calculated as outlined in Section 3.2.3 The change in TSS will be summarized by treatment group by scheduled timepoint using descriptive statistics, with 95% CIs of the mean reported based on the t-distribution. Note the TSS is set to 0 prior to the onset of symptoms, even in cases where participants have a pre-existing COVID-19 symptom at screening. An analysis of covariance (ANCOVA) model will be applied to perform pairwise comparison of the change in TSS between the S-217622 and placebo groups. Randomization factors will be used as covariates in the ANCOVA model. In addition, the summary statistics will be calculated by treatment group. Intercurrent events will not be considered for this endpoint.

8.2.11. Change in total score of the five key COVID-19 symptoms at each Timepoint

This secondary endpoint is defined as the change from baseline (at onset of symptoms, defined in section 3.2.1) in TSS at each scheduled timepoint, with the TSS calculation (described in Section 3.2.3) modified to only consider the five key COVID-19 symptoms in its total. This modified Total Symptoms Score (mTSS) will range from 0 to 15. Analysis of this objective will be performed in the manner described above in section 8.2.10 for the summary of the full TSS at each timepoint. Intercurrent events will not be considered for this endpoint.

8.2.12. Time from first confirmed SARS-CoV-2 to report of ≥1 COVID-19 symptom through Day 28

This secondary endpoint is defined as the time from CLC positive RT-PCR test to time of first reporting at least 1 COVID-19 symptom at greater-than-baseline severity through Day 28. Kaplan-Meier methods will be used to analyze this objective (see Section 8.2). Because time zero will be set to the sample collection time of the participant's first positive test, only participants who test positive at least once prior to Day 28 will be included in the analysis. Events occur on the entry time for the first participant symptoms diary entry where any symptom severity is greater than the baseline level. Results at intermediate timepoints will not be presented. Event-free participants will be censored at the date and time of the last recorded symptoms diary entry up to and including Day 28. Participants with symptom onset (defined in Section 3.2.2) occurring before a CLC positive RT-PCR test will be considered as having event times of 0 for this outcome. The Kaplan-Meier estimate of proportion of PCR-positive participants with at least one symptom at Day 28, and the 95% CI, will be displayed. If a large proportion of subjects (e.g. 20% or more) have event times set to zero, a descriptive summary of time to symptoms from onset may be provided in addition or instead of the Kaplan-Meier analysis. This analysis will be performed for subjects in all geographies, but will be repeated for participants in Japan and North America separately. Intercurrent events will not be considered for this endpoint.

8.2.13. Time from first confirmed SARS-CoV-2 until COVID-19 symptoms onset through Day 28

This secondary endpoint is defined as the time from confirmation RT-PCR positive (CLC) to onset of COVID-19 symptoms (as defined in Section 3.2.2) through Day 28. Kaplan-Meier methods will be used to analyze this objective (see Section 8.2). The distinction between this secondary endpoint and the endpoint described above in section 8.2.12 is that for this analysis, the event time will occur at the first symptoms diary entry time reporting a COVID-19 symptom that persists for at least 48 hours, in concordance with the symptoms onset definition in 3.2.1. However, it is not required that symptoms onset and positive PCR tests occur within 10 study days of one another for this secondary endpoint to be met. Because Day 0 will be set to the sample collection time of the participant's first positive test, only participants who test positive at least once prior to Day 28 will be included in the analysis. Event-free participants will be censored at the date and time of the last recorded symptoms diary entry up to and including Day 28. Participants for whom symptoms onset occurred before a CLC positive RT-PCR test will be considered as having event times of 0 for this outcome. Intercurrent events will not be considered for this endpoint. The Kaplan-Meier estimate of the proportion of PCR-positive participants with symptoms onset at Day 28, and the 95% CI, will be displayed. Results at intermediate timepoints

will not be presented. The analysis will be performed for subjects in all geographies combined, but will be repeated for participants in Japan and North America separately.

8.2.14. AUC over time of the total symptom Score associated with COVID-19 from the onset of symptoms through Day 28

This secondary endpoint is defined as the AUC of total score of COVID-19 symptoms from the onset of COVID-19 symptoms, as defined in section 3.2.1, to Day 28. TSS is calculated for each symptoms diary entry as described in Section 3.2.3. AUC of the TSS will be determined using the trapezoidal rule described in Section 8.2 of this SAP. The same analyses as used for the AUC of change in Section 8.2.4 will be used to assess this endpoint as well, but note that Day 28 will be the last day of assessments of this secondary endpoint rather than Day 10. Intercurrent events will not be considered for this endpoint. Participants who do not have a Day 28 TSS will not be included in the analysis.

8.2.15. AUC over time of the daily total symptom score for the five key COVID-19 symptoms from the participant's first onset of the five key symptoms through Day 28

This secondary objective uses a modified version of the endpoint described above in section 8.2.14, where calculation of AUC is performed similarly, except instead of area under the curve of TSS over time, the curve heights are instead based on the mTSS, which is calculated similarly, but considers only the 5 key COVID-19 symptoms (see 8.2.11 for details). Other aspects of the analysis of this objective will be treated as described above in section 8.2.14.

8.2.16. Hospitalization or death from any cause through Day 28

This secondary endpoint is defined as the proportion of participants with hospitalization or death from any cause through Day 28. Hospitalization is defined as ≥ 24 hours of acute care for any reason, in a hospital or similar acute care facility, including emergency rooms or urgent care clinics. The same analyses as the primary endpoint will be performed for this endpoint, except that intercurrent events will be ignored.

8.3. Exploratory endpoints

The protocol defines twelve exploratory endpoints related to S-217622. Additional exploratory endpoints may be added by the sponsor. No type I error control methods will be used for hypothesis tests in pursuit of exploratory objectives. Intercurrent events will not be considered in analysis of exploratory endpoints.

Up to 1 participant from each household may be designated as a household survey respondent, leading to their inclusion in the Household Member Survey Analysis Set defined in Section 4.3.10. Per the schedule of assessments (see the appendix in Section 15.1), designated respondents will be prompted to report any new diagnoses of COVID-19 among nonparticipating family members on study Days 1, 3, 6, 10, 15, 21, and 28. Household survey data will be used as part of the exploratory objective outlined in Section 8.3.5. All household survey data will be presented in a listing.

While not part of a protocol-defined exploratory objective, data is also collected on study Day 1 regarding participant exposure to the index patient and again on the final visit on Day 28. This data will be presented in a listing for participants in the ITT Analysis Set. Likewise, data on index patients symptoms will be collected apart from any study objectives, and displayed in a listing for the Index Patients Analysis set.

8.3.1. Days of hospital and intensive care unit stay in participants with SARS-CoV-2-related hospitalization through Day 28

For this endpoint, hospitalizations include any episode recorded on the Hospitalization or Acute Care eCRF, according to the definitions in Sections 3.2.4 and 8.2.16, for which the investigator also indicates SARS-CoV-2 relatedness on the Hospitalization and Acute Care CRF. Days hospitalized and days in an ICU will be summarized by treatment group using descriptive statistics. Analysis will be performed in the mITT Analysis Set. A listing will be displayed for the Safety Analysis Set.

8.3.2. S-217622 antiviral activity

This endpoint is defined as a phenotypic assay (EC_{50}) of S-217622 against SARS-CoV-2 clinical isolates derived from the NP swabs from a participant's first CLC positive RT-PCR test through Day 28. Only participants treated with S-217622 will be analyzed. Antiviral assay results will be summarized with descriptive statistics by treatment group, and a listing will be presented for the mITT Analysis Set.

8.3.3. Change from baseline in EQ-5D-5L scores

The EuroQol EQ-5D-5L Questionnaire is a 5-question survey plus a visual analog scale (VAS) item that indicate a participant's overall health. Each of the 5 questions corresponds to a health domain (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression), and participants will provide an ordinal 5-level response that reflects their perceived quality of life, with higher values indicating greater disability or worse health. An EQ-5D utility index will be calculated to represent the participant's overall quality of life using index values derived from a US reference population value set, using the composite time trade-off method. Parameter estimates derived by Pickard et al. will be used to calculate participants' utility index scores based on their responses to each question in the survey. See Appendix 15.5 for a full list of coefficients and an example calculation.

EQ-5D surveys will be completed at the Days 1, 15, and 28 visits. The exploratory endpoint is defined as the EQ-5D utility index score at Day 28 minus the EQ-5D summary index score at Day 1. The EQ-5D scores at Days 1, 15, and 28, as well as the pre-post change in EQ-5D scores will be summarized with descriptive statistics and a 95% CI of the 28-day change based on the t-distribution. Results will be presented for all geographic regions combined, as well as separately for each geographic stratum. This analysis will be performed in the mITT population, but only participants who complete all 5 questions at both Day 1 and Day 28 will be included, as missing values of 28-day change in EQ-5D scores will not be imputed.

8.3.4. Proportion of participants reporting baseline-equivalent or better health at Day 28

Self-reported overall health is assessed at Days 1, 15, and 28 by the VAS included with the EQ-5D-5L. Possible VAS scores range from 0 to 100, with 100 representing perfect overall health. The number and percentage of participants reporting VAS scores on Day 28 that are greater than or equal to their VAS scores from Day 1 will be summarized by treatment group. Additionally, a descriptive summary of VAS results by study intervention and scheduled time point will be displayed. This exploratory objective with be analyzed within the mITT population, but participants with one or more missing EQ-5D-5L component scores or ≥ 1 missing VAS on the EQ-5D-5L assessment at Days 1 or 28 will not be included in the analysis.

8.3.5. Correlation between the index patient's amount of SARS-CoV-2 viral RNA and 10-day incidence of COVID-19 in participants

For this objective, the index patient's amount of (log-transformed) viral RNA will be added as an independent variable (as a fixed effect) to (1) a modified version of the model used for the analysis of the primary endpoint (see section 8.1.1) and (2) first secondary objective (see Section 8.2.1). The two endpoints for this exploratory analysis will also be the same, respectively:

- The proportion of participants who are infected with SARS-CoV-2 (CLC positive RT-PCR test) and have COVID-19 symptoms onset through Day 10
- The proportion of participants who are infected with SARS-CoV-2 regardless of occurrence of COVID-19 symptoms.

However, for this exploratory analysis, intercurrent events will not be considered. For each endpoint, the estimate for the coefficient of increasing viral RNA in the index patient at Day 1 will be presented along with the estimates by treatment and overall. Summary of results from the regression model will be performed on participants in the mITT Analysis Set.

Index patient viral RNA measures will be presented in a data listing.

8.3.6. Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the COVID-19 cases in the household among non-participants, as reported on the Household Members Questionnaire

For this analysis, the index patient's viral RNA on Day 1 will also be used as an independent variable (like in the analysis described immediately above in section 8.3.5); however, the dependent variable will COVID-19 cases from the household as reported on the Household Members Questionnaire. Survey responses on Days 3, 6, 10, 15, 21, and 28 will be analyzed. Because household survey respondents can report more than one non-participating household member with newly diagnosed COVID-19, a GEE Poisson regression model will be used, with an AR(1) covariance structure to account for correlation of results from the same Household Members Questionnaire respondent across timepoints. Time from index patient symptoms onset (< 48 hours, ≥ 48 hours) and pooled geographic region will be included as covariates. An offset term for the number of non-participating members in the household (plus 1 x 10^{-6}, to account for responses of 0) will be included initially, but may be dropped from the model in case of non-

convergence. Household cases at each timepoint will be modeled as following a Poisson distribution, and a log link function will be used. Intercurrent events will not be considered. This analysis will be performed in the Household Survey Members Analysis Set and Index Patient Analysis Set.

8.3.7. SARS-CoV-2 variant based on NP swab spike gene sequence

The investigator or designee will take an NP swab from participants according to the schedule of assessments (see Appendix 15.1) and at event-driven visits. The amount of viral RNA will be measured, and central-laboratory confirmed RT-PCR results (positive or negative) will be determined. The analysis of this endpoint will be performed by the sponsor.

8.3.8. Treatment-emergent amino acid substitutions based on NP swab NSP5 and its cleavage site gene sequence

Treatment-emergent amino acid substitutions in 3CL protease (NSP5) and its cleavage site will be summarized. The analysis of this endpoint will be performed by the sponsor.

8.3.9. Change from Baseline in GIQ

The GIQ will be administered and analyzed for participants after the participant develops a symptomatic CLC positive SARS-CoV-2 infection during the study. If the participant is told by the study staff that he/she has developed COVID-19 infection, the participant will be asked to complete a questionnaire about the participant's global impression of his/her health, activities, and severity of symptoms during the past 24 hours. The questionnaire consists of three questions and is shown in Section 15.6.

The proportion of 'Yes' responses to the first two questions (return to usual health and return to usual activities) will be summarized by treatment group and scheduled timepoint, with 95% confidence intervals calculated using the Clopper-Pearson method. Only complete responses will be counted in the denominator. For calculation of change in overall symptoms since baseline, the baseline level of symptoms will be determined as the maximum severity of all symptoms reported by the participant in the pre-dose symptoms diary entry. For each participant, the maximum severity at each timepoint will be converted to numeric values (None = 0, Mild = 1, Moderate = 2, Severe = 3) and the change from baseline will be summarized by treatment group.

8.3.10. Proportion of participants who achieve baseline or better health through Day 28 in GIQ

The proportion of participants who achieve baseline or better health through Day 28 will be based on responses to the GIQ's first question, "In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?". This will be summarized as the number of subjects with a "Yes" response the GIQ at each scheduled timepoint, divided by the number of subjects with a valid response to that question on that assessment. To provide context for the increasing time since symptoms onset at later visits, the days since symptoms onset will be summarized descriptively at each timepoint.

Only questionnaires completed after COVID-19 symptoms onset will be included. The Clopper-Pearson exact 95% confidence interval of the proportion will be reported. Summaries will be

performed by treatment group and overall, and all GIQ questionnaire data will be displayed in a listing. This analysis will be performed in the mITT analysis set.

8.3.11. Proportion of participants who are coinfected with influenza and SARS-CoV-2

A laboratory test for influenza may be collected. Analyses of the co-infection of influenza and SARS-CoV-2 will be described in a separate document by the sponsor.

8.3.12. Proportion of participants with viral RNA and/or COVID-19 symptom rebound

The aim of this exploratory objective is to assess the effect of S-217622 upon two outcomes related to COVID-19 rebound:

1. Viral RNA rebound from Day 6 Visit up to Day 28 Visit
   Viral RNA rebound will be defined as any of the following:
   - At least 1.0 $\log_{10}$ increase at any visits of Day 10, 15, 21 and 28 compared to the previous non-missing visit (i.e., Day 6 or after) at which viral RNA was detected;
   - At least LLoQ for viral rebound evaluation (=2.27 $\log_{10}$) + 1.0 $\log_{10}$ increase (i.e., $\geq$3.27 $\log_{10}$ observed) at any visits of Day 10, 15, 21 and 28 when viral RNA at the previous non-missing visit (i.e., Day 6 or after) was below LLoQ;
   - At least LoD for viral rebound evaluation (=2.27 $\log_{10}$) + 1.0 $\log_{10}$ increase (i.e., $\geq$3.27 $\log_{10}$ observed) at any visits of Day 10, 15, 21 and 28 when the previous non-missing visit (i.e., Day 6 or after) was undetected.

The endpoint will be evaluated using the data at non-missing scheduled visits on or after Day 6 (Day 6, 10, 15, 21 and 28), with scheduled visits selected according to the windowing rules outlined in section 4. If the participants have not any RT-PCR data on Day 6 or after, the participants will be excluded from the analysis. For participants with CLC-positive RT-PCR tests at baseline (Visit 1), the frequency and proportions, and Clopper-Pearson 95% confidence intervals for the proportions will be described (both overall and by planned study intervention group).
Analysis of the viral RNA rebound objective will be performed in the ITT baseline positive analysis set. As with other exploratory analyses, intercurrent events will not be considered.

1. Symptomatic rebound after the sustained resolution of COVID-19 symptoms through Day 28
   Symptomatic rebound after the sustained resolution of COVID-19 symptoms will be defined as meeting all of the bullet points: The sustained resolution of COVID-19 symptoms through Day 28 (see section 8.2.7) is achieved;
   - ♦ After the sustained resolution of COVID-19 symptoms through Day 28, there is at least one new or reoccurring symptom (except for loss of smell/loss of taste) with moderate or severe symptom score AND the symptom persists 48 hours or more;
   - ♦ However, for pre-existing symptoms, the following rule will be applied :
     i. In the case of the pre-existing symptom with none or mild score at baseline, the symptom should become moderate and that persists 48 hours or more

ii. In the case of the pre-existing symptom with moderate score at baseline, the symptom should become severe and that persists 48 hours or more
iii. In the case of the pre-existing symptom with severe score at baseline, the symptom should not be used in the evaluation of the symptomatic rebound

The symptomatic rebound endpoint will be evaluated using the diary data after the sustained resolution of COVID-19 symptoms through Day 28. Participants who meet the primary endpoint and sustained resolution of COVID-19 symptoms through Day 28, frequency and proportion, and its corresponding Clopper-Pearson 95% confidence interval will be described overall and by planned study intervention group.

Analysis of the COVID-19 symptoms rebound endpoint will be analyzed in both the ITT and mITT analysis sets. As with other exploratory analyses, intercurrent events will not be considered.

9. SAFETY ANALYSIS

All summaries of safety data will be done in the Safety analysis population. Participants will be analyzed by study intervention group according to the first treatment they actually received.

9.1. Adverse events

An adverse event (AE) is any untoward medical occurrence in a clinical participant, after the participant has signed the informed consent, whether or not considered related to the study intervention. Note that an AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) after the participant has signed the informed consent and through end of study or early termination.

AEs may or may not be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a healthcare provider). The participants or participant's parent(s)/legally authorized representatives will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of the participant/participant's parent(s)/LAR(s) concern. Detailed information about reported AEs will be collected by qualified site personnel and documented in the participant's records. Examples of events meeting and not meeting the definition of an AE are provided in Section 10.3.1 of the protocol.

All information relevant to AEs and SAEs (see Section 9.1.1) will be reviewed by investigators and recorded in the respective eCRF's. Investigators will assign a diagnosis based on clinical presentation, and that will be documented as the AE/SAE. Events will be classified by SOC and PT and coded according to the MedDRA dictionary version 26.0 or higher. Adverse events reported on the AE or SAE eCRFs that occur after the first dose of study intervention and through end of study or early termination are considered treatment-emergent adverse events (TEAEs), and will be used for safety analyses.

Time to sustained resolution of symptoms, as defined in the protocol, will be reported by treatment as part of the safety analysis.

9.1.1. Incidence of treatment-emergent adverse events

AEs are reported by investigators on the Adverse Event or Serious Adverse Event eCRFs. Adverse events that occur after the first dose of study intervention and through end of study or early termination are considered TEAEs. Incidence of TEAEs will be presented by treatment group (S-217622 or placebo) and summarized as the total number of TEAEs, the number and percentage of participants with at least 1 TEAE, and the number and percentage of participants with at least 1 TEAE by SOC and PT. Statistical uncertainty around percentages of participants with TEAEs will be described using exact Clopper-Pearson 95% CIs. Participants will only count once at each level of summarization (overall, SOC, PT), but all TEAEs will be included in the total event count.

In addition, summaries by treatment group will be presented for the following subsets of TEAEs:

- TEAEs related to the study drug (see Section 9.1.2)
- Severe TEAEs (see Section 9.1.3)
- Serious Adverse Events (see Section 9.1.3)
- TEAEs leading to study intervention discontinuation (see Section 9.1.5)

An overall summarization by treatment group will display number and percentage of participants with serious TEAEs, study intervention-related TEAEs, serious study intervention-related TEAEs, and TEAEs leading to discontinuation of the study intervention. The number and percentage of participants with TEAEs will also be summarized according to outcome and by time from onset (i.e., by study day from Days 1 to 28). All AEs (treatment-emergent or otherwise) will be presented in a data listing.

9.1.2. Relationship of adverse events to study drug

TEAEs that are assessed as "related" to S-217622 will be considered as adverse drug reactions, and summarized in the same manner as for all TEAEs as described in Section 9.1.1. For tables of TEAEs considered related to S-217622, missing relatedness will be counted with related events. Relationship to S-217622, including missing relatedness, will be displayed in the data listing as captured on the AE or SAE eCRF.

9.1.3. Severity of adverse events

AE severity will be assessed according to the Division of AIDS (DAIDS) AE Grading Table (see Appendix 15.3 for additional detail). For each reported AE or SAE, investigators will assign a severity grading of Grade 1 (for mild events), Grade 2 (for moderate intensity events), Grade 3 (for severe events), or Grade 4 (for potentially life-threatening events). "Severe" TEAEs are therefore inclusive of both Grade 3 and 4 events. Note that AEs related to abnormal (or worsening) lipid levels will be graded according to the DAIDS grading table, even though participants are not required to be fasting at the time of sample collection. Also, AEs related to abnormal (or worsening) renal function will be assessed according to the DAIDS grading table using only the creatinine clearance and estimated GFR (i.e., ignoring percentage change from baseline and absolute creatinine).

Missing severity will not be imputed for TEAEs.

The severity of TEAEs will be described by SOC and PT according to study intervention. Severity of all AEs will be displayed in a data listing.

9.1.4. Serious adverse events

Serious Adverse Events (SAEs) are a subset of AEs that meet at least 1 of the following standard criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other situations considered serious according to the investigator's medical or scientific judgment (e.g. invasive cancer, intensive treatment for allergic bronchospasm, blood dyscrasia, development of drug dependency)

Note that SAEs are recorded on a separate CRF vs. nonserious AEs. However, analysis of SAEs will be performed in a similar manner to what is described for all TEAEs in Section 9.1.1. Incidence of SAEs will be summarized via the total number of treatment-emergent SAEs (or, equivalently, serious TEAEs), the number and percentage of participants with at least 1 treatment-emergent SAE, and the number and percentage of participants with at least 1 treatment-emergent SAE by SOC and PT. Statistical uncertainty around percentages of participants with treatment-emergent SAEs will be described using exact Clopper-Pearson 95% CIs. Participants will only count once toward each level of summary (subject, SOC, PT). All SAEs (treatment-emergent or otherwise) will be presented in a data listing.

9.1.5. Adverse events leading to study intervention discontinuation

A summary of TEAEs leading to discontinuation of the study intervention will be displayed by SOC and PT. All AEs leading to discontinuation of treatment will be presented in a data listing.

9.1.6. Death

A data listing will display all TEAEs with an outcome of death. The listing will include details such as autopsy status, death certificate availability, cause of death, and whether the event was related to a study procedure.

9.1.7. Liver events

Liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology. Any of the following events based on the blood chemistry panel (see Section 9.2.2) will meet the predefined stopping criteria:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 5× upper limit of normal (ULN)
- ALT or AST ≥ 3×ULN for 4 or more weeks
- ALT or AST ≥ 3×ULN and bilirubin ≥ 2*ULN (> 35% direct bilirubin)
- ALT or AST ≥ 3×ULN and international normalized ratio (INR) > 1.5, if INR obtained
- ALT or AST ≥ 3×ULN and the participant cannot be monitored weekly for 4 weeks

- ALT or AST ≥ 3×ULN with symptoms (new or worsening) believed to be related to worsening liver injury or hypersensitivity.

Further detail on liver event criteria, actions, and suggested follow-up is available in Appendix 5 of the protocol.

Any observed liver events, associated findings and actions, and clinical narratives (as recorded on eCRF) will be displayed in a data listing.

9.2. Clinical laboratory evaluations

Scheduled clinical laboratory assessments are performed on samples collected at Days 1, 6, and 15 visits, and unscheduled assessments will be performed on samples collected from unscheduled visits. Protocol-specified laboratory assessments will be analyzed at a central laboratory. Clinical lab results include hematology, serum chemistry, and coagulation parameters, as well as baseline serology test parameters If applicable, results will be graded at the laboratory according to DAIDS criteria.

Abnormal laboratory test results are defined as values outside the reference range. Any test results that are considered to be clinically significant by the investigator will be recorded as AEs. Abnormalities are considered Newly Notable if the participant did not meet the abnormality criteria at Screening.

Laboratory test values and (where applicable) changes from Screening/Day 1 will be summarized by scheduled visit and treatment group using descriptive statistics. In addition, the qualitative change in graded values at each visit from baseline will be summarized by treatment group in shift tables. Hematology, blood chemistry, coagulation, serology, and pregnancy testing data will be presented in data listings.

9.2.1. Hematology

The following hematology assessments will be performed:

- Platelet count (10^9/L)
- Red blood cell count (10^{12}/L)
- Hemoglobin (g/L)
- Hematocrit (L/L)
- Red blood cell index
    - Mean corpuscular volume (fL)
    - Mean corpuscular hemoglobin (pg)
    - Reticulocyte count (%)
- White blood cell count (10^9/L)
- Differential white blood count (10^9/L for all)
    - Neutrophils
    - Lymphocytes
    - Monocytes
    - Eosinophils
    - Basophils

Results from hematology testing will be presented as described in Section 9.2.

9.2.2. Blood chemistry

Protocol-required blood chemistry assessments include:

- CRP (nmol/L)
- Ferritin (mcg/L)
- Glucose (mmol/L)
- Nonfasting lipid profile
    - HDL-C (mmol/L)
    - LDL-C (mmol/L)
    - Triglycerides (mmol/L)
- Liver function tests
    - ALT (U/L)
    - AST (U/L)
    - ALP (U/L)
    - Total bilirubin (mcmol/L)
    - Direct bilirubin (mcmol/L)
    - Albumin (g/L)
    - Total protein (g/L)
- Renal function tests
    - BUN (mmol/L)
    - Creatinine (mcmol/L)
    - Potassium (mmol/L)
    - Sodium (mmol/L)
    - CrCl (calculated; mL/min)
- Chloride (mmol/L)
- Calcium (mmol/L)
- Phosphorus (mmol/L)

Lab values will be assessed according to the DAIDS AE Grading Table, corrected Version 2.1, July 2017. However, the following exceptions are noted:

- lipids will be conducted as non-fasting.
- Renal function will be graded according to DAIDS Grading Table, but only using CrCl or estimated glomerular filtration rate.
- Absolute creatinine and percentage change from baseline will not be used to grade renal AEs in this protocol.

See Section 9.2 for details on how blood chemistry test results will be summarized. Note that, per the protocol, sites will be blinded to HDL-C levels.

9.2.3. Coagulation

The coagulation parameters prothrombin time (seconds), APTT (seconds), fibrinogen (g/L), and PT-INR will be tested at visits per the Schedule of Assessments. Refer to Section 9.2 for further details on summarization of coagulation parameters.

9.2.4. Serology

Anti-SARS-CoV-2 spike (S) and nucleocapsid (N) antibody serology testing will be performed in participants at the Day 1 screening visit. Counts and percentages of participants with S- and N-antibody results above the lower limit of detection at Day 1/Screening will be summarized in a table. Screening visit serology results will also be summarized by median, min, max, and geometric mean, and will be presented in a data listing.

9.2.5. Serum or urine pregnancy testing

Pregnancy is an exclusion criterion for the study, and urine pregnancy tests will be performed for participants who are women of childbearing potential at screening. Additionally, urine or serum pregnancy tests may be administered at the Day 28 visit. Urine and serum pregnancy test results will be displayed in a data listing.

9.3. Vital sign measurements

Vital signs (pulse rate, systolic and diastolic blood pressure, respiratory rate, and resting peripheral oxygen saturation) will be assessed at the Day 1 visit and at symptom-focused physical exams (see Section 9.4) per protocol. Temperature will be measured by the site staff at Screening.

Depending on how temperature is measured, fever is defined as:
≥ 38.0° C per tympanic or rectal thermometer
≥ 37.5° C per axillary, oral or forehead/temporal thermometer

Observed values and change from baseline will be summarized by treatment group at time points at which vital signs data are collected (including baseline). Vital sign data listings will be provided for both data collected at in-person visits, as well as for participant assessments of temperature recorded in diaries.

9.4. Physical examinations

Full physical examinations, including body weight, will be performed at Screening and at the Day 28 scheduled visit. Height will be collected at the Day 1 scheduled visit only. In addition, symptom-focused physical examinations will be performed at study Days 3, 6, 10, and as needed as a consequence of clinical events. The symptom-focused physical examination includes vital sign measurements (pulse rate, systolic and diastolic blood pressure, respiratory rate, and resting peripheral oxygen saturation), as well as [at a minimum) assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems, and examinations driven by any previously identified or new AE/targeted condition that the participant has experienced and as deemed necessary by the investigator. Frequency and proportions of abnormal and or clinically significant physical examination findings will be summarized by body system and treatment group for full physical examinations at Screening Day 1 and Day 28 scheduled visits. A similar summarization of symptom focused physical examination findings will be presented for visits within the Day 3, Day 6, and Day 10 visit windows. All physical examination data will be presented in a data listing.

9.5. Special situations

A special situations report is required for four issues related to the study intervention:

- Abuse (intentional excessive use of a study intervention, accompanied by harmful physical or psychological effects)
- Misuse (intentional and inappropriate use of the study intervention other than as directed)
- Overdose (intake of study intervention in excess of the assigned dose)
- Medication Errors (unintended errors in the prescribing, dispensing, or administration of the study intervention)

An event requiring a special situations report may meet more than 1 definition. Data captured on the Special Situations eCRF will be presented in a listing.

10. PHARMACOKINETICS

Planned Pharmacokinetics (PK) analyses include describing the endpoint for the PK-related secondary objective (to confirm the pharmacokinetics of S-217622 in participants following multiple doses of S-217622 for 5 days). The plasma concentrations of S-217622 will be listed by participant and visit along with the time elapsed from the last dosing of study intervention prior to blood sampling plasma concentration data. Plasma concentrations of S-217622 within 20 to 28 hours after the previous dose on Day 2 and prior to dose on Day 3 will be summarized as plasma trough concentrations (C_{trough}) based on the Section 9.3.4 of the protocol. In addition, the time elapsed from the previous dose and the plasma S-217622 concentration will be graphically presented in a scatter plot.

For summary of C_{trough}, plasma concentration below limit of quantification will be treated as zero (0) for calculations of mean, standard deviation, CV%, median, minimum, and maximum and treated as missing for calculation of geometric mean and CV% Geometric Mean.

The PK parameter (C_{trough}) will be presented same precision as per the observed values.

Descriptive statistics will be presented as follows:

- N: no decimal place
- Mean, geometric mean, standard deviation, median, minimum, and maximum: same precision as per each concentration or PK parameter in the listing.
- CV% and CV% Geometric Mean: one decimal place

After plasma concentration measurement, the data that the person in charge of PK analysis at the sponsor can clearly explain as inappropriate for analysis will be excluded. The reason for any exclusion should be described in the clinical study report (CSR).

If possible, population PK analysis will be performed using nonlinear mixed effect model (NONMEM version 7.4 or higher). When the population PK analysis is performed, the analysis plan and its report will be prepared separately from the CSR. Exploration of relationships between exposures of S-217622 and laboratory markers and/or clinical outcomes may be

approached using conventional and accepted methods for PK/PD data analyses. When these analyses are performed, the analysis plan and its report will be prepared separately.

11. PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

12. INTERIM ANALYSIS

There are no interim analyses planned for this study.

13. CHANGES IN THE PLANNED ANALYSIS

- The geographic region randomization stratification factor will have lower-enrolling regions combined when used as a covariate in Generalized Estimating Equation models for purposes of obtaining convergence, and is referred to as pooled geographic region.
- The GEE model used for all subgroup analyses will not contain covariates for time from index patient onset and pooled geographic region, for consistency between subgroup analyses.
- This SAP introduces an additional restriction to the mITT analysis population not stated in protocol v5: all mITT participants must receive at least one dose of study treatment.
- The analyses performed in the per-protocol population will use actual rather than planned treatment groups (section 4.3.6).
- For participants who take investigational product from more than one kit, the assignment of their actual treatment group will be ‘S-217622’ if any of the kits contained S-217622 (section 4.3.7).
- The ITT baseline positive analysis set, used for supplemental analyses of the primary endpoint, is not found in the protocol, and has been defined in this SAP.
- Per the protocol, missing data will not be imputed. This SAP introduces caveats to the rule in Section 8.1 to allow for:
  - Implementation of the intercurrent events strategy in the case of hospitalizations and all-cause death related to SARS-CoV-2.
  - Prior and concomitant medications now use imputation in order to categorize medications into the respective categories.
  - Participants missing Day 1 symptoms diary data may have baseline symptom(s) imputed as 0.
  - Participants missing symptoms diary data on Day 10 will have a Day 10 entry imputed from their most recent non-missing diary entry prior to Day 10.
- Baseline diary is now derived using first records prior to dosing. See Section 3.2.1 for details.
- Section 9.3.2.2 of the protocol states that the log-rank test in the Kaplan-Meier analyses used for secondary objectives will be stratified by geographic region. However, section 8.2 of this SAP has clarified that Kaplan-Meier analyses will be stratified by the time from index patient symptoms randomization factor, but pooled across geographic region to reduce the number of analytical strata. It is noted that analyses will be repeated within the Japan and North America geographic regions to allow for reporting within those particular strata.

14. REFERENCES

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15. APPENDICES

15.1. Schedule of study procedures – participants

	Screening		Study Intervention Period				Follow-up Period					Event Driven[a]
Day	**1**		**2**	**3**	**4**	**5**	**6**	**10**	**15**	**21**	**28**	**1 to 28**
Acceptable time window (days)				**+ 2**			**+ 2**	**± 1**	**± 2**	**± 3**	**± 3**	**+ 3**
Visit	**1 Randomization Before**	**After**		**2**			**3**	**4**	**5**	**6**	**7 (Discontinuation)**	
Procedure												
Informed consent/assent[b]	X											
Inclusion and exclusion criteria	X											
Demographics	X											
Medical history including prior medications and therapies	X											
Urine pregnancy test	X										X	
Full physical examination	X[c]										X	
Symptom-focused physical examination[d]				X			X	X	X			X
Vital signs[e]	X			X			X	X	X		X	X
Staff-collected body temperature	X											
Staff-collected NP swabs (central laboratory virology test)		X[f]		X			X	X	X	X	X	X
Diagnostic testing for SARS-CoV-2 (site local test)[g]	X											X
Laboratory assessments[h]	X						X		X		X	X
SARS-CoV-2 serology test[i]	X											
Blood sampling for drug concentration measurement				X			X					X
EQ-5D-5L		X							X		X	

	Screening		Study Intervention Period				Follow-up Period					Event Driven[a]
Day	**1**		**2**	**3**	**4**	**5**	**6**	**10**	**15**	**21**	**28**	**1 to 28**
Acceptable time window (days)				**+ 2**			**+ 2**	**± 1**	**± 2**	**± 3**	**± 3**	**+ 3**
Visit	**1 Randomization**			**2**			**3**	**4**	**5**	**6**	**7 (Discontinuation)**	
	Before	**After**										
Procedure												
Participant Exposure Questionnaire[j]		X							X			
Household Members of Participant Questionnaire		X		X			X	X	X	X	X	
Participant COVID-19 symptoms diary[k]		← Twice daily (Days 1 to 28) →										
Participant COVID-19 symptoms diary review by site		←									→	
Global Impression Questionnaire[l]		← Once daily (Days 1 to 28) →										
Adverse event review	←										→	
Concomitant medication review		←									→	
Special situations (abuse, misuse, overdose, or medication error of the study intervention)		←									→	
Randomization[m]	X											
Study kit dispensed		X										
Study intervention administration[n]		X	X	X	X	X						
Study intervention compliance				X			X					
Study intervention retrieval							X					

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; COVID-19 = coronavirus disease 2019; CrCl = creatinine clearance; CRP = C-reactive protein; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NP = nasopharyngeal; PT-INR = prothrombin time-international normalized ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = resting peripheral oxygen

a The investigator will initiate an Event-driven Visit if deemed clinically needed or if in the event of COVID-19 symptoms onset as the occurrence (or worsening in the case of preexisting COVID-19-like symptoms) of ≥ 1 of the 14 specified COVID-19 symptoms for at least 48 hours. The 14 specified COVID-19 symptoms are (1) fever (defined as body temperature ≥ 38.0°C per tympanic or rectal thermometer or ≥ 37.5°C per axillary, oral, or forehead/temporal thermometer; see Section 8.2.3) (2) shortness of breath or difficulty breathing, (3) cough, (4) sore throat, (5) nasal congestion or runny nose, (6) chills, (7) fatigue, (8) body or muscle pain or aches, (9) headache, (10) nausea, (11) vomiting, (12) diarrhea, (13) change in sense of taste, and (14) change in sense of smell.

If an Event-driven Visit occurs within the allowable timeframe for Days 3, 6, 10, 15, 21, or 28, the specified assessments on Days 3, 6, 10, 15, 21, or 28 can be performed at the same visit. A study participant can have multiple Event-driven Visits if COVID-19 symptom onset definition is met multiple times.

After the initial Event-driven Visit, additional Event-driven Visits will be triggered if new symptom(s) meet the criteria of symptom onset definition after all other COVID-19 symptoms resolved (based on the symptoms resolution definition in the study protocol).

b Informed consent/assent from the participant must be provided ≤ 72 hours from onset of COVID-19 symptoms (see Appendix 6 [Section 10.6]) in the index patient and ≤ 1 calendar day from the time that the index patient provides consent.

c Height and weight will be measured only at the Screening Visit.

d The symptom-focused physical examination is driven by any previously identified or new adverse event/targeted condition that the participant has experienced and as deemed necessary by the investigator.

e Collection of vital signs should be preceded by at least 5 minutes of rest and include pulse rate, systolic and diastolic blood pressure, respiratory rate, and resting SpO_2.

f Staff-collected NP swabs for Day 1 (Screening Visit) should be performed before the administration of the first dose of study intervention.

g For study participants with negative home rapid antigen diagnostic test, additional confirmation is needed with additional direct SARS-CoV-2 viral testing such as a nucleic acid amplification test or antigen test at the site.

h Hematology: complete blood cell count with automated differential and platelet count (platelet count, red blood cell count, hemoglobin, hematocrit, red blood cell index [mean corpuscular volume, mean corpuscular hemoglobin, reticulocyte count], white blood cell count, differential white blood cell count [neutrophils, lymphocytes, monocytes, eosinophils, basophils]); blood chemistry: CRP, ferritin, glucose, non-fasting lipid profile (HDL-C, LDL-C, triglycerides), liver function tests (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, total protein), renal function tests (BUN, creatinine, potassium, sodium, CrCl will be calculated, chloride, calcium, and phosphorus); and coagulation tests (PT-INR, APTT, fibrinogen). After reviewing the study participant medical history, the investigator can enroll the study participant and start the study intervention prior to receiving the safety laboratory results from the central laboratory.

i SARS-CoV-2 serology testing will include anti-SARS-CoV-2 S-protein antibody and anti-SARS-CoV-2 N-protein antibody.

j Participant Exposure Questionnaire will include questions about his/her method of infection prevention and frequency of contact with the index patient.

k Participant will collect COVID-19 symptoms (including body temperature) twice daily from Days 1 to 28. The Day 1 COVID-19 symptoms will be collected after randomization and during the evening.

l Global Impression Questionnaire will be administered **only** if the participant develops SARS-CoV-2 infection during the study.

m Participant must be randomized ≤ 72 hours from onset of COVID-19 symptoms (see Appendix 6 [Section 10.6]) in the index patient.

15.2. Schedule of study procedures – index patients

	Screening Visit 1, Day 1	Optional Visit Visit 2, Day 3
Acceptable time window (days)		+2
Procedure		
Informed consent/assent	X	
Inclusion and exclusion criteria	X	
Demographics	X	
Staff-collected body temperature	X	
Diagnostic testing for SARS-CoV-2 (site local test)[a, b]	X	
Staff-collected NP swabs (central laboratory virology test)	X	X
Index patient COVID-19 symptom questionnaire[c]	X	X

COVID-19 = coronavirus disease 2019; ICF = informed consent form; NP = nasopharyngeal; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

a Must be from a sample collected ≤ 72 hours prior to randomization of the participant. Any documentation of positive SARS-CoV-2 viral testing (such as nucleic acid amplification test or antigen test) from a sample collected within 72 hours from the index patient ICF signature time is acceptable.

b For index patients with positive home rapid antigen diagnostic test, additional confirmation is needed with additional direct SARS-CoV-2 viral testing such as a nucleic acid amplification test or antigen test.

c If the index patient is a minor, the legally authorized representative, parent(s), or legal guardian may need to help with completion of the questionnaire.

15.3. Division of AIDS grading table

Severity of AEs will be recorded and graded as follows:

- Grade 1: (Mild) clinical AE defined as mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated will continue with study participation.
- Grade 2: (Moderate) clinical AE defined as moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated will continue with study participation if interventions are not contraindicated and the investigator and medical monitor agree to continue.
- Grade 3: (Severe) clinical AEs defined as severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated will discontinue study drug administration and continue with study follow-up assessments.
- Grade 4: (Potentially Life-Threatening) clinical AEs are defined as potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability; and will discontinue study participation.

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

15.4. Intercurrent events

Label	Intercurrent Event Type
IcEv1 (Treatment Discontinuation)	Withdrawal of study intervention due to use of rescue or prohibited medication before occurrence of the event for the primary endpoint
IcEv2 (Hospitalization or Death)	Death or hospitalization from any cause before occurrence of the event for the primary endpoint
IcEv3 (Withdrawal from Study)	Withdrawal from the study before occurrence of the event for the primary endpoint

15.5. EQ-5D utility index coefficients (composite time trade-off) for US reference population

Dimension/level	Model 1: cTTO (Tobit with heteroscedasticity, censored at −1, RE) (preferred model)		
	Estimate	SE	*P* value
MO2	−0.096	0.015	<.0001
MO3	−0.122	0.016	<.0001
MO4	−0.237	0.018	<.0001
MO5	−0.322	0.016	<.0001
SC2	−0.089	0.014	<.0001
SC3	−0.107	0.017	<.0001
SC4	−0.220	0.018	<.0001
SC5	−0.261	0.016	<.0001
UA2	−0.068	0.015	<.0001
UA3	−0.101	0.016	<.0001
UA4	−0.255	0.013	<.0001
UA5	−0.255	0.013	<.0001
PD2	−0.060	0.013	<.0001
PD3	−0.098	0.017	<.0001
PD4	−0.318	0.015	<.0001
PD5	−0.414	0.017	<.0001
AD2	−0.057	0.014	<.0001
AD3	−0.123	0.018	<.0001
AD4	−0.299	0.016	<.0001
AD5	−0.321	0.015	<.0001

Example: A participant indicates they have “slight problems” with mobility, “no problems” with self-care, “some/moderate problems” with usual activities, “extreme pain or discomfort”, and are “severely anxious or depressed”. This corresponds to a health state of 21354, and an overall utility index score of 1 – (MO2 + SC1 + UA3 + PD5 + AD4) = 1 – (0.096 + 0 +0.101 +0.414 +0.299) = 0.090. Note that coefficients are equal to zero for level 1 (least affected) responses in all domains.

Source: “United States Valuation of EQ-5D-5L Health States Using an International Protocol” (Pickard et al., 2019).

15.6. Global impression questionnaire

The Global Impression Questionnaire will be administered only if the participant develops SARS-CoV-2 infection during the study. If the participant is told by the study staff that he/she has developed COVID-19 infection, the participant will be asked to complete the following questions:

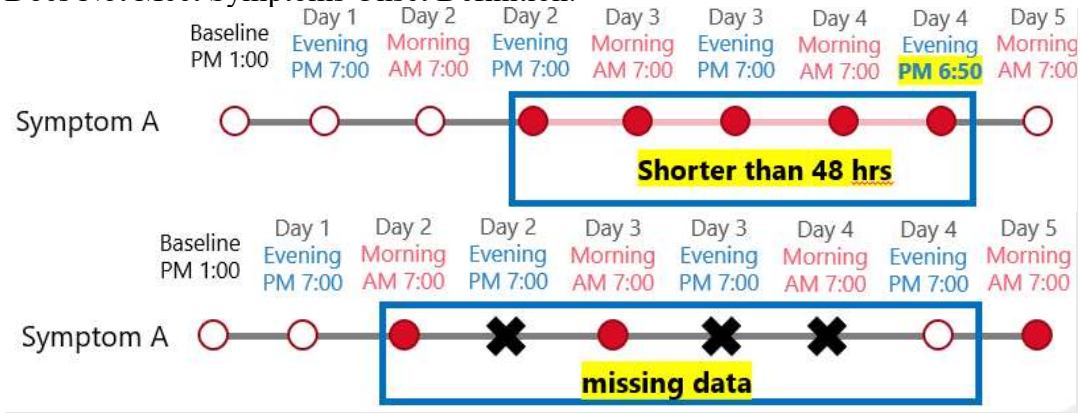
- In the past 24 hours, have you returned to your usual health (before your COVID 19 illness)? (Yes/No)
- In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)? (Yes/No)
- In the past 24 hours, what was the severity of your overall COVID-19-related symptoms at their worst? (None, Mild, Moderate, or Severe)

15.7. Symptoms onset illustrations

Meets Symptoms Onset Definition:



Does Not Meet Symptoms Onset Definition:



DocuSign

Certificate Of Completion

Envelope Id: 5078A7BA17F044D4B7062A657E8FE429
Status: Completed
Subject: Complete with Docusign: Shionogi 2206T1331 SAP v3.0.pdf
Source Envelope:
Document Pages: 68
Signatures: 3
Envelope Originator:
Certificate Pages: 3
Initials: 0
[redacted]
AutoNav: Enabled
[redacted]
EnvelopeId Stamping: Disabled
[redacted]
Time Zone: (UTC) Monrovia, Reykjavik
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
16 October 2024 | 02:09
Holder: [redacted]
[redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] x Security Level: Email, Account Authentication (Required), Login with SSO	[redacted] Signature Adoption: Pre-selected Style Signature ID: A0E0EEF8-59C1-463F-A170-FE97A65E84BA Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 16 October 2024 | 02:22 Viewed: 16 October 2024 | 02:36 Signed: 16 October 2024 | 02:47
Electronic Record and Signature Disclosure: Accepted: 16 October 2024 | 02:36 ID: 8c5b0a6e-271b-49d8-a764-d47e838193be		
[redacted] Shionogi SBV Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 08B07949-1B22-4AC1-BCDC-225B208D2E87 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 16 October 2024 | 02:47 Viewed: 16 October 2024 | 07:47 Signed: 16 October 2024 | 07:48
Electronic Record and Signature Disclosure: Accepted: 16 October 2024 | 07:47 ID: 083c0a71-dd04-4ac2-aeaf-44f3059b7b35		

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Drawn on Device Signature ID: EE93108E-B537-40EE-9785-0B7D9472FBC9 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 16 October 2024 | 07:48 Viewed: 16 October 2024 | 12:31 Signed: 16 October 2024 | 12:33
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
[redacted] Security Level: Email, Account Authentication (Required)	COPIED	Sent: 16 October 2024 | 12:33
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Security Level: Email, Account Authentication (Required)	COPIED	Sent: 16 October 2024 | 12:33
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	16 October 2024 | 02:22
Certified Delivered	Security Checked	16 October 2024 | 12:31
Signing Complete	Security Checked	16 October 2024 | 12:33
Completed	Security Checked	16 October 2024 | 12:33
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

[redacted] has established a corporate policy regarding the appropriate use of electronic records and electronic signatures, POL-00392, Appropriate Use of Electronic Records and Electronic Signatures