CLINICAL STUDY PROTOCOL

Study Title:	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
Protocol Number:	2206T1331
Amendment Number:	Version 5, Amendment 4
Compound:	S-217622
Brief Title:	Phase 3 study of S-217622 in prevention of symptomatic SARS-CoV-2 infection
Study Phase:	3
Acronym:	SCORPIO-PEP
Sponsor Name:	SHIONOGI*
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Regulatory Agency Identifying Number(s):	2022-002898-28 (EudraCT) 2023-503200-91-00 (EU-CTR number)
Issue Date:	08 Jul 2024

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 5 (Amendment 4)	08 Jul 2024
Version 4 (Amendment 3)	03 Nov 2023
Version 3.1 (Amendment 2.1 - EU)	30 Oct 2023
Version 3 (Amendment 2)	19 Apr 2023
Version 2 (Amendment 1)	28 Oct 2022
Version 1 (Original Protocol)	25 Aug 2022

Version 5 (Amendment 4): (08 Jul 2024)

Overall Rationale for the Amendment:

The primary purpose of this protocol amendment is to clarify that the sample size may vary from the original estimate. As per the original protocol, the sample size was to be determined based on the targeted number of events (92 events) and was permitted to be adjusted to ensure the targeted number of events was achieved. The wording in the prior versions of the protocol was not clear regarding this, and the text was revised accordingly.

A high-level description of the primary change and additional changes and brief rationale are outlined in the following table. Minor editorial changes such as word changes, consistency additions, or formatting revisions are not summarized.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 4.1 Overall Design, 9.5 Sample Size Determination	Clarified that the sample size may vary from the original estimate based on the targeted number of events	Clarification
Table 1-1, Table 3-1, and 9.3.2.3 Exploratory Endpoints	Modified exploratory endpoint to focus on index patient's amount of viral RNA rather than the index patient's symptoms	Revised/changed exploratory endpoint
Table 1-1, Table 3-1, and 9.3.2.3 Exploratory Endpoints	Modified exploratory endpoint to be more specific for participants who have viral RNA rebound from Day 6 up to Day 28 and COVID-19 symptomatic rebound after the sustained resolution of COVID-19 through Day 28	Clarification

Section # and Name	Description of Change	Brief Rationale
Table 1-1, Table 3-1, 8.1.1 Nasopharyngeal Swabs (Virology Test), 8.10.3 Treatment-emergent Amino Acid Substitutions in 3CL Protease (Nonstructural Protein 5) and Its Cleavage Site, 8.10.4 Antiviral Activity Against SARS-CoV-2 Clinical Isolates, 9.3.2.3 Exploratory Endpoints	Clarified that NSP5 also includes its cleavage site	Clarification
2.3.1 Risk Assessment	For the clinical safety data, updated with current clinical data	Updated clinical data with the current version of the Investigator's Brochure (Edition 07, issued 28 Jun 2024)
	For the postmarketing data, updated with risk of anaphylactic shock	Updated postmarketing data with current version of the Investigator's Brochure (Edition 07, issued 28 Jun 2024)
5.2 Exclusion Criteria	Criterion 15: added exclusion that participants cannot live in a household with ≥ 10 people	Added exclusion criterion to limit large number from same household
8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting, 10.3.1 Definition of AE	Deleted reference and text related to solicited and unsolicited AEs	Clarification on the AEs collected in the study
9.2 Analysis Sets	Clarified that mITT definition includes participants who are associated with index patients who meet the inclusion criteria	Updated for consistency with the SAP
10.3.1 Definition of AE	Clarified that clinically significant screening assessments at baseline should be recorded on the Medical History/Current Medical Conditions sections of the eCRF not the AE section	Clarification

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1. PROTOCOL SUMMARY

1.1 Synopsis

Study Title:

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

Protocol Number: 2206T1331

Compound: S-217622

Brief Title: Phase 3 study of S-217622 in prevention of symptomatic SARS-CoV-2 infection

Rationale:

S-217622 is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 3C-like (3CL) protease inhibitor demonstrating antiviral activity at nanomolar concentrations that is being developed as a treatment for SARS-CoV-2 infection. This directly-acting antiviral has undergone preclinical and clinical testing. The current study is being conducted to assess the prevention of symptomatic SARS-CoV-2 infection in household contacts of an individual with symptomatic coronavirus disease 2019 (COVID-19).

Objectives and Endpoints:

The objectives and endpoints for this study are shown in Table 1-1.

Table 1-1 Objectives and Endpoints

Objective	Endpoint
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 (hereinafter referred to as "participants") of SARS-CoV-2-infected patients (hereinafter referred to as "index patients") through Day 10 (using the mITT population)	• Proportion of participants in the mITT population 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[a] through Day 10
Key secondary	
• 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 index patients through Day 10 (using the ITT population)	• Proportion of participants in the ITT population with a negative screening SARS-CoV-2 infection (local laboratory-confirmed negative test) who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have COVID-19 symptoms onset[a] through Day 10

Objective	Endpoint
Secondary	
• To compare S-217622 with placebo in the prevention of SARS-CoV-2 infection in participants (defined as central laboratory-confirmed positive RT-PCR test)	• Proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) through Days 10, 15, 21, or 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 central laboratory-confirmed positive RT-PCR result • Proportion of participants with central laboratory-confirmed positive RT-PCR result at each timepoint • 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 (central laboratory-confirmed positive RT-PCR test) for SARS-CoV-2 through Day 10	• Proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have no COVID-19 symptoms onset[a] through Day 10 • Proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have no COVID-19 symptoms through Day 10 • Proportion of participants with sustained resolution[b] 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[b] of each COVID-19 symptom through Day 28 • Change in total[c] score of COVID-19 symptoms at each timepoint • Change in total score of the 5 key COVID-19 symptoms at each timepoint • Time from first confirmed SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) until at least 1 COVID-19 symptom through Day 28 • Time from first confirmed SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) until COVID-19 symptoms onset[a] through Day 28

Objective	Endpoint
	• AUC of the daily total[c] symptom score associated with COVID-19 over time from COVID-19 symptoms onset[a] through Day 28 • AUC of the daily total symptom score for the 5 key COVID-19 symptoms over time from onset[a] 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 (central laboratory-confirmed positive RT-PCR test) during the study	• Proportion of participants with hospitalization[d] 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 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 the index patient's amount of viral RNA and the participant's positive central laboratory-confirmed RT-PCR test	• Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the central laboratory-confirmed positive RT-PCR reported cases in the household
• 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	• Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the incidence of SARS-CoV-2 ill case 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

Objective	Endpoint
• 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}) 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 EQ-5D-5L • 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 during the study	• Change from baseline in Global Impression Questionnaire • Proportion of participants who achieve baseline or better health through Day 28
• To investigate coinfection with influenza and SARS-CoV-2 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

AUC = area under the curve; COVID-19 = coronavirus disease 2019; EC_{50} = 50% effective concentration; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; ITT = intention-to-treat; mITT = modified intention-to-treat; NP = nasopharyngeal; NSP5 = nonstructural protein 5; QOL = quality of life; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TEAE = treatment-emergent adverse event

COVID-19 symptoms are defined as: (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.

a COVID-19 symptoms onset in study participants 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.

b Time to sustained symptoms resolution is defined as the time from first COVID-19 symptom onset until the first day of 2 consecutive days with complete resolution (or improvement to baseline for study participants with pre-COVID-19 symptoms) of COVID-19 symptoms (except for loss of smell or taste) based on participant symptoms diary.

c Total symptom score is the sum of scores for the targeted symptoms in the participant's study diary (each individual symptom score is 0 = none, 1 = mild, 2 = moderate, and 3 = severe; see Section 8.1.2.1 for definitions).

d Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms or urgent care clinics.

Overall Design:

This is a randomized, double-blind, multicenter, parallel-group, placebo-controlled comparative study in participants who are household members of symptomatic SARS-CoV-2-infected index patients. Participants will be randomly assigned in a 1:1 ratio to receive study intervention (S-217622 or placebo).

Brief Summary:

The purpose of this study is to measure the proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive reverse transcription polymerase chain reaction [RT-PCR] test) and have COVID-19 symptom(s) with S-217622 tablets compared with placebo tablets in participants who are household contacts of an individual with symptomatic COVID-19.

Study details include (see schema in Figure 1-1 and Figure 1-2):

Index patients (SARS-CoV-2 infected patients):

- The study duration will be a minimum of 1 day and maximum of 3 days. Day 3 is an optional visit for collection of nasopharyngeal (NP) swabs for virology tests and COVID-19 symptom recording.
- No study intervention will be administered.

Participants (household members of the index patient):

- The study duration will be up to 28 days.
- The study intervention duration will be up to 5 days.
- The study visits will occur on Days 1 (Screening Visit), 3, 6, 10, 15, 21, and 28. The investigator will initiate an Event-driven Visit on Days 1 through 28 if deemed clinically needed or in the event of COVID-19 symptoms onset.

Number of Participants:

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.

The assumed screening failure rate is approximately 15%.

Note: A screened participant is one who has completed the informed consent form (ICF) process (the participant may subsequently withdraw consent and/or may not meet all eligibility criteria). If a participant, their parent(s), legal guardian, or other legally authorized representative (LAR) has agreed to participate in the clinical study following completion of the informed consent process, the participant has completed all screening assessments, and the participant has met all eligibility requirements, then he/she will meet the definition of enrolled and is eligible for randomization.

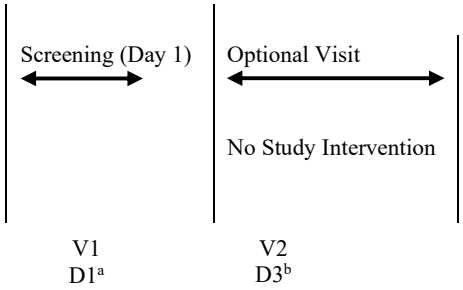
Intervention Groups and Duration:

- Placebo orally once daily for 5 days OR
- S-217622 at a dose of 375 mg for Day 1 and 125 mg once daily for Days 2 to 5

Data Monitoring/Other Committee: Yes

1.2 Schema

Figure 1-1 Study Schematic – Index Patient

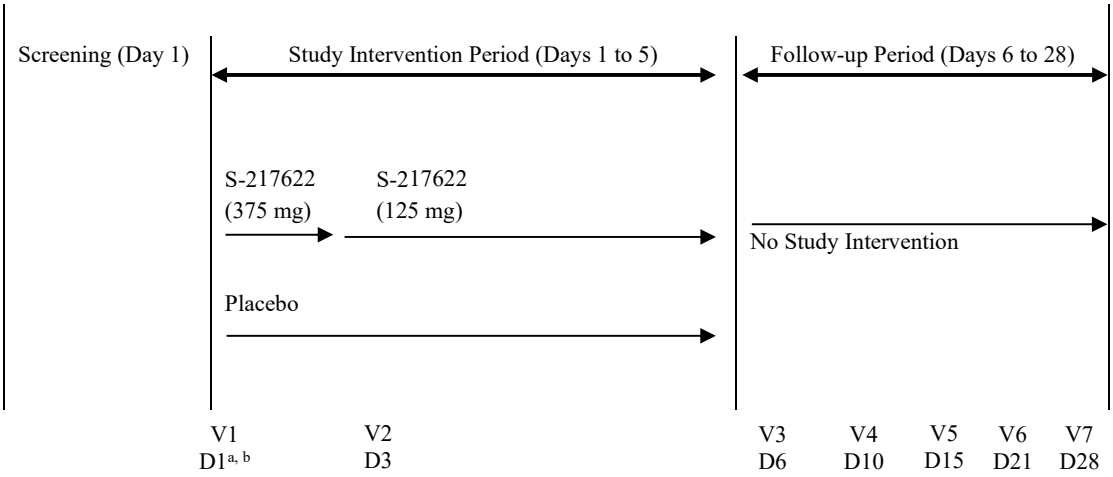


COVID-19 = coronavirus disease 2019; D = Day; V = Visit

a Visit 1, Day 1 for the index patient will not necessarily be the same day as Visit 1, Day 1 for the participant. However, the participant must provide informed consent ≤ 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.

b Nasopharyngeal swabs for virology tests and COVID-19 symptoms recording will be conducted at an optional visit for the index patient.

Figure 1-2 Study Schematic – Participant



COVID-19 = coronavirus disease 2019; D = Day; V = Visit

a Visit 1, Day 1 for the index patient will not necessarily be the same day as Visit 1, Day 1 for the participant. However, the participant must provide informed consent ≤ 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.

b If a participant qualifies for the study, study intervention will be administered on site at the end of the Screening Visit immediately after randomization (if home-visit medical care is deployed, the first dose should be administered immediately after randomization in the home).

c After participants are enrolled, the investigator will initiate an Event-driven Visit if clinically indicated on Days 1 through 28 or 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).

1.3 Schedule of Activities (SoA)

Figure 1-3 Schedule of Activities – Index Patient

	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.

Figure 1-4 Schedule of Activities – Participant

	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 Before**	**After**		**2**			**3**	**4**	**5**	**6**	**7 (Discontinuation)**	
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.

n Study intervention at Day 1 should be administered on site (if home-visit medical care is deployed, the first dose should be administered immediately after randomization in the home).

2. INTRODUCTION

S-217622 is a compound developed by Shionogi & Co., Ltd. for the treatment and prevention of COVID-19. S-217622 is an inhibitor of SARS-CoV-2 3CL protease, which is essential for the processing of the polyprotein encoded by a SARS-CoV-2 gene as well as for the replication of the virus.

2.1 Study Rationale

S-217622 is a SARS-CoV-2 3CL protease inhibitor demonstrating antiviral activity at nanomolar concentrations that is being developed as a treatment for SARS-CoV-2 infection. This directly acting antiviral has undergone extensive preclinical testing and has been assessed for pharmacokinetics (PK), safety, and tolerability in healthy male participants. A Phase 2a/2b/3 study (Study 2108T1221) in participants with SARS-CoV-2 infection is underway (see Section 2.3.1). The current study is being conducted 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.

The household secondary attack rate characterizes virus transmissibility. Household members are at increased risk of infection as they are in 3Cs environments (crowded places, close-contact settings, confined and enclosed spaces) because of the close contacts with the infected family members [1]. Crowded indoor environments with sustained close contact, such as households, are a particularly high-risk setting [2].

While current United States (US) Centers for Disease Control and Prevention COVID-19 prevention recommendations are to maintain 6 feet (2 meters) of distance from an infected household member [3], this may be difficult to achieve in practice and not be fully effective. Furthermore, it was reported that after 2 doses, vaccine effectiveness waned rapidly with very limited vaccine effects seen from 20 weeks after the second dose of any vaccine. Booster doses resulted in a substantial increase in protection against mild infection; however, waning of protection against symptomatic disease was also seen after booster doses [4, 5]. Even with the availability of COVID-19 vaccination and treatment, there is significant need to develop treatment to prevent symptomatic COVID-19.

2.2 Background

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 [6]. 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.

COVID-19 vaccines are now available, and vaccination campaigns are underway globally with variable reach, course completion, and uptake. Variants of SARS-CoV-2 have emerged that are more transmissible and may reduce vaccine efficacy [7]. Further, an ongoing risk of severe disease with hospitalization and death has been observed in

vaccinated individuals with serious co-existing medical conditions [8]. Due to waning vaccine efficacy or risk factors for infection such as immunocompromised or older age, fully vaccinated individuals are still at risk of developing COVID-19. Thus, additional interventions are needed to address the ongoing COVID-19 disease burden.

There are currently few available effective agents for postexposure prophylaxis to stop SARS-CoV-2 spreading. Intravenously (IV)- and subcutaneously (SC)-administered monoclonal antibodies (mAbs) have received Food and Drug Administration (FDA) emergency use authorization (EUA). These agents still require medical personnel to administer and monitor for allergic reactions after injection and have been subject to severe shortages. New variants of SARS-CoV-2 have emerged that are resistant to mAbs.

Oral COVID-19 treatment will be more convenient than currently available injectable therapies. Given the global burden of COVID-19, there is a need for safe, effective oral options to ensure widespread access. Thus, the availability of an effective oral antiviral agent remains an unmet clinical need.

2.3 Benefit/Risk Assessment

S-217622 is being developed 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. Due to the COVID-19 pandemic, there is currently a high unmet need for new efficacious and safe treatments for patients with SARS-CoV-2 infection and those who have been exposed to SARS-CoV-2. Detailed information about the known and expected benefits and risks and adverse events (AEs) of S-217622 can be found in the Investigator's Brochure.

2.3.1 Risk Assessment

Nonclinical Safety Data

Single-dose toxicity of S-217622 was evaluated based on results from the day of the first dose in the 2-week oral toxicity studies in rats and monkeys and the micronucleus test in rats. In rats, no dead or moribund animals or abnormal clinical signs were found on the day of the first dose up to the highest dose, 1000 mg/kg in oral toxicity study and 2000 mg/kg in the micronucleus study. In the 2-week oral toxicity study in monkeys, no dead or moribund animals were found on the day of the first dose up to the highest dose, 1000 mg/kg (males) or 300 mg/kg (females), although vomiting and decreased food consumption were observed in males. The approximate lethal doses of S-217622 were > 2000 mg/kg in rats and > 1000 mg/kg in monkeys.

Further, in the 2-week oral toxicity study in rats (doses: 20, 100, and 1000 mg/kg/day), no dead or moribund animals were found during the administration period. No adverse effects were observed up to the highest dose, 1000 mg/kg/day, in males or females; the no-observed adverse effect level (NOAEL) was 1000 mg/kg/day. In the 2-week oral toxicity study in monkeys (doses in males: 10, 50, and 1000/300/100 mg/kg/day [dose reduction on Days 3 and 8 of dosing]; doses in females: 10, 50, and 300/100 mg/kg/day [dose reduction on Day 9 of dosing]), 1 dead male and 1 moribund male were found at

1000/300/100 mg/kg/day, and 1 moribund female at 300/100 mg/kg/day. The adverse findings noted in the 2-week repeat-dose oral toxicity study in monkeys were death/moribundity, vomiting, decreased food consumption, decreased erythrocyte parameters, decreased platelet count and inflammatory changes in multiple organs. Overall, the NOAEL was 10 mg/kg/day.

In the 4-week oral toxicity study in rats (doses: 20, 50, and 1000 mg/kg/day), no adverse changes were observed up to 1000 mg/kg/day. The NOAEL was considered to be 1000 mg/kg/day in both sexes. In the 4-week oral toxicity study in monkeys (doses: 3, 10, and 30 mg/kg/day), the following adverse changes were observed at 30 mg/kg/day: decreased food consumption and body weights, inflammatory changes in the muscle layer of uterus and muscle layer/fibrous membrane of gallbladder, and a decrease in erythrocytic parameters. All changes showed reversibility with 4-week drug withdrawal. The NOAEL was considered to be 10 mg/kg/day in both sexes.

S-217622 fumaric acid did not induce malformations or embryo-fetal lethality up to 1000 mg/kg/day in rats. Low food consumption and body weight in dams and slight fetal growth retardation and a high frequency of short supernumerary rib were noted at 1000 mg/kg/day. The NOAEL was considered to be 60 mg/kg/day for general toxicity in dams and embryo-fetal development and 1000 mg/kg/day for maternal reproductive function in dams.

S-217622 fumaric acid induced axial skeletal malformations at 100 mg/kg/day or above and embryo-fetal lethality associated with maternal toxicity at 300 mg/kg/day in rabbits. Furthermore, low food consumption and body weight in dams, abortion associated with maternal toxicity, and high frequencies of full supernumerary rib and/or supernumerary lumbar vertebra were noted at 100 mg/kg/day or above. The NOAEL was considered to be 30 mg/kg/day for general toxicity, maternal reproductive function in dams, and embryo-fetal development.

In males of the 1000 mg/kg/day group, low values were noted in weight of caudal epididymis, sperm activity, motile sperm rate, and total sperm count in caudal epididymis when compared with the control group. However, no effects were noted in the abnormal sperm rate. Additionally, histopathological examination of the reproductive organs in males (prostate, testis, and epididymis) of the 1000 mg/kg/day group showed no effects from the administration of S-217622 fumaric acid. These changes were not considered to be adverse because the changes were so slight (−6% to −15% when compared to the mean control value) that the values were within or almost within the range of the control background data, and there were no changes in fertility index or early embryonic development. In the 20- and 60-mg/kg groups, no effects were noted in the weight of caudal epididymis, sperm activity, motile sperm rate, sperm count, or abnormal sperm rate.

Regarding genotoxicity with S-217622, the bacterial reverse mutation test, micronucleus test in cultured mammalian cells, and micronucleus test in rats were all negative.

Clinical Safety Data

To date, 7 Phase 1 studies (Studies 2130T1215, 2102T1211, 2135T1216, YQ-M-22-04, 2127T1213, 2128T1214, and 2305T1218) and 1 Phase 2/3 study (Study 2108T1221) have been completed. Two Phase 3 studies (Studies ACTIV-2d/A5407 and 2208T1231) in participants with SARS-CoV-2 infection are ongoing. The Phase 2a/2b and Phase 3 parts of Study 2018T1221, which enrolled participants with SARS-CoV-2 infection who had at least 1 moderate symptom and mild or moderate COVID-19 resulted in emergency approval of S-217622 in Japan.

In the Phase 1 study (Study 2130T1215), the effects of S-217622 on the PK of digoxin (P-glycoprotein [P-gp] substrate), rosuvastatin (breast cancer resistance protein [BCRP], organic anion transporter polypeptide [OATP] 1B1 and OATP1B3 substrate), and metformin (organic cation transporter [OCT1] and multidrug and toxin extrusion [MATE1] substrate) were assessed following single-dose administration of S-217622 500 mg. No deaths, serious treatment-emergent adverse events (TEAEs), or TEAEs leading to discontinuation of study intervention were reported. The only TEAE was diarrhea that occurred in 1 participant (7.1%) each in Period 1 and 2 of 2-period 2-group crossover design. These events were mild, resolved, and were considered unrelated to study intervention.

A Phase 1 single-ascending dose and multiple-ascending dose study (Study 2102T1211) was performed in healthy adult participants across different doses of S-217622 or placebo. No deaths or other serious TEAEs were reported. Treatment-emergent adverse events leading to discontinuation of the study were reported in 2 participants (1 participant [in Part 4] due to COVID-19 and 1 participant [in Part 2] due to rash, headache, and feeling hot). All TEAEs were mild or moderate in severity and resolved or were resolving at the time of the last follow-up. The most frequent TEAE in the S-217622 group was high-density lipoprotein decreased (60.2%; 97/161). In general, S-217622 was well tolerated with no major safety concerns in the healthy adult participant study.

Of the other 2 Phase 1 completed studies, Study 2135T1216 was a single-center, single-arm open-label study in healthy adult male participants and Study YQ-M-22-04 was a single-center, randomized, open-label, crossover bioequivalence study in Chinese healthy adult participants. In Study 2135T1216, a total of 6 participants were enrolled and no deaths, serious TEAEs, or TEAEs leading to study discontinuation were reported. In Study YQ-M-22-04, a total of 100 participants were enrolled to receive a single dose of the test and reference drugs. No deaths or serious TEAEs were reported. Treatment-emergent adverse events leading to discontinuation of study intervention were reported in 1 participant in the fed state (gamma-glutamyltransferase increased, alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased, blood bilirubin unconjugated increased, bilirubin conjugated increased, blood bilirubin increased) and 1 participant in the fasted state (ureterolithiasis); these events except for ureterolithiasis were considered related to the reference drug.

Phase 1 Studies 2127T1213 and 2128T1214 were open-label, single-dose, parallel-group studies in participants with mild and moderate hepatic impairment (Study 2127T1213) and mild, moderate, and severe renal impairment (Study 2128T1214) and healthy control participants. A total of 25 participants were enrolled in Study 2127T1213. Treatment-related TEAEs were reported in 2 participants (8.0%): 1 diarrhea (12.5%) in the normal group and 1 glomerular filtration rate decreased (11.1%) in the mild hepatic impairment group. A total of 32 participants were enrolled in Study 2128T1214. No deaths or serious TEAEs were reported. Treatment-related TEAEs were reported in 2 participants (6.3%): 1 dry mouth (12.5%) in the mild renal impairment group and 1 glomerular filtration rate decreased (12.5%) in the moderate renal impairment group.

The Phase 1 Study 2305T1218 was a single-center, single-arm, open-label study in healthy adult participants that evaluated the effect of itraconazole (CYP3A inhibitor) in Cohort A or carbamazepine (CYP3A inducer) in Cohort B on the PK of S-217622. A total of 28 participants (14 in each cohort) were enrolled. No deaths or serious TEAEs were reported. One participant in Cohort A had a TEAE (nasopharyngitis) that led to discontinuation of study intervention. Six participants in Cohort B had a TEAE that led to discontinuation of study intervention. The events included COVID-19 in 1 participant, erythema in 2 participants, erythema and pruritus in 2 participants, and erythema, pruritus, and C-reactive protein increased in 1 participant. Erythema, pruritus, and C-reactive protein increased are known adverse drug reactions of carbamazepine, and none of the TEAEs were considered related to S-217622. All TEAEs were considered mild or moderate, and resolved.

The Phase 2/3 Study 2108T1221 was a multicenter, randomized, double-blind, placebo-controlled study consisting of 4 Parts: Phase 2a Part where the primary objective is to investigate the antiviral effect in participants with mild/moderate or asymptomatic SARS-CoV-2 infection; Phase 2b Part where the primary objective is to investigate early improvement of clinical symptoms and the antiviral effect against SARS-CoV-2 in participants with mild/moderate SARS-CoV-2 infection; Phase 3 Part where the primary objective is to demonstrate efficacy in participants with mild/moderate SARS-CoV-2 infection; and Phase 2b/3 Part where the primary objective was to demonstrate efficacy in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection.

Each Part consisted of the intervention period (Days 1 to 5), the follow-up period (Days 6 to 28), and the exploratory period (Days 29 to 337).

Participants with mild/moderate and asymptomatic SARS-CoV-2 infection for Phase 2a Part, participants with mild/moderate SARS-CoV-2 infection for Phase 2b Part or Phase 3 Part, and participants with asymptomatic/mild symptoms only SARS-CoV-2 infection for Phase 2b/3 Part were randomly allocated at a ratio of 1:1:1 to 1 of the 3 treatment groups, ie, 375/125-mg group, 750/250-mg group, and placebo group. The study period for each participant was 28 days and efficacy (for 21 days) and safety (for 28 days) of S-217622 were assessed in Phase 2a Part, Phase 3 Part, or Phase 2b/3 Part. In Phase 2b Part, efficacy and safety of S-217622 were assessed for 6 days, and efficacy for 21 days and safety for 28 days has been confirmed.

Phase 2a Part: Of the 69 randomized participants, 1 participant did not receive the study intervention and was excluded from the Safety Analysis Population. A total of 68 participants with mild/moderate or asymptomatic SARS-CoV-2 infection (21 in the 375/125-mg group, 23 in the 750/250-mg group, and 24 in the placebo group) composed in the Safety Analysis Population in Phase 2a Part.

No deaths, serious TEAEs, or TEAEs leading to discontinuation of study intervention were reported.

The overall incidence of TEAEs in Phase 2a Part was 52.4% (11/21 participants) in the 375/125-mg group, 69.6% (16/23 participants) in the 750/250-mg group, and 37.5% (9/24 participants) in the placebo group. The overall incidence of treatment-related TEAEs was 23.8% (5/21 participants) in the 375/125-mg group, 43.5% (10/23 participants) in the 750/250-mg group, and 0% (0/24 participants) in the placebo group.

No severe TEAEs were reported, and most of TEAEs were categorized as mild. Three moderate TEAEs were reported, but all these were considered unrelated to the study intervention.

Phase 2b Part: Of the 428 randomized participants, 7 participants did not receive the study intervention and were excluded from the Safety Analysis Population. A total of 421 participants with mild/moderate SARS-CoV-2 infection (140 in the 375/125-mg group, 140 in the 750/250-mg group, and 141 in the placebo group) were included in the Safety Analysis Population in Phase 2b Part.

No deaths or serious TEAEs were reported in the S-217622 groups. Three TEAEs leading to discontinuation of study intervention were reported in 2 participants in the 375/125-mg group; these 3 events were considered related to the study intervention and resolved after the discontinuation of the study intervention.

The overall incidence of TEAEs in Phase 2b Part was 34.3% (48/140 participants) in the 375/125-mg group, 42.9% (60/140 participants) in the 750/250-mg group, and 31.2% (44/141 participants) in the placebo group. The overall incidence of treatment-related TEAEs was 13.6% (19/140 participants) in the 375/125-mg group, 22.1% (31/140 participants) in the 750/250-mg group, and 5.0% (7/141 participants) in the placebo group.

No severe TEAEs were reported in the 375/125- and the 750/250-mg groups. Seven moderate TEAEs were reported, but most TEAEs were categorized as mild.

Phase 3 Part: A total of 1808 participants with mild/moderate SARS-CoV-2 infection (604 in the 375/125-mg group, 599 in the 750/250-mg group, and 605 in the placebo group) composed the Safety Analysis Population in Phase 3 Part.

No deaths were reported in any of the intervention groups. Serious TEAEs, which occurred in 1 participant in the 375/125-mg group (heavy menstrual bleeding) and

1 participant in the placebo group (cholecystitis acute), were considered unrelated to the study intervention. Treatment-emergent adverse events leading to discontinuation of study intervention were reported in 4 participants (4 events) in the 375/125-mg group, 6 participants (7 events) in the 750/250-mg group, and 2 participants (3 events) in the placebo group. All these events resolved or were resolving after discontinuation of study intervention.

The overall incidence of TEAEs in Phase 3 Part was 44.2% (267/604 participants) in the 375/125-mg group, 53.6% (321/599 participants) in the 750/250-mg group, and 24.8% (150/605 participants) in the placebo group. The overall incidence of treatment-related TEAEs was 24.5% (148/604 participants) in the 375/125-mg group, 36.2% (217/599 participants) in the 750/250-mg group, and 9.9% (60/605 participants) in the placebo group. The most common TEAE was high-density lipoprotein decreased (31.1% [188/604] in the 375/125-mg group, 38.6% [231/599] in the 750/250-mg group, and 3.8% [23/605] in the placebo group). Most of the TEAEs were categorized as mild.

Phase 2b/3 Part: A total of 604 participants with asymptomatic/mild symptom only SARS-CoV-2 infection (201 participants in the 375/125-mg group, 202 participants in the 750/250-mg group, 201 participants in the placebo group) composed the Safety Analysis Population in Phase 2b/3 Part.

No deaths were reported in any of the intervention groups. Serious TEAEs were reported in 2 participants in the 750/250-mg group (1 event each of diverticulitis and nausea), both of which were considered unrelated to the study intervention. No serious TEAEs were reported in the 375/125-mg group or the placebo group. Treatment-emergent adverse events leading to discontinuation of the study intervention were reported in 1 participant in the 375/125-mg group (moderate drug eruption) and 2 participants in the 750/250-mg group (moderate headache and mild headache). Of these events, drug eruption reported in the 375/125-mg group and moderate headache reported in the 750/250-mg group were considered related to the study intervention and were resolved or resolving after the discontinuation of the study intervention. No TEAEs leading to discontinuation of the study intervention were reported in the placebo group.

The overall incidence of TEAEs in Phase 2b/3 Part was 43.8% (88/201 participants) in the 375/125-mg group, 56.9% (115/202 participants) in the 750/250-mg group, and 21.4% (43/201 participants) in the placebo group. The overall incidence of treatment-related TEAEs in Phase 2b/3 Part was 23.4% (47/201 participants) in the 375/125-mg group, 37.1% (75/202 participants) in the 750/250-mg group, and 7.0% (14/201 participants) in the placebo group. The most common TEAE was high density lipoprotein decreased (30.3% [61/201] in the 375/125-mg group, 45.0% [91/202] in the 750/250-mg group, and 2.0% [4/201] in the placebo group). Most of the TEAEs were categorized as mild.

Other ongoing studies (Studies ACTIV-2d/A5407 and 2208T1231) are Phase 3 multicenter, randomized, double-blind, placebo-controlled studies in high-risk nonhospitalized participants (ACTIV-2d/A5407) and pediatric participants aged 6 to

< 12 years with mild/moderate SARS-CoV-2 infection in Japan. As of 10 May 2024, 2093 participants were enrolled in Study ACTIV-2d/A5407 to receive S-217622 or placebo. Two deaths were reported. A total of 33 serious TEAEs were reported in 23 participants. No deaths or serious TEAEs were considered related to the study intervention. As of 10 May 2024, a total of 78 participants were enrolled to receive S-217622 or placebo in Study 2208T1231. No deaths or serious TEAEs were reported.

Postmarketing Experience

In Japan, S-217622 (ensitrelvir) obtained an emergency regulatory approval on 22 Nov 2022 and a regulatory approval on 05 Mar 2024. During the postmarketing period with ensitrelvir and at the time of issuing the Investigator's Brochure (current Edition 07, issued 28 Jun 2024), anaphylaxis was reported in 3 cases and anaphylactic shock was reported in 5 cases as serious adverse reactions. Because such reactions are reported spontaneously from a population of uncertain size, it is not possible to estimate the frequency in relation to drug exposure with sufficient reliability. If signs and symptoms of clinically significant anaphylaxis or anaphylactic shock occur, S-217622 should be immediately discontinued, and appropriate medications and/or supportive care should be initiated.

2.3.2 Benefit Assessment

Due to the ongoing COVID-19 pandemic, the availability of an effective oral antiviral agent remains an unmet clinical need. Contributing to the process of developing new therapies in an area of unmet needs may ultimately be considered beneficial for participants.

2.3.3 Overall Benefit Risk Conclusion

No significant safety risks related to S-217622 were identified in the clinical studies conducted to date. The potential risks identified in association with S-217622 are justified by the anticipated benefits of developing an effective oral antiviral agent in the prevention of symptomatic SARS-CoV-2 infection in household contacts of an individual with symptomatic COVID-19.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

This study is being conducted to assess the prevention of symptomatic SARS-CoV-2 infection in household contacts of an individual with symptomatic COVID-19. The objectives and endpoints for this study are shown in Table 3-1.

Table 3-1 Objectives and Endpoints

Objective	Endpoint
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 (hereinafter referred to as "participants") of SARS-CoV-2-infected patients (hereinafter referred to as "index patients") through Day 10 (using the mITT population)	• Proportion of participants in the mITT population 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[a] through Day 10
Key secondary	
• 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 index patients through Day 10 (using the ITT population)	• Proportion of participants in the ITT population with a negative screening SARS-CoV-2 infection (local laboratory-confirmed negative test) who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have COVID-19 symptoms onset[a] through Day 10
Secondary	
• To compare S-217622 with placebo in the prevention of SARS-CoV-2 infection in participants (defined as central laboratory-confirmed positive RT-PCR test)	• Proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) through Days 10, 15, 21, or 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 central laboratory-confirmed positive RT-PCR result • Proportion of participants with central laboratory-confirmed positive RT-PCR result at each timepoint • 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 (central laboratory-confirmed positive RT-PCR test) for SARS-CoV-2 through Day 10	• Proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have no COVID-19 symptoms onset[a] through Day 10

Objective	Endpoint
	• Proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have no COVID-19 symptoms through Day 10 • Proportion of participants with sustained resolution[b] 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[b] of each COVID-19 symptom through Day 28 • Change in total[c] score of COVID-19 symptoms at each timepoint • Change in total score of the 5 key COVID-19 symptoms at each timepoint • Time from first confirmed SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) until at least 1 COVID-19 symptom through Day 28 • Time from first confirmed SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) until COVID-19 symptoms onset[a] through Day 28 • AUC of the daily total[c] symptom score associated with COVID-19 over time from COVID-19 symptoms onset[a] through Day 28 • AUC of the daily total symptom score for the 5 key COVID-19 symptoms over time from onset[a] 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 (central laboratory-confirmed positive RT-PCR test) during the study	• Proportion of participants with hospitalization[d] 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 TEAEs, deaths, other serious TEAEs, and TEAEs leading to discontinuation of study intervention

Objective	Endpoint
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 the index patient's amount of viral RNA and the participant's positive central laboratory-confirmed RT-PCR test	• Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the central laboratory-confirmed positive RT-PCR reported cases in the household
• 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	• Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the incidence of SARS-CoV-2 ill case 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}) 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 EQ-5D-5L • 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 during the study	• Change from baseline in Global Impression Questionnaire • Proportion of participants who achieve baseline or better health through Day 28
• To investigate coinfection with influenza and SARS-CoV-2 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

AUC = area under the curve; COVID-19 = coronavirus disease 2019; EC_{50} = 50% effective concentration; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; ITT = intention-to-treat; mITT = modified intention-to-treat; NP = nasopharyngeal; NSP5 = nonstructural protein 5; QOL = quality of life; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TEAE = treatment-emergent adverse event

COVID-19 symptoms are defined as: (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.

a COVID-19 symptoms onset in study participants 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.

b Time to sustained symptoms resolution is defined as the time from first COVID-19 symptom onset until the first day of 2 consecutive days with complete resolution (or improvement to baseline for study participants with pre-COVID-19 symptoms) of COVID-19 symptoms (except for loss of smell or taste) based on participant symptoms diary.

c Total symptom score is the sum of scores for the targeted symptoms in the participant's study diary (each individual symptom score is 0 = none, 1 = mild, 2 = moderate, and 3 = severe; see Section 8.1.2.1 for definitions).

d Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms or urgent care clinics.

4. STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, multicenter, parallel-group, placebo-controlled comparative study in participants who are household members of symptomatic SARS-CoV-2-infected index patients. Participants will be randomly assigned in a 1:1 ratio to receive study intervention (S-217622 or placebo).

4.2 Scientific Rationale for Study Design

Despite the EUA of anti SARS-CoV-2 mAbs for postexposure prophylaxis use in the US and some other countries, there are still limitations with the available treatments. For instance, these agents still require medical personnel to administer and monitor for allergic reactions after injection, they have been subject to severe shortages, and the effectiveness wanes with a new emergent variant. The options for prevention of SARS-CoV-2 household infection are very limited. Developing an easy-to-use oral antiviral medication for COVID-19 household prophylaxis is a significant unmet need.

Rationale for Placebo-controlled Study

This randomized, placebo-controlled Phase 3 design provides a rigorous evaluation of the safety and efficacy of the oral protease inhibitor S-217622 in the prevention of symptomatic SARS-CoV-2 infection in household contacts of an individual with symptomatic COVID-19. Oral COVID-19 treatment will be much more scalable than injectables, and given the global burden of COVID-19, there is a need for multiple safe, effective oral options to ensure widespread access.

In addition to potential COVID-19 treatment, this study offers close clinical monitoring that may not be available outside of the study, increasing the likelihood of timelier referral for escalated level of care, if needed. As a global study, health needs outside of the US are recognized by the study, and the design informed by local investigators and community advisors.

The inclusion of a placebo group, rather than an untreated open-label control group, is considered important for the integrity of the study to reduce the possibility of differential retention of participants randomized to S-217622 vs. the control group, as well as to minimize subjective bias in completion of symptom diaries by participants.

Rescue Medications for Index Patient and Study Participant

Index patients may receive any locally available standard-of-care COVID-19 therapies as indicated in their regions.

Participants who test positive for SARS-CoV-2 infection during the study and meet the study definition for COVID-19 symptoms onset (occurrence or worsening of ≥ 1 of the 14 specified COVID-19 symptoms for at least 48 hours) may receive any locally standard-of-care COVID-19 therapies available and indicated in their regions, as long as compatible with study intervention. Compatible therapies include, but are not limited to,

anti-SARS-CoV-2 mAbs, outpatient IV remdesivir, molnupiravir, convalescent plasma, inhaled budesonide, and fluvoxamine after study enrollment. If Paxlovid™ (nirmatrelvir/ritonavir) is administered after the treatment period of S-217622, which is only anticipated in the case the study participant tests positive for SARS-CoV-2 and meets the study definition for COVID-19 symptoms onset (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), careful monitoring with caution of therapeutic and adverse effects are highly recommended due to the potential increase of nirmatrelvir area under the curve (AUC) and maximum plasma concentration (C_{max}) (see Section 6.8.1 for additional information). The use of S-217622 outside of the study (if commercially available in the local region) is not allowed during the study participation.

Outcome Measures

This study primarily evaluates the potential effect of S-217622 on the primary endpoint of proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have COVID-19 symptoms onset through Day 10.

In addition to evaluating safety, as secondary measures, this study will also evaluate the intervention's treatment efficacy on viral shedding by quantitative RT-PCR and COVID-19 associated symptoms, as well as all-cause hospitalization and death.

The study includes a 10-day period of intensive monitoring to collect information on the virologic and clinical symptom outcomes. This 10-day period is deemed sufficient to detect the primary endpoint since the median interval between index patient onset date and household contact onset date was 4 days (interquartile range, 2 to 7 days) [9]. Furthermore, the Japanese National Institute of Infectious Diseases reported that in 99% of Omicron strain cases, the time from exposure to symptom onset was less than 10 days. In addition, in a study of household transmission of SARS-CoV-2 in the US, a similar conclusion was met where 84% of polymerase chain reaction (PCR)-positive secondary cases in household members were detected within 10 days from the index patient symptoms onset date [10]. Another study reported that most household infection cases occurred within 10 days from the index patient symptoms onset [11]. In the Phase 3 Part of Study 2108T1221 (participants with mild/moderate SARS-CoV-2 infection), 99% and 100% of participants had undetectable viral titers on Days 10 and 15, respectively, in the placebo group. This indicates that the transmission from the index patient in this prevention study is less likely to happen after Day 10.

Multisite Design

In any multi-site study, outcomes can potentially differ due to variation in site populations, stage of epidemic spread, diagnostic capability, and clinical management. Although it is expected that any differences between sites will be balanced between groups through randomization.

Investigational Agent: S-217622

The SARS-CoV-2 3CL protease is a virally encoded enzyme, which is essential for viral replication [12]. 3CL protease cleaves the virus P1a and P1ab polyproteins at multiple junctions to generate a series of proteins critical for virus replication and transcription, including RNA-dependent RNA polymerase (RdRp), 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. S-217622 is a SARS-CoV-2 3CL protease inhibitor demonstrating antiviral activity at nanomolar concentrations.

4.3 Justification for Dose

The S-217622 dosage regimen used in this study has been or is being studied in the Phase 2/3 and Phase 3 studies of S-217622 for the treatment indication (Studies 2108T1221 and ACTIV-2d/A5407).

S-217622 fumaric acid exhibited potent and dose-dependent inhibitory effects on the replication of hCoV-19/Japan/TY38-873/2021 (Pango Lineage: B.1.1.529/BA.1) strain in primary human nasal and bronchial epithelial cells, and the mean 90% effective concentration (EC_{90}) values were 0.160 and 0.195 µmol/L (0.0851 and 0.104 µg/mL), respectively, after 2 days after virus inoculation in nasal epithelial cells and 4 days after virus inoculation in bronchial epithelial cells (Reports S-217622-EB-149-N and S-217622-EB-150-N). The human serum protein binding of S-217622 was 97.7% at 50 µg/mL (Report S-217622-PB-001-N). The human serum protein binding adjusted EC_{90} values (calculated by EC_{90} value divided by free protein binding of 2.3%) were 3700 and 4520 ng/mL for nasal and bronchial epithelial cells, respectively.

A 5-day dosage regimen of S-217622 is expected to have a prophylactic effect based on nonclinical studies (Reports S-217622-EB-171-N and S-217622-EB-149-N). In particular, 24 hours after a single SC administration of S-217622, mice were inoculated with SARS-CoV-2, and the prophylactic effect of S-217622 was evaluated based on survival time and body weight. An S-217622 dose of ≥ 64 mg/kg significantly reduced mortality and suppressed body weight loss. The plasma drug concentration 24 hours after administration of 64 mg/kg was 2.99 µg/mL. Because S-217622 is not a substrate for uptake transporters, the protein-unbound concentration in plasma is expected to be similar to plasma drug concentrations in the respiratory tract and lungs. Therefore, a postexposure prophylactic effect against SARS-CoV-2 in humans can be anticipated based on the plasma concentrations of S-217622 in humans and the target plasma concentrations based on the protein-binding adjusted EC_{90} from the in vitro study (3.70 µg/mL: Report S-217622-EB-149-N) and in the in vivo study in mice (2.99 µg/mL; Report S-217622-EB-171-N). By maintaining plasma S-217622 concentrations in humans at least at this same level, a postexposure prophylactic effect of S-217622 against SARS-CoV-2 may be demonstrated in humans.

Based on the PK analysis of plasma drug concentrations following a once-daily regimen of a loading dose of S-217622 375 mg on Day 1 and a maintenance dose of S-217622 125 mg on Days 2 to 5 in Japanese female participants (Study 2102T1211 Cohort N), the geometric mean plasma drug concentration on Days 1 and 5 was 14.0 and 17.7 µg/mL, respectively, at 24 hours (C_{24}) and 6.56 µg/mL at 192 hours (C_{192}) after the initial dose of S-217622. The terminal elimination half-life ($t_{1/2,z}$) was 51.4 hours. In white participants administered the same S-217622 dosage regimen in Study 2102T1211 Cohort Q, the C_{24} on Days 1 and 5 was 12.2 and 16.9 µg/mL, respectively, and the C_{192} after the initial dose of S-217622 was 6.86 µg/mL; the $t_{1/2,z}$ was 57.6 hours. Thus, plasma S-217622 concentrations in humans will likely exceed the protein-binding adjusted-EC_{90} (3.70 µg/mL) for approximately 234 hours after the initial dose in Japanese female participants and 243 hours in the initial dose in white participants. In addition, plasma S-217622 concentrations will likely exceed the target plasma concentration (2.99 µg/mL) for approximately 250 hours after the initial dose in Japanese female participants and 261 hours after the initial dose in white participants. These data supported the selection of the once-daily regimen of a loading dose S-217622 375 mg on Day 1 and a maintenance dose of S-217622 125 mg on Days 2 to 5 in this study.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 1.3).

The end of the study is defined as the date of last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study globally.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Participants will be recruited and enrolled into this study solely based on their meeting the aforementioned eligibility criteria. No eligible participants will be excluded from this study on the basis of age, gender, race, or ethnicity. Thus, the distribution of participants is expected to reflect local demographics at the sites where the study will be conducted. To the best of our knowledge, the indications being studied in this clinical study are equally prevalent in individuals of all racial and ethnic backgrounds.

5.1 Inclusion Criteria

Index Patients (Patients with SARS-CoV-2 Infection)

Patients are eligible to be included as an index patient if all of the following criteria apply:

Age

1. Pediatric patients or adult patients (of any age)

Type of Participant and Disease Characteristics

2. The index patient must:
   a. Have at least 1 COVID-19 symptom as listed below within 24 hours before the index patient providing informed consent. COVID-19 symptom(s) must be deemed by the investigator as related to the current SARS-CoV-2 infection (not related to preexisting comorbidities) or deemed as preexisting and worsened due to SARS-CoV-2 infection.
      - 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)
      - Shortness of breath or difficulty breathing
      - Cough
      - Sore throat
      - Nasal congestion or runny nose
      - Chills
      - Fatigue
      - Body or muscle pain or aches
      - Headache
      - Nausea
      - Vomiting
      - Diarrhea

- Change in sense of taste
- Change in sense of smell

b. Must have positive SARS-CoV-2 test (a nucleic acid amplification test or antigen test) from any respiratory tract specimen (eg, oropharyngeal, NP or nasal swab, or saliva) from a sample collected ≤ 72 hours prior to randomization of the participant

c. Be the only index patient from each household enrolled in the study. In the case of multiple members in the household with confirmed SARS-CoV-2 infection, the household member with the earliest positive test for SARS-CoV-2 (a nucleic acid amplification test or antigen test) or the earliest onset of COVID-19 symptoms will be considered the index patient. Other household members who have a positive test for SARS-CoV-2 or COVID-19-like symptoms will be ineligible to enroll as study participants.

3. Must have a potential study participant who can participate in the study within 72 hours after onset of COVID-19 symptoms in an index patient

Informed Consent

4. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) that includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Consent must be obtained prior to Screening.

   For index patients under the legal age, written informed consent must be obtained from the parent(s)/legal guardian, or other LAR of the index patient. Written informed assent must also be provided in the case of index patients ≥ 12 years and should be provided for index patients < 12 years when feasible.

Study Participants

Multiple study participants from the same household are allowed to be enrolled in the study. The study intervention randomization will be performed based at the study participant's level. Participants will be eligible to be included in the study only if all of the following criteria apply:

Age

1. ≥ 12 years of age, at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Has a negative screening SARS-CoV-2 infection, as determined by SARS-CoV-2 test (a nucleic acid amplification test or antigen test) from any respiratory tract specimen (eg, oropharyngeal, NP or nasal swab, or saliva) at the local laboratory.
3. Has lived in household with index patient (see index patient Criterion 2) and will continue to live in same household and share common areas such as dining rooms and bathrooms until the end of the study

4. Must not be considered by the investigator or subinvestigator to have SARS-CoV-2 infection and:
   a. No measured fever at Screening (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)
   b. No COVID-19 symptoms at Screening (if a participant has COVID-19-like preexisting symptoms caused by comorbidities, only 1 preexisting symptom will be allowed)
5. Capable and willing to complete a participant diary

Sex and Contraceptive/Barrier Requirements

6. Male or female
   a. Male participants:

      Participants with partners that are woman of childbearing potential (WOCBP) are strongly advised to inform their partners and must agree to use effective contraception from study entry through 14 days after the last dose of study intervention. Effective methods of contraception are described in Appendix 4 (Section 10.4).

      Participants with pregnant partners must agree to use condoms during vaginal intercourse from study entry through 14 days after the last dose of study intervention administration.

      Participants assigned male sex at birth must agree to refrain from sperm donation from study entry through 14 days after the last dose of study intervention administration.

   b. Female participants:

      A female participant is eligible to participate if she is not pregnant or breastfeeding, and the following conditions applies:

      - Is not a WOCBP

        OR

      - All of the following apply:
        – Is a WOCBP and using a contraceptive method that is effective as described in Appendix 4 (Section 10.4) during the study intervention period and for at least 14 days after the last study intervention administration. She must also agree not to donate her eggs (ova, oocytes) for the purpose of reproduction during the study and least 14 days after the last study intervention administration.
          – A WOCBP must have a negative urine pregnancy test within 24 hours before the first dose of study intervention.
          – If a urine pregnancy test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test must be negative.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.5.
- The investigator/subinvestigator will review medical history, menstrual history, and recent sexual activity to decrease the risk of inclusion of a woman with an early undetected pregnancy.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) that includes compliance with the requirements and restrictions listed in the ICF and in this protocol. Consent must be obtained prior to Screening.

   For participants under the legal age, written informed consent must be obtained from the parent(s)/legal guardian/ or other LAR of the participant. Written informed assent must also be provided in the case of participants ≥ 12 years.

   Participants must provide consent/assent

   a. ≤ 72 hours from onset of COVID-19 symptoms (see Appendix 6 [Section 10.6]) in the index patient
   b. ≤ 1 calendar day from the time that the index patient provides consent
8. Participant must be randomized ≤ 72 hours from onset of COVID-19 symptoms (see Appendix 6 [Section 10.6]) in the index patient

5.2 Exclusion Criteria

Index Patients (Patients with SARS-CoV-2 Infection)

Patients will be excluded from the study if the following criterion applies:

Medical Conditions

1. Documented respiratory infection (eg, flu virus infection) other than COVID-19 within 14 days prior to the Screening Visit

Study Participants

Participants will be excluded from the study if any of the following criteria apply:

Medical Conditions

1. Documented respiratory infection (eg, flu virus infection) other than COVID-19 within 14 days prior to the Screening Visit
2. Tested positive for SARS-CoV-2 in the past 6 months
3. Have an underlying disease requiring systemic corticosteroids (excluding topical) or antipyretics/analgesics
4. Known current renal impairment defined as creatinine clearance (CrCl) < 30 mL/min by Cockcroft Gault or requiring dialysis

5. Participants with severe liver dysfunction, such as known history of cirrhosis or liver decompensation (including ascites, variceal bleeding, or hepatic encephalopathy)

Prior/Concomitant Therapy

6. Received approved, authorized, or investigational convalescent plasma, or other anti-SARS-CoV-2 biologic products within 3 months of the Screening Visit
7. Received approved, authorized, or investigational anti-SARS-CoV-2 mAbs in the last 3 months.
8. Received any SARS-CoV-2 vaccine within 6 months prior to the Screening Visit or is expected to receive a SARS-CoV-2 vaccine or other approved, authorized, or investigational postexposure prophylaxis treatments until the end of the study
9. Current use of or anticipated need for any medications prohibited with study intervention, as described in Section 6.8.1. After the confirmation of symptomatic infection (positive SARS-CoV-2 test and meeting the study definition of COVID-19 symptoms onset), locally available SARS-CoV-2 treatment (including but not limited to molnupiravir, mAbs, outpatient administration of IV remdesivir, convalescent plasma, inhaled budesonide, and fluvoxamine) will be permitted, as long as there are no concerns for drug-drug interactions (DDIs) as outlined in Section 6.8.1. Receipt of any investigational treatments for the current episode of SARS-CoV-2 at any time during the study is exclusionary. The use of S-217622 outside of the study (if commercially available in the local region) is not allowed during the study participation.
10. Participants who have used any of the following drugs within 14 days prior to enrollment:
    a. Strong cytochrome P450 (CYP) 3A inducer
    b. Products containing St. John's wort

Prior/Concurrent Clinical Study Experience

11. Exposed to an investigational drug within 30 days or 5 half-lives of the drug prior to the Screening Visit

Other Exclusions

12. Positive urine pregnancy test at Screening Visit or are lactating
13. Known allergy/sensitivity or any hypersensitivity to components of S-217622 or placebo for S-217622
14. Any condition or circumstance that, in the opinion of the investigator or subinvestigator, would compromise the safety of the participant or the quality of the study data
15. Lives in household with ≥ 10 people in total

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should refrain from consumption of products containing St. John's wort during the study.

5.4 Screen Failures

A screen failure is defined as a participant who consents to participate in the clinical study but is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Index patients or study participants who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the discretion of the investigator. Rescreened individuals should be assigned a new participant number for every screening/rescreening event and these numbers should be linked.

5.5 Criteria for Temporarily Delaying Enrollment/Randomization/ Administration of Study Intervention

Not applicable.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to, or used by, a participant according to the study protocol.

6.1 Study Interventions Administered

Details of the study intervention are provided in Table 6-1.

Table 6-1 Study Interventions

Intervention Name	S-217622	Placebo
Intervention Description	375 mg (3 tablets) on Day 1 and 125 mg (1 tablet) on Days 2 to 5	Matching placebo (3 tablets on Day 1 and 1 tablet daily on Days 2 to 5)
Type	Drug	Drug
Dosage Form	Tablet	Tablet
Unit Dose Strength(s)	Each tablet contains 125 mg of S-217622	Matching placebo
Dosage Level(s)	375 mg for 1 day followed by 125 mg for 4 days	Matching placebo (3 tablets for 1 day followed by 1 tablet daily for 4 days)
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by sponsor	Provided centrally by sponsor
Packaging and Labeling	S-217622 will be provided in wallets. Each wallet will contain 7 tablets and will be labeled as required.	Matching placebo will be provided in wallets. Each wallet will contain 7 tablets and will be labeled as required.

IMP = investigational medicinal product; NIMP = non-investigational medicinal product

6.1.1 Regimen, Administration, and Duration

The study intervention tablets should be swallowed whole and should not be chewed, broken, or crushed.

The first dose of study intervention will be taken at the study site on Day 1 (if home-visit medical care is deployed, the first dose will be administered immediately after randomization in the home). All subsequent doses (ie, Days 2 to 5) will be self-administered outside the study site (eg, at home). The second dose must be taken 24 ± 8 hours after the first dose, allowing the participant to select a convenient 24-hour dosing schedule thereafter to complete a total of 5 doses.

Ideally, subsequent doses of S-217622 or matching placebo should be separated by 24 ± 2 hours. If a dose is delayed, it should be taken as soon as possible, but not more than 12 hours later than expected. If the delay is greater than 12 hours, the dose must be skipped and the next dose taken as scheduled. Dosing will be stopped at the end of the

5-day treatment period. Missed doses and remaining tablets at the end of 5 days should be returned to the site.

If a participant vomits after dosing, the dose should not be repeated.

6.2 Preparation, Handling, Storage, and Accountability of Study Intervention

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study and randomized may receive or self-administer study intervention and only the investigator and authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

The study intervention randomization will be performed based at the study participant's level. All participants determined to be eligible by screening will be centrally and randomly assigned to S-217622 group and placebo group at a ratio of 1:1 using an interactive web response system (IWRS). Stratified randomization method 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, Japan, Asia excluding Japan). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3).

This will be a double-blind study in which participants/investigators will be blinded to study intervention. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for unblinding must be recorded.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

Laboratory/analyte results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded. Given possible decreases in high-density lipoprotein cholesterol (HDL-C) with S-217622 dosing, HDL-C will not be reported to the sites. These observed laboratory changes are temporary and transient and do not represent a safety concern.

6.4 Study Intervention Compliance

Compliance with study intervention will be assessed at each visit. Compliance will be assessed by participant self-report and counting of returned tablets by the study staff, during the site visits at Days 3 and 6 and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF). Date of administration of each dose will be recorded in the eCRFs.

A record of the quantity of S-217622 and placebo dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates and times, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.5 Dose Modification

There will be no dose modifications in this study.

6.6 Continued Access to Study Intervention After the End of the Study

There are no plans to provide S-217622 for poststudy treatment.

6.7 Treatment of Overdose

For this study, any dose of study intervention (S-217622 or placebo) greater than the designated dose (375 mg on Day 1 or 125 mg on Days 2 to 5) will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Treat participants with any AE/SAE resulting from overdose according to the standard of care.
2. Contact the medical monitor immediately.

3. Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
4. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 4 days).
5. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
6. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

The investigator must report the overdose to the medical monitor (see Section 8.3.7).

6.8 Prior/Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF. Any medications specific for COVID-19 (other than symptom alleviation treatment) used by the index patient must also be recorded in the eCRF. Other information collected in the eCRF includes:

- Reason for use
- Dates of administration including start and end dates
- Route of administration/dosage information including dose, route of administration and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor. Please see the following section for prohibited and precautionary medications.

6.8.1 Prohibited and Precautionary Medications

Use of the following therapies will be prohibited from the time of informed consent through 28 days after the first dose of study intervention:

- Sensitive CYP3A substrates with narrow therapeutic index. S-217622 is considered to be a strong inhibitor of CYP3A4. (Note: remdesivir and combined oral contraceptives are permitted). Examples of sensitive CYP3A substrates with narrow therapeutic index include the following medications: alfentanil, cyclosporine, dihydroergotamine, ergometrine, ergotamine, everolimus, methylergometrine, pimozide, quinidine, sirolimus, tacrolimus, terfenadine, and venetoclax.

Use of the following therapies is prohibited from the time of informed consent through 10 days after the last dose of study intervention. However, even if a prohibited concomitant therapy is used, the participant should continue the study procedures according to the specified SoA (Section 1.3) to the extent possible.

- Hydroxychloroquine, and ivermectin are prohibited due to DDIs with S-217622. Hydroxychloroquine and ivermectin are both CYP3A substrates and thus may also be substantially impacted by S-217622 with an increase in drug levels.
- Paxlovid (nirmatrelvir/ritonavir): Potential clinically significant interaction is likely expected when administered with S-217622. Coadministration of itraconazole, strong CYP3A4 inhibitor (200 mg once daily 8 doses), and nirmatrelvir/ritonavir (300/100 mg twice daily 5 doses) increased nirmatrelvir AUC and C_{max} by 39% and 19%, respectively. Given the limited safety information of coadministration of S-217622 and Paxlovid, coadministration of S-217622 and Paxlovid is not allowed. If Paxlovid is administered after the treatment period of S-217622, which is only anticipated in the case the study participant tests positive for SARS-CoV-2 and meets the study definition for COVID-19 symptoms onset (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), careful monitoring with caution of therapeutic and adverse effects are highly recommended due to the aforementioned potential increase of nirmatrelvir AUC and C_{max}.
- Corticosteroids administered via any route (including intranasal, inhaled, oral, intra-articular but excluding topical). However, prednisolone is permitted (unless specifically used to treat COVID-19) based on a lack of significant interaction in a clinical DDI study. Intranasal or inhaled fluticasone is permitted (unless specifically used to treat COVID-19) because the DDI potential by CYP3A inhibitor would be low. Furthermore, intranasal or inhaled beclomethasone is allowed based on demonstration of the lack of a significant interaction with darunavir/ritonavir [13], and dexamethasone can be administered the day after the last dose of study intervention administration based on the results of clinical DDI study with dexamethasone. If dexamethasone is required earlier and during treatment with S-217622 for urgent treatment of deteriorating disease, investigators should be aware of the continuing interaction and increased exposure to dexamethasone.
- CYP3A substrates except for sensitive CYP3A substrates with narrow therapeutic index. S-217622 is considered to be a strong inhibitor of CYP3A4. (Note: remdesivir and combined oral contraceptives are permitted). Examples of prohibited CYP3A substrates include the following medications: alprazolam, anamorelin, aprepitant, atorvastatin, avanafil, azelnidipine, blonanserin, budesonide, buspirone, chloroquine, colchicine, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eliglustat, eplerenone, felodipine, finerenone, ibrutinib, indinavir, ivabradine, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, rilpivirine, riociguat, rivaroxaban, saquinavir, sildenafil, simvastatin, suvorexant, tadalafil,

ticagrelor, tipranavir, triazolam, tolvaptan, and vardenafil. For additional CYP3A substrates, see the DDI tool provided for this study.

Use of the following therapies is prohibited from the time of informed consent through the day after the last study intervention.

- Strong CYP3A inducers. Examples include apalutamide, carbamezpine, enzalutamide, mitotane, phenytoin, phosphenytoin, rifampin and St. John's wort. For additional strong CYP3A inducers, see the DDI tool provided for this study.
- Methotrexate as organic anion transporter 3 (OAT3) substrate with a narrow therapeutic index.
- Digoxin and dabigatran as P-gp substrates with a narrow therapeutic index.
- High dose of rosuvastatin (20 to 40 mg, as it is considered BCRP substrate and S-217622 may influence the treatment by rosuvastatin when high dose of rosuvastatin is administered).

The above are examples of prohibited medications. Sites should confirm the route of metabolism of all medications to ensure not prohibited; this can be done using the DDI tool provided for this study.

6.8.2 Rescue Medications

Rescue medications administered to the study participant must be recorded in the eCRF. COVID-19 symptomatic-relief medications (such as aspirin, ibuprofen, acetaminophen, other nonsteroidal inflammatory drugs [NSAIDs], zinc, dietary supplements, herbal remedies, decongestants, cough suppressants, and antihistamines) will not be supplied as part of the study. The use of these symptomatic-relief medications for COVID-19 symptom control will be allowable at any time after symptoms develop. The participant is encouraged to start symptomatic-relief medications only after SARS-CoV-2 positive infection confirmation. Symptomatic-relief medication for prophylaxis use is prohibited.

Index patients may receive any locally available standard-of-care COVID-19 therapies as indicated in their regions.

Participants who test positive for SARS-CoV-2 infection during the study and meet the study definition for COVID-19 symptoms onset (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) may receive any locally standard-of-care COVID-19 therapies available and indicated in their regions, as long as compatible with study intervention. Compatible therapies include, but are not limited to, anti-SARS-CoV-2 mAbs, outpatient IV remdesivir, molnupiravir, convalescent plasma, inhaled budesonide, and fluvoxamine after study enrollment. If Paxlovid (nirmatrelvir/ritonavir) is administered after the treatment period of S-217622, which is only anticipated in the case the study participant tests positive for SARS-CoV-2 and meets the study definition for COVID-19 symptoms onset, careful monitoring with caution of therapeutic and adverse effects are highly recommended due to the potential increase of nirmatrelvir AUC and C_{max} (see

Section 6.8.1 for additional information). The use of S-217622 outside of the study (if commercially available in the local region) is not allowed during the study participation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1.9).

7.1 Discontinuation of Study Intervention

The investigator should make every effort to complete the study for each participant. However, study intervention will be discontinued for a participant who meets liver chemistry stopping criteria (Section 7.1.1), becomes pregnant (Section 8.3.5), or meets any of the conditions listed below. Even if study intervention is discontinued, the participant should continue the study participation and continue the study procedures according to the specified SoA (Section 1.3) as much as possible.

- If Day 1 chemistry shows an ALT or AST ≥ 5 × upper limit of normal (ULN) range or ALT or AST ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN (> 35% direct bilirubin). Blood chemistry must be repeated urgently.
- If Day 1 CrCl is < 30 mL/min (by Cockcroft-Gault).
- At the time of hospitalization (≥ 24 hours of acute care in a hospital or similar acute care facility), should this occur.
- If a Grade ≥ 3 event occurs that is deemed related to the study intervention.
- An SAE that is considered related to study intervention.
- Requirement for prohibited concomitant medications (see Section 6.8.1), if the reason the medications are prohibited is due to DDIs or other concern for toxicity.
- Request by participant to terminate treatment. NOTE: The reason for treatment discontinuation should be documented (eg, concern for AE, lack of efficacy, or other reason).
- Clinical reasons believed life threatening by site clinical staff.

To appropriately handle the intercurrent events (Table 9-1 in Section 9.3.2.1) for the primary estimand, for the participants who withdraw study intervention due to use of rescue or prohibited medication before occurrence of the event for the primary endpoint, the participants should continue participating in the study and their data should be continuously collected after withdrawal of study intervention as possible.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets 1 of the conditions outlined in Appendix 5 (Section 10.5) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.2 Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request or may be discontinued at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. However, unless there is a safety reason, the participant should only be discontinued from study intervention, while continuing to remain in the study and continuing to follow the SoA scheduled visits (Section 1.3), even while off-drug to protect the integrity of the study and the participant's well-being.

If the participant withdraws consent, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she fails to return for scheduled visits and is unable to be contacted by the site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site staff must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant by phone and the contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have discontinued from the study.

Discontinuation of specific sites or of the study as whole are handled as part of Appendix 1 (Section 10.1.9).

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Sites should, in discussion with participants and at the investigator discretion, determine the most appropriate place to conduct study visits, whether at the study site or remote based on the telehealth and the home-visit medical care options available for the site. In person visits will take place at the clinic, at the participant's home, or at another non-clinic location if the site is able to accomplish all of the scheduled study visit evaluations.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator must maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Index and/or participant demographics and other baseline characteristics will be recorded in the eCRF, such as sex, age, race, smoking, number of household contacts, vaccination status, history of infection, medical/surgical history (including history of seasonal allergies); prior and concomitant medication; target disease duration, severity, and treatment; and hospitalization status. Other items such as isolation measures status will be collected.

The number of the household members living in the same house and the number of participants from the same household members enrolled in the study will be documented.

Study participants will be asked about any preexisting COVID-19 symptoms (related to other comorbidities in the past 30 days) at the baseline. This will be collected in the eCRF.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Blood collection will be performed 5 times over the course of 7 visits for a total of approximately 62.5 mL of blood during the study.

Similar blood sample volume will be collected in pediatric study participants. Refer to the recommendations of blood samples volume in the “ethical considerations for clinical trials on medicinal products conducted with minors” guidance [14].

Blood sample collection per the SoA in Section 1.3 (including for pediatric study participants) is a critical assessment to ensure the safety of the participants enrolled in the study.

8.1 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1 Nasopharyngeal Swabs (Virology Test)

The investigator or designee will take an NP swab from index patients and participants according to the SoA (Section 1.3). The date of each sample collection will be recorded in the eCRF. Procedures for collection, storage, shipping, and measurement of samples will be specified in a separate written procedure.

At the laboratory, the amount of viral RNA will be measured, and central laboratory-confirmed RT-PCR results (positive or negative) will be determined.

Spike gene, nonstructural protein 5 (NSP5) and its cleavage site sequence analyses and phenotypic assay (see Section 8.10) will be conducted using the NP swab collected.

In NP samples with positive SARS-CoV-2 RNA, influenza RNA will be measured to investigate coinfections.

Samples may be stored and used for further analyses, such as viral titer to better understand COVID-19 transmission and progress and the effect of S-217622.

8.1.2 Participant COVID-19 Symptoms Diary

Participant-completed COVID-19 Symptoms Diary

Participants will be asked to keep a log of COVID-19 symptoms (see Appendix 6 [Section 10.6]) in a study diary. On Day 1, participants will complete the study diary prior to initiating S-217622 or placebo and during the evening. Participants will be asked to complete entries twice daily on their own from Days 1 to 28. The diary should be completed at approximately the same time every day.

Participants will be asked to measure their body temperature twice daily from Days 1 to 28 and enter the temperature in the diary. For the symptom of fever, the definition is included in Section 8.2.3. When acetaminophen is administered, it is recommended that the participant wait 4 hours prior to COVID-19 symptoms diary recording or body temperature check.

Staff Review of COVID-19 Symptoms Diary

The study diary will be reviewed by study staff in person or remotely with each participant according to the SoA (Section 1.3).

Participants who report worsening symptoms from any cause during the trial may be referred to their healthcare provider or closest emergency room, as medically indicated. Such instances will be recorded in the eCRF at the time of the notification, and during follow-up to assess study endpoints, including time to symptom resolution, hospitalization, or death.

8.1.2.1 Participants Symptom Diary - COVID-19 Severity Ranking

Participants will enter the severity of COVID-19 symptoms in the diary based on self-reported symptom severity scores. Most symptoms will be scored on a 4-point scale (none, mild, moderate, or severe); change in the sense of taste and smell will be scored on a 3-point scale (same as usual, less than usual, no sense).

8.1.3 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 a questionnaire about the participant's global impression of his/her health, activities, and severity of symptoms during the past 24 hours (see Appendix 7 [Section 10.7]).

8.1.4 Household Members of Participant Questionnaire

The participant will be asked to complete a questionnaire about the household. At Screening/Days 1, 3, 6, 10, 15, 21, and 28, the participant will be asked about the infection status of the household members who did not participate in this study (see Appendix 8 [Section 10.8]).

If multiple household members are participants in the study, only 1 household member will provide responses.

8.1.5 Participant Exposure Questionnaire

The participant will be asked to complete a questionnaire about exposure to the index patient and lifestyle before and during the COVID-19 symptomatic period of the index patient. At Screening/Day 1, the participant will be asked about the duration of time that he/she spent with the index patient before and after the onset of COVID-19 symptoms in the index patient. At Day 15, the participant will be asked about his/her method of infection prevention (eg, did you disinfect doorknobs and other common areas) and frequency of contact with the index patient (eg, did you eat meals with the index patient) (see Appendix 9 [Section 10.9]).

8.1.6 Index Patient COVID-19 Symptoms Questionnaire

At Day 1, the index patient will be asked by the investigator or designee about his/her COVID-19 symptoms. At the optional visit at Day 3, index patients who sign optional consent will be asked by the investigator or designee about his/her COVID-19 symptoms. This information will be documented in the eCRF. 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.

8.1.7 Viral RNA/Symptom Rebound

Using viral RNA from NP swabs and symptoms from participants symptom diary, the proportion of participants who have viral RNA and/or COVID-19 symptom rebound will be calculated. The viral RNA and/or COVID-19 symptom rebound will be defined in the statistical analysis plan (SAP).

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

For any abnormal laboratory test results (hematology, blood chemistry) or other safety assessments (eg, physical examination) that worsen following exposure to the study intervention from baseline, the investigator will consider whether those results are clinically significant. Abnormal laboratory test results are defined as values outside the reference range. For test results which are abnormal at baseline and significantly worsen following the initiation of the study, the investigator must also consider whether those results are clinically significant. Any test results which are considered to be clinically significant by the investigator are to be recorded as AEs. If abnormal laboratory finding is associated with disease or organ toxicity, the investigator should report only the disease or organ toxicity as an AE.

The investigator will consider test results to be clinically significant in the following circumstances (at their own discretion in the other circumstances):

- Test results that lead to any of the outcomes included in the definition of an SAE (see Section 8.3).
- Test results that lead to discontinuation from the study.
- Test results that lead to a concomitant drug treatment or other therapy.
- Test results that require additional diagnostic testing (except for a confirmatory test) or other medical intervention.
- Test results that meet the management and stopping criteria for abnormal liver function tests identified in Appendix 5 (Section 10.5).

In addition, when any test results meet the management and stopping criteria for liver function abnormalities (Section 7.1 and Appendix 5 [Section 10.5]), the results of further assessments and required follow-up should be recorded in the Liver Event Form.

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded at the Screening Visit.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

The symptom-focused physical examination (see SoA in Section 1.3) is driven by any previously identified or new AE/targeted condition that the participant has experienced and as deemed necessary by the investigator.

8.2.2 Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure, respiratory rate, and resting peripheral oxygen saturation [SpO_2]) will be measured and should be preceded by at least 5 minutes of rest prior to collection.

8.2.3 Body Temperature

- Body temperature will be measured by the site staff at the Screening Visit.
- Body temperature will be measured by the participant twice daily and recorded in his/her study diary.
- Depending on how body 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

8.2.4 Clinical Safety Laboratory Tests

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

The investigator must review the laboratory test results, document this review, and record any clinically significant changes occurring during the study as an AE. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition (see Appendix 3 [Section 10.3]). The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator. If clinically significant abnormal values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 Pregnancy Testing

Pregnancy testing will be at Screening and Day 28 (see SoA in Figure 1-4).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during participation in the study.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3).

All AEs reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent[s], legal guardian, or other LAR) must be captured in source documents.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on SAEs considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

When an AE occurs, the investigator should take appropriate medical measures such as treatment, if necessary.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

The scale used in the study diary for participant symptoms does NOT equate to the AE grading as found in the DAIDS (Division of AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017 (Appendix 3 [Section 10.3]).

The DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used and is available on the DAIDS Regulatory Support Center (RSC) website at: DAIDS AE Grading Tables | DAIDS Regulatory Support Center (RSC) (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables).

Lipids will be graded according to the DAIDS Grading Table, but will be conducted as nonfasting.

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.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs for the study participant will be collected from the date of signing of the ICF until after the Follow-up visit or 14 days after discontinuation of study intervention at the timepoints specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the contract research organization (CRO)/sponsor or designee immediately and under no circumstance should this exceed 24 hours from the timepoint when the investigator first becomes aware of the SAE, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study (out of period specified in SoA in Section 1.3), and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the CRO/sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or other documents and will notify the IRB/IEC, if appropriate, according to local requirements.

The sponsor must prepare investigator safety reports for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

The investigator must collect pregnancy information when female participants and female partners of male participants become pregnant after the initiation of study intervention and until 2 weeks after the last dose of S-217622.

If a pregnancy is reported, the investigator will record pregnancy information on the Pregnancy Form and submit it to the CRO/sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The pregnant participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the pregnant participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in pregnant former participants or pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.3.6 Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or nonserious) is defined as an AE or SAE of scientific and medical concern specific to the investigational agent, for which ongoing monitoring and rapid communication by the investigator to the sponsor is appropriate. There are no AESI defined for this study.

8.3.7 Special Situations - Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error of the study intervention (Special Situations, as defined below) must be reported to the medical monitor by the investigator using a Special Situations Report Form as soon as possible. If there are associated SAEs, the investigator must also complete and submit an SAE submission.

- Abuse - persistent or sporadic, intentional excessive use of a study intervention(s), which is accompanied by harmful physical or psychological effects.
- Misuse - intentional and inappropriate use of a study intervention(s) other than as directed or indicated at any dose.
- Overdose - intentional or unintentional intake of study intervention(s) in excess of the assigned dose in the protocol (see Section 6.7).
- Medication Error - any unintended error in the prescribing, dispensing or administration of a study intervention(s) (including intercepted error). Cases of participants missing doses of study intervention(s) are not considered reportable as medication error.

8.4 Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of S-217622 as specified in the SoA (Section 1.3). Dates and times of all PK sample collections and date and time of each dose and food condition (whether within 2 hours after food intake or not) will be recorded in the eCRF. If a PK sample is not able to be collected, the missed collection will not be considered a protocol deviation.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of S-217622. Each plasma sample will be divided into 2 aliquots (1 each for PK and a back-up). Samples for plasma concentration of S-217622 may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.5 Pharmacodynamics

Pharmacodynamic (PD) parameters will not be evaluated in this study.

8.6 Genetics/Pharmacogenomics

Genetics will not be evaluated in this study.

8.7 Biomarkers

Biomarkers will not be evaluated in this study.

8.8 Immunogenicity Assessments

Not applicable.

8.9 Health Economics/Medical Resource Utilization

8.9.1 Quality of Life Questionnaire: EQ-5D-5L

EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) will be evaluated as a health economics/medical resource utilization and health economics parameter in this study.

The EQ-5D-5L questionnaire will be collected at timepoints as specified in the SoA (Section 1.3).

The EQ-5D-5L is a standardized questionnaire developed by the EuroQol (EQ) Group to enable a simple evaluation of general health status for clinical and economic appraisal. The EQ-5D-5L questionnaire consists of 2 pages: EQ-5D-5L descriptive questionnaire and EQ Visual Analog Scale (VAS) (see Appendix 10 [Section 10.10]). The descriptive questionnaire assesses 5 parameters (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on a 5-point scale. The EQ VAS scores assess the participant's current health on a 20-cm VAS, where the best state is 100 and the worst state is 0.

The age-appropriate EuroQol-5 Dimension (EQ-5D) version will be used. Proxy versions, for completion by a caregiver or someone who knows the person well, are also available.

8.10 Other Assessments

8.10.1 SARS-CoV-2 Lineage

Analysis of SARS-CoV-2 lineage will be performed for SARS-CoV-2-infected participants. Spike gene sequence analysis will be performed using the NP swab (see Section 8.1.1) for participants who test positive for SARS-CoV-2 and for the participants corresponding index patient.

8.10.2 SARS-CoV-2 Serology Testing

SARS-CoV-2 serology testing will be collected as indicated in the SoA (Section 1.3) and includes anti-SARS-CoV-2 S-protein antibody and anti-SARS-CoV-2 N-protein antibody. Procedures for collection, storage, and shipping of samples will be specified in a separate written procedure.

8.10.3 Treatment-emergent Amino Acid Substitutions in 3CL Protease (Nonstructural Protein 5) and Its Cleavage Site

Treatment-emergent amino acid substitutions in 3CL protease (NSP5) and its cleavage site will be analyzed for SARS-CoV-2-infected participants. The NP swabs (see Section 8.1.1) will be used for a gene sequence analysis of NSP5 and its cleavage site.

8.10.4 Antiviral Activity Against SARS-CoV-2 Clinical Isolates

The antiviral activity of S-217622 against SARS-CoV-2 clinical isolates derived from NP swabs (see Section 8.1.1) of participants who have confirmed treatment-emergent amino acid substitutions in NSP5 and its cleavage site will be evaluated.

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints. Any unplanned additional analyses after unblinding will be mentioned in the clinical study report (CSR) separately from the planned analyses.

9.1 Statistical Hypotheses

For each of the 2 populations, ie, the population of all participants randomly assigned to study intervention with a negative screening SARS-CoV-2 infection, confirmed by RT-PCR result (central laboratory) based on NP swab sample at Visit 1 (pre-intervention) (modified intention-to-treat [mITT] population defined in Section 9.2) and the population with all participants randomly assigned to study intervention (intention-to-treat [ITT] population defined in Section 9.2), the primary endpoint (the proportion of participants who are infected with SARS-CoV-2 [central laboratory-confirmed positive RT-PCR test] and have COVID-19 symptoms onset through Day 10) will be compared between S-217622 group and placebo group at a 2-sided significance level of 0.05 based on a statistical hypothesis test. For the 2 statistical tests with different populations, the fixed-sequence procedure will be applied with the order of the mITT population first and the ITT population next for multiplicity adjustment; details are described in Section 9.3.2.

For the secondary endpoints, while comparison between the S-217622 group and the placebo group will be performed, multiplicity adjustment will not be performed.

9.2 Analysis Sets

Consisting of participants in whom the study has been conducted in compliance with Good Clinical Practice (GCP), the populations are defined as follows.

Participant Analysis Set	Description
Enrolled	All participants who sign the ICF, complete screening assessments, and have met all eligibility requirements
Intention-to-treat (ITT) Population	All participants randomly assigned to study intervention
Modified Intention-to-treat (mITT) Population	All participants randomly assigned to study intervention with a negative screening SARS-CoV-2 infection, confirmed by RT-PCR result (central laboratory) based on NP swab sample at Visit 1 (pre-intervention), and who are associated with index patients who meet the inclusion criteria. Participants will be analyzed according to the assigned study intervention.
Per Protocol Set	All participants in the mITT population and without any major protocol deviations

Participant Analysis Set	Description
Safety Analysis Population	All participants randomly assigned to study intervention and received at least 1 dose of study intervention; participants will be analyzed according to the initial study intervention they actually received
PK Analysis Set	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

The ITT and mITT populations and the Per Protocol Set will be used to analyze endpoints related to the efficacy objectives, and the Safety Analysis Population will be used to analyze the endpoints and assessments related to safety.

9.3 Statistical Analyses

9.3.1 General Considerations

For continuous variables, summary statistics will be calculated for number of participants (N), 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.

Missing data will not be imputed. All statistical tests will be performed at a 2-sided significance level of 0.05 unless otherwise specified. In general, baseline will be defined as the last value obtained before receiving the first dose of study intervention. All participant data will be presented in listings by participant. All analyses and tabulation of listings will be performed using SAS version 9.4 (or higher).

9.3.2 Efficacy Analyses

9.3.2.1 Primary Endpoint

The primary estimand, the primary endpoint, and the related information for the primary estimand are described in Table 9-1.

Table 9-1 Summary of the Primary Estimand and the Primary Endpoint

Primary estimand	The occurrence of infection with SARS-CoV-2 (central laboratory-confirmed 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 study before occurrence of the event for the primary endpoint Treatment policy strategy will be used to evaluate treatment effects irrespective of intercurrent events (eg, 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 intercurrent events "b or c", the participant will be assumed to have been infected with SARS-CoV-2 with symptoms from the time of death, hospitalization, or withdrawal.
Primary endpoint	Proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed 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 (central laboratory-confirmed positive RT-PCR test) and have COVID-19 symptoms onset through Day 10 between S-217622 and placebo

COVID-19 = coronavirus disease 2019; mITT = modified intention-to-treat; RT-PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

The primary endpoint is proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have COVID-19 symptoms onset through Day 10.

Missing data that are not a result of an intercurrent event will not be imputed.

The participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have COVID-19 symptoms through Day 10 are defined as the study participants who met both of the following criteria in the mITT population:

- SARS-CoV-2 infection through Day 10 after the first study intervention confirmed by central laboratory-confirmed RT-PCR positive
- The onset of COVID-19 symptoms (see definition below) through Day 10 after the first study intervention

COVID-19 symptoms onset in study participants 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 ≥ 38.0°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.

The primary analysis for the primary endpoint will compare the proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have COVID-19 symptoms onset through Day 10 between the 2 treatment arms and express the effect by risk ratio in the mITT population. The comparison will be based on a model providing population-averaged estimates using a generalized estimating equations (GEE) approach for a Poisson regression and accounting for clustering within households and the stratification factors of 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, Japan, Asia excluding Japan). In the GEE approach, an exchangeable structure will be applied to model the correlation between any pair of participants within the same household and the sandwich estimator for the structure will be used for the robust inference. Under this model, risk ratio of S-217622 group to placebo group will be estimated, 95% confidence interval (CI) of the risk ratio and the p-value for testing the null hypothesis that the risk ratio is 1 will be calculated using the Poisson regression model. When the model will be applied, the intercurrent events and missing data will be handled according to Table 9-1.

As the key secondary analysis of the primary endpoint, the same analysis as that of the primary analysis will be conducted in 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, 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.

If estimation by the GEE approach in the primary analysis and the key secondary analysis cannot be done due to failure of parameter convergence, the analysis method will be changed from the GEE approach to the modified Poisson regression model with robust variance, which includes 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, Japan, Asia excluding Japan) as covariates.

Supplemental analyses for the primary endpoint

The proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have COVID-19 symptoms onset through Days 10, 15, 21, and 28 will be analyzed using the same analysis method as that of the primary analysis in the mITT and ITT populations.

For the primary endpoint, the same analysis method as that of the primary analysis will be performed by changing symptoms duration from at least 48 hours to at least 24 hours in the definition of COVID-19 symptoms onset. The analyses will be performed in the mITT and ITT populations.

The analysis with the following handling of intercurrent events and missing data will be performed by the same method as the primary analysis of the primary endpoint in the mITT and ITT populations.

- Handling of intercurrent events
  - While on treatment strategy will be used to evaluate treatment effects when completing study intervention before occurrence of intercurrent events.
    - Intercurrent events a (Table 9-1): the participants with intercurrent events a will be excluded from the analysis.
    - Intercurrent events b (Table 9-1): the participants with intercurrent events b will be excluded from the analysis.
- Missing data handling
  - Participants who withdraw the study (lost to follow-up) prior to occurrence of the event for the primary endpoint will be excluded from the supplemental analysis.

For the Per Protocol Set, the same analysis as the primary analysis will be performed.

Sensitivity analyses for the primary endpoint

The following analyses will be performed as sensitivity analyses for the primary endpoint in the mITT and ITT populations:

- Proportion of the participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have COVID-19 symptoms onset through Day 10, along with the associated 95% CI calculated using the Clopper-Pearson method, will be presented by each treatment group.
- Comparison based on risk difference in the proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have COVID-19 symptoms onset through Day 10 will be performed between S-217622 and placebo using the Mantel-Haenszel test 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, Japan, Asia excluding Japan).

- Comparison between groups using the modified Poisson regression model [15] with robust variance will be performed. Risk ratio of S-217622 group to placebo group will be estimated and 95% CI of the risk ratio and the p-value for testing the null hypothesis that the risk ratio is 1 will be calculated using the modified Poisson regression model. The model will include 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, Japan, Asia excluding Japan) as covariates.

9.3.2.2 Secondary Endpoints

- Proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) through Days 10, 15, 21, or 28, regardless of occurrence of COVID-19 symptoms

  This is defined as the proportion of study participants who are infected with SARS-CoV-2 by central laboratory-confirmed RT-PCR positive until Day 10 after the first administration of study intervention regardless of occurrence of COVID-19 symptoms. The same analyses as described for the evaluation of the primary endpoint will be performed for the mITT and ITT populations. As supplemental analyses for this secondary endpoint, the same analysis method will be conducted through Days 10, 15, 21, and 28.

- Time to the first central laboratory-confirmed positive RT-PCR result

  This is defined as the time from the start of the study intervention to the first confirmation of a central laboratory-confirmed positive RT-PCR result. For the mITT and ITT populations, Kaplan-Meier curves will be plotted for each treatment group and pairwise comparison between S-217622 and placebo will be performed using a log-rank test 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, Japan, Asia excluding Japan). Restricted mean survival time (RMST) with a follow-up time of 28 days and its 95% CI will be estimated by treatment group, and the difference in RMST between S-217622 and placebo and its 95% CI will be calculated. Furthermore, p-value for the null hypothesis that the difference in RMST is 0 will be calculated. 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, Japan, Asia excluding Japan) will be used as stratification factors when calculating the p-value.

- Proportion of participants with central laboratory-confirmed positive RT-PCR result at each timepoint

  This is defined as the proportion of study participants who tested central laboratory confirmed-positive RT-PCR at each timepoint. The proportion of participants with central laboratory-confirmed positive RT-PCR results will be calculated by each treatment group and each timepoint for the mITT and ITT populations. In addition, the Mantel-Haenszel test will be applied to perform a comparison between S-217622 and placebo group. 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, Japan, Asia excluding Japan) will be used as the stratification factors of the Mantel-Haenszel test.

- AUC of change in amount of SARS-CoV-2 viral RNA

  This is defined as the AUC of change from baseline in amount of SARS-CoV-2 viral RNA. Baseline will be defined as the last value obtained before receiving the first dose of study intervention (at the enrollment with central laboratory-confirmed RT-PCR negative) and baseline value will be used as lower limit of quantification of SARS-CoV-2 viral RNA. The AUC will be evaluated from Days 1 to 10 and will be calculated by the trapezoidal method. For the mITT and ITT populations with central laboratory-confirmed RT-PCR positive from Days 1 to 10, analysis of covariance (ANCOVA) model will be applied to perform pairwise comparison of the AUC between S-217622 and placebo group. 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, Japan, Asia excluding Japan) will be used as covariates in the ANCOVA model. In addition, the summary statistics will be calculated by each treatment group.

- Proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have no COVID-19 symptoms onset through Day 10

  This is defined as the proportion of study participants who are infected with SARS-CoV-2 by central laboratory-confirmed RT-PCR positive and have no COVID-19 symptoms onset development until Day 10 after administration of study intervention. The same analyses as described for the evaluation of the primary endpoint will be performed for the mITT and ITT populations.

- Proportion of participants who are infected with SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) and have no COVID-19 symptoms through Day 10

  This is defined as the proportion of study participants who met both of 2 criteria in the mITT and ITT populations.

  – SARS-CoV-2 infection until Day 10 after the first study intervention confirmed by central laboratory-confirmed RT-PCR positive
  – No COVID-19 symptoms occurrence during Day 10 after the first study intervention

  The same analyses as described for the evaluation of the primary endpoint will be performed for the mITT and ITT populations.

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

  This is defined as the proportion of study participants who achieved the sustained resolution in all COVID-19 symptoms (except for loss of smell or taste) through

Day 28. This analysis will include the participants in the mITT and ITT populations who experience the event for primary endpoint. Sustained symptoms resolution is defined as complete resolution (or improvement to the status before start of study intervention for study participants with pre-COVID-19 symptoms) of COVID-19 symptoms (except for loss of smell or taste) based on participant symptoms diary which continues for 2 or more consecutive days.

For the participants who experience the event for the primary endpoint in the mITT and ITT populations, the same analyses as described for the evaluation of the primary endpoint will be performed.

- 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

  This is defined as the proportion of study participants who achieved the sustained resolution in the 5 key COVID-19 symptoms (nasal congestion or runny nose, sore throat, cough, fever, and fatigue) through Day 28. This analysis will include the participants in the mITT and ITT populations who experience the event for the primary endpoint, and who have at least 1 of the 5 key COVID-19 symptoms.

  Sustained symptoms resolution is defined as complete resolution (or improvement to the status before start of study intervention for study participants with pre-COVID-19 symptoms) of the 5 key COVID-19 symptoms based on participant symptoms diary which continues for 2 or more consecutive days.

  For the participants who experience the event for the primary endpoint in the mITT and ITT populations, and who have at least 1 of the 5 key COVID-19 symptoms, the same analyses as described for the evaluation of the primary endpoint will be performed.

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

  This is defined as the proportion of study participants who achieved the sustained resolution in each COVID-19 symptoms (except for loss of smell or taste) through Day 28. This analysis will include the participants in the mITT and ITT populations who experience the event for primary endpoint. Sustained symptoms resolution is defined as complete resolution (or improvement to the status before start of study intervention for study participants with pre-COVID-19 symptoms) of each target COVID-19 symptom (except for loss of smell or taste) based on participant symptoms diary which continues for 2 or more consecutive days. The target COVID-19 symptom in this analysis is the symptom confirmed when the participants experience the event for primary endpoint. For the participants who experience the event for the primary endpoint in the mITT and ITT populations, the same analyses as described for the evaluation of the primary endpoint will be performed.

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

  This is defined as the change from baseline in total score of COVID-19 symptoms at each timepoint. For the endpoint, baseline will be defined as the first day when the participants experience the event of the primary endpoint. For the participants who experience the event for the primary endpoint in the mITT and ITT populations, the same analyses as described for the evaluation of AUC of change in amount of SARS-CoV-2 viral RNA will be performed.

- Change in total score of the 5 key COVID-19 symptoms at each timepoint

  This is defined as the change from baseline in the total score of the 5 key COVID-19 symptoms at each timepoint. For the endpoint, baseline will be defined as the first day when the participants experience the event for primary endpoint, and who have at least 1 of the 5 key COVID-19 symptoms. For the participants who experience the event for the primary endpoint in the mITT and ITT populations, and who have at least 1 of the 5 key COVID-19 symptoms, the same analyses as described for the evaluation of AUC of change in amount of SARS-CoV-2 viral RNA will be performed.

- Time from first confirmed SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) until at least 1 COVID-19 symptom through Day 28

  This is defined as the time from confirmation RT-PCR positive (central laboratory-confirmed) to onset of at least 1 COVID-19 symptom through Day 28. The same analyses as described for the evaluation of the time to first positive RT-PCR result will be performed for the participants who confirmed RT-PCR positive in the mITT and ITT populations.

- Time from first confirmed SARS-CoV-2 (central laboratory-confirmed positive RT-PCR test) until COVID-19 symptoms onset through Day 28

  This is defined as the time from confirmation RT-PCR positive (central laboratory-confirmed) to COVID-19 symptoms onset (see definition in Appendix 6 [Section 10.6]) through Day 28. The same analyses as described for the evaluation of the time to first positive RT-PCR result will be performed for the participants who confirmed RT-PCR positive after start of study intervention in the mITT and ITT populations.

- AUC of the daily total symptom score associated with COVID-19 over time from COVID-19 symptoms onset (see definition in Appendix 6 [Section 10.6]) through Day 28

  This is defined as the AUC of total score of COVID-19 symptoms from baseline to Day 28. The baseline in the endpoint will be defined as the first day when the participants experience the event of the primary endpoint. The total symptom score on a given day is defined as the sum of scores for the targeted symptoms in the participant's study diary (each individual symptom is scored 0 if reported as none, 1 if mild, 2 if moderate, and 3 severe). The same analyses as described for the evaluation of the AUC of change in SARS-CoV-2 viral RNA will be

performed for the participants who experience the event for the primary endpoint in the mITT and ITT populations.

- 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

  This is defined as the AUC of the total score of the 5 key COVID-19 symptoms from baseline to Day 28. The baseline in the endpoint will be defined as the first day when the participants experience occurrence (or worsening in the case of preexisting COVID-19 symptoms) of at least 2 of the 5 key COVID-19 symptoms for at least 24 hours. The total symptom score on a given day is defined as the sum of scores for the 5 key symptoms in the participant's study diary (each individual symptom is scored 0 if reported as none, 1 if mild, 2 if moderate, and 3 severe). The same analyses as described for the evaluation of the AUC of change in SARS-CoV-2 viral RNA will be performed for the participants who experience occurrence (or worsening in the case of preexisting COVID-19 symptoms) of at least 2 of the 5 key COVID-19 symptoms for at least 24 hours in the mITT and ITT populations.
- Proportion of participants with hospitalization or death from any cause through Day 28

  This is defined as the proportion of participants with hospitalization or death from any cause through Day 28 in the mITT and ITT populations. Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms or urgent care clinics. The same analyses as described for the evaluation of the primary endpoint will be performed for the mITT and ITT populations.

9.3.2.3 Exploratory Endpoints

Selected exploratory endpoints are listed below; additional exploratory endpoints may be added. Additional exploratory endpoints and the detail of the exploratory analyses for these will be described in the SAP.

- 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
- Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the central laboratory-confirmed positive RT-PCR reported cases in the household
- Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the incidence of SARS-CoV-2 ill case within their household contacts
- SARS-CoV-2 variant based on NP swab spike gene sequence
- Treatment-emergent amino acid substitutions based on NP swab NSP5 and its cleavage site gene sequence
- S-217622 antiviral activity (50% effective concentration [EC_{50}])
- Change from baseline in EQ-5D-5L

- Proportion of participants who achieve baseline or better health through Day 28 in EQ-5D-5L
- Change from baseline in Global Impression Questionnaire
- Proportion of participants who achieve baseline or better health through Day 28 in Global Impression Questionnaire
- Proportion of participants who are coinfected with influenza and SARS-CoV-2
- 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 symptoms through Day 28

9.3.2.4 Subgroup Analyses of Efficacy Endpoints

- Age of the study participants
- Treatment of the index patient
- Index patients with COVID-19 upper respiratory symptoms at baseline
- Time from onset of COVID-19 symptoms in the index patient to randomization of study participant
- High-risk factors (with any high-risk factors and without any high-risk factors)

9.3.3 Safety Analyses

All safety analyses will be performed using the Safety Analysis Population.

9.3.3.1 Adverse Events

Adverse events will be classified by System Organ Class and Preferred Term according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Medical Dictionary for Regulatory Activities (MedDRA). Adverse events reported on the eCRF that occur after the first dose of study intervention (ie, TEAEs) will be used for safety analyses.

The number and proportion of participants with TEAEs, deaths, other serious TEAEs, and TEAEs leading to treatment discontinuation will be tabulated by treatment groups. The 95% CIs of these incidences will be calculated by the Clopper-Pearson method. The number of AEs reported will also be presented. AEs assessed as “related” to study intervention will be defined as adverse drug reactions and summarized in the same manner as TEAEs. For summary of TEAEs by System Organ Class and Preferred Term, the number and proportion of participants with TEAEs will be presented by treatment group. They will also be summarized by severity, outcome, and time of onset.

9.3.3.2 Laboratory Tests

Summary statistics for observed values and changes from baseline at each scheduled timepoint after randomization (including baseline) will be calculated by treatment group. Qualitative laboratory data will be summarized in shift tables for test categories between baseline and scheduled timepoints.

9.3.3.3 Vital Signs

Summary statistics for observed values and changes from baseline at each scheduled timepoint after randomization (including baseline) will be calculated by treatment group.

9.3.3.4 Body Temperature

Summary statistics for observed values and changes from baseline at each scheduled timepoint after randomization (including baseline) will be calculated by treatment group.

9.3.4 Pharmacokinetic Analyses

Pharmacokinetic samples will be collected at Visits 2 (anytime) and 3 (anytime), and the Event-driven Visit.

For the PK concentration population, plasma concentrations of S-217622 will be listed by participants and visit along with the time elapsed from the last dosing of study intervention prior to blood sampling. 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}) on Day 3 with N, mean, SD, coefficient of variation (CV%, calculated as SD/mean × 100), geometric mean and its coefficient of variation (CV% geometric mean), median, minimum and maximum values. The CV% geometric mean will be calculated according to the following formula: CV% geometric mean = $[\exp(SD^2) - 1]^{1/2} \times 100$, where SD is the standard deviation for natural log (ln)-transformed data. C_{trough} may be also summarized by the age and/or body weight group.

If C_{trough} is below the lower limit of quantification, mean, SD, CV%, minimum, median, and maximum will be calculated as 0, and that value will not be included in the calculation of geometric mean and CV% geometric mean.

After plasma concentration measurement, the data for which inappropriateness for analysis can be clearly explained by the person in charge of PK analysis at the sponsor will be excluded. The reason for any exclusion should be described in the 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.

9.3.5 Disposition of Participant Population

Analyses will be performed for all randomized participants. The number and proportion of participants who received study intervention, the number and proportion of participants who completed the study, and the number and proportion of participants who prematurely discontinued the study will be summarized by treatment group. In addition,

reasons leading to discontinuation will be summarized by treatment group. The number of participants in each analysis population and the proportion of participants to those allocated to each treatment group will also be presented. The number and proportion of participants included in and excluded from each analysis population will be summarized. Participants with protocol deviations will be listed.

9.3.6 Demographics and Baseline Characteristics

Analyses will be performed for the mITT population and Safety Analysis Population. For each analysis population, demographics and baseline characteristics will be summarized by treatment group using descriptive statistics.

9.3.7 Medical Histories and Complications

Analyses will be performed for the mITT population and Safety Analysis Population. For each analysis population, medical histories, and complications will be summarized by treatment group. Participants with medical histories and complications will also be listed.

9.3.8 Prior and Concomitant Therapies

Analyses will be performed for the mITT population and Safety Analysis Population. Prior/concomitant medication will be coded using the World Health Organization Drug Dictionary (WHODD). For each analysis population, the number of participants who received prior medications will be tabulated by treatment group. Participants who received prior medications will be also listed. The same tabulation and listing will be performed for prior therapies, concomitant medications, and concomitant therapies.

9.3.9 Treatment Compliance

For randomized participants whether or not at least 1 study intervention was administered will be tabulated. Summary statistics of the number of days of administration of study intervention, accumulated dosage and the compliance rate will be calculated by treatment group for the mITT, ITT and the Safety Analysis Populations.

9.4 Interim Analysis

No interim analysis will be planned in this study.

9.5 Sample Size Determination

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.

For the analysis of the primary endpoint, a total of 92 participants who experience an event (event defined as meeting definition of the primary endpoint) within the primary analysis population will be required to detect the difference between S-217622 and placebo in the proportion of participants who experience the event using an exact conditional test with at least 90% power at a 2-sided significance level of 0.05. This is assuming that the proportion in the placebo group is 7.0%, the risk ratio (vs. placebo) is 0.5, and the number of event occurrences follows the Poisson distribution [16].

In the report published by CDC [9], the proportion of the secondary infection (occurrence of household onset or positive test) after the fourth day of the first index patient's symptom onset or positive result was approximately 35%. In addition, in the Phase 2b/3 part of Study 2108T1221 for asymptomatic/mildly symptomatic SARS-CoV-2-infected patients for therapeutic administration of S-217622, the proportion of participants who had asymptomatic infection at randomization and met the definition of symptom onset (at least 1 of the 14 COVID-19 symptoms, for at least 48 hours) through Day 10, was 18.2% (4/22) (95% CI: 5.2%, 40.3%) in participants who were asymptomatic at randomization and were enrolled after March 2022, when an epidemic of the Omicron strain was confirmed. Based on this result, it is assumed that 20% of the participants in the placebo group who are RT-PCR positive will meet the symptom onset in Study 2206T1331. By assuming that 35% of randomized participants will show central laboratory positive tests and 20% of those with central laboratory-confirmed RT-PCR positive tests will develop symptoms, 7.0% of participants in the placebo group who test negative for RT-PCR prior to dosing will meet symptoms onset. Based on this consideration, the assumed proportion of participants in the placebo group is set to 7.0% (35% × 20%).

As an assumed value of the risk ratio, which is the difference between groups, it is clinically meaningful to halve the risk of SARS-CoV-2 infection and occurrence of COVID-19 symptoms in a family member who has close contact with family members living together. A risk ratio of 0.5 was set for detecting a prevention effect of S-217622. In the postexposure prophylaxis study of bamlanivimab/etesevimab and REGEN-COV, the risk ratio was 0.43 at Day 57 and 0.17 at Day 28 [17]. However, considering that the efficacy is reported to wane for the Omicron variant [18] and S-217622 is administered orally, the risk ratio of 0.5 is clinically meaningful. Based on these results, the proportion of placebo group is set to 7.0% and the risk ratio is set to 0.5 to detect as the treatment effect of S-217622 in this study.

A total of 1754 participants will be required for the primary analysis of the primary endpoint based on the above assumptions. Assuming that 20% of enrollment will be excluded from the mITT population as a result of central laboratory-confirmed positive RT-PCR at baseline due to the high false negative rates reported by a rapid antigen test, approximately 2200 participants will be randomized in the study.

The number of participants to be randomized may be changed based on the proportion of participants who are central laboratory-confirmed RT-PCR positive at baseline and the number of participants meeting the primary endpoint definition calculated during the study because the enrollment will continue until the number of events reaches the required number of events (92 events). For example, a total of 2080 participants will be required for the primary analysis of the primary endpoint if the proportion of participants in the placebo group were reduced from 7.0% to 5.9%, and the risk ratio assumption was maintained at 0.5. With the same assumption that 20% of enrollment will be excluded from the mITT population as a result of central laboratory-confirmed positive RT-PCR at baseline due to the high false negative rates reported by a rapid antigen test, approximately 2600 participants would need to be randomized in the study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted by all involved parties in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations (including European regulation 536/2014 Annex I Section D No. 17 lit. a)
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated. Competent authority notification, review and approval may be required as appropriate according to local country requirements.
- Protocols and any amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to participants as appropriate according to local country requirements.
- For studies to be submitted as part of a European Union marketing authorisation application (MAA), the sponsor will select a CSR Coordinating Investigator who will sign the CSR.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

The investigator and sub-investigator(s) will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

The information on financial disclosure for investigators will be addressed in a separate agreement between the sponsor and the investigator.

10.1.3 Informed Consent Process

- The investigator or designee must explain and answer all questions regarding the nature of the study, including the risks and benefits, to the index patient, participant or their LAR(s). A LAR is an individual or judicial or other body authorized under applicable law to consent on behalf of a perspective participant to the participation in the procedures involved in the research. The LAR may be a parent, grandparent, or caregiver who has the legal authority to grant consent on behalf of the index patient or participant.
- Index patient and participants must be informed that their participation is voluntary. Index patient, participants or their LAR(s) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and privacy and data protection requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent was obtained before the index patient and participant was enrolled in the study and the date that written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- The investigator or designee must explain the exploratory study of the association between the index patient's viral RNA. If the index patient signs a statement of informed consent for the study and agrees to complete an optional visit, the index patient will have an optional visit completed at the site.
- Index patients and participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed ICF(s) must be provided to the index patient, participant or their LAR(s).

10.1.3.1 Minor Index Patients and Participants

- Index patients, participants, and their parent(s), legal guardian, or other LAR, must be informed that their participation is voluntary. Index patients, participants or their LAR will be required to provide a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that the parent(s), legal guardian, or other LAR consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained before the index patient and participant was enrolled in the study and the date the written consent was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICF was the index patient's or participant's parent(s), legal guardian, or other LAR. The acceptable person obtaining the informed consent must also sign the ICF.
- Index patients, participants and their parent(s), legal guardian, or other LAR must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.
- Minor index patients and participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.
- A copy of the ICF(s) must be provided to the index patient, participant or their parent(s), legal guardian, or other LAR.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant directly identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- In the event of an unauthorized disclosure of the study data that compromises the security, confidentiality or integrity of the study data maintained by the sponsor or CRO, the sites shall notify the study participants without delay after becoming aware of any personal data breach and provide reasonable information under the Data Protection Laws.

10.1.4.1 Organizational Measures to Protect Personal Data

Information technology systems are used by site staff to transfer pseudonymized study data to the sponsor and CRO. Access to the study data will be restricted and carefully managed by the CRO and sponsor. The sponsor and CRO members assigned to the study will have access to these systems throughout the study, furthermore access may be limited according to the individual's roles and responsibilities and on a need-to-know basis to carry out his/her role. Access will be revoked when team members change or stop working on the study.

At the end of the study, the pseudonymized clinical data may be made available to members of the sponsor who require access for further research and product development. The sponsor may make coded participant-level study data available to qualified researchers for approved future scientific research to be conducted in the country or abroad. Data sharing requests will be subject to formal approval processes, and safeguards will be put in place to control access and protect privacy.

10.1.5 Committee Structure

A data safety monitoring board (DSMB) will review interim safety results.

There will be interim analyses of safety data for review by the DSMB after prespecified enrollment milestones are met. The frequency of these interim analyses reviews will be decided by the sponsor and the DSMB. All available appropriate follow-up data will be reviewed at each of these interim analyses.

Further details of the DSMB reviews are described in the DSMB Charter.

10.1.6 Dissemination of Clinical Study Data

Results of this study will be made public on the US National Institutes of Health's website www.ClinTrials.gov.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF by the investigator or authorized designee unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in case report form (CRF) completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined in the appropriate study plans to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and

important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator or the site for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

- Source documents provide evidence of the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents are defined as original documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical study).
- The investigator must maintain accurate documentation (source data) that supports the information recorded in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

Study Start

The start date of the study is defined as the date of informed consent obtained from the first participant.

End of Study

The end of study is defined in Section 4.4.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Reasons for premature termination of the study by the sponsor may be safety concerns, new information that changes the risk benefit assessment negatively, if the study is not found to be feasible with reasonable effort, or if the development of the study intervention is discontinued

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected, data have been collected, and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development or other reasons as described above

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no (evaluated after a reasonable amount of time) recruitment of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

- All information regarding study intervention supplied by the sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and must not use it for other purposes without consent from the sponsor.
- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed as specified in the laboratory manual.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 10-1 Protocol-required Safety Laboratory Assessments

Laboratory assessments	Parameters
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[a]	CRP, ferritin, glucose, non-fasting lipid profile (HDL-C, LDL-C, triglycerides), liver function tests (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, and total protein), renal function tests (BUN, creatinine, potassium, sodium, CrCl will be calculated, chloride, calcium, and phosphorus)
Coagulation test	PT-INR, APTT, fibrinogen

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CrCl = creatinine clearance; CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; PT-INR = prothrombin time-international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal

a Details of liver chemistry stopping criteria and suggested actions and follow-up assessments after liver stopping are given in Appendix 5 (Section 10.5). All events of ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and INR > 1.5, if INR measured which may indicate severe liver injury, must be reported as an SAE.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An 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: 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.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, blood chemistry, or urinalysis) or other safety assessments (eg, electrocardiograph (ECG), radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or severity of the condition. • New condition detected or diagnosed after study intervention administration even though they may have been present before the initiation of the study. • Signs, symptoms, or the clinical sequelae of a suspected DDI. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or results in death. • Hospitalization for preplanned and elective procedures to treat a preexisting condition that did not worsen after initiation of study will not be considered an AE,

and therefore will not be considered an SAE despite requiring hospitalization. These procedures will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section. The exception is when the participant experiences another event during/following the procedure.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the initiation of the study that do not worsen.
- Any clinically significant screening assessments (baseline). These events will be recorded on the Medical History/Current Medical Conditions sections of the eCRF not the AE section.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

f. Other situations

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor/CRO in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor/CRO. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor/CRO.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at:

DAIDS AE Grading Tables | DAIDS Regulatory Support Center (RSC) (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables).

Lipids will be graded according to the DAIDS Grading Table, but 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.

The investigator or qualified designee will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following DAIDS categories:

- Grade 1 (Mild): Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
- Grade 2 (Moderate): Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.
- Grade 3 (Severe): Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
- Grade 4 (Potentially life-threatening): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
  - The relationship of an event to the study intervention will be determined by the investigator according to the following criteria:
    - Related: An AE which can be reasonably explained as having been caused by the study intervention. For example, the occurrence of the AE can be explained by any of the following: a pharmacological effect of the study intervention (eg, a similar event had been reported previously); an increase/decrease of the dose affects the occurrence or seriousness of the AE; or all other causative factors (eg, medical history, concomitant medication, etc) can be ruled out after careful analysis of sufficient information.
    - Not related: An AE which cannot be reasonably explained as having been caused by the study intervention.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- The investigator should provide rationale for the causality assessment in the eCRF or if reporting via paper, the rationale for causality should be provided in the narrative section of SAE form.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor/CRO. However, **it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor/CRO.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor/CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

Follow-up of AEs and SAEs
• If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor/CRO with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor/CRO within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

All SAEs must be reported to the sponsor/CRO in detail via electronic data capture (EDC) within 24 hours from the timepoint when the investigator first becomes aware of the SAE.

SAE Reporting to the sponsor/CRO via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor/CRO will be EDC.
- If EDC is unavailable, then the site will use the paper SAE form to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a participant or receives updated data on a previously reported SAE after EDC has been taken off-line, then the site can report this information on a paper SAE form to the medical monitor/sponsor's safety group by fax.
- Contacts for SAE reporting can be found in the safety management plan and below:

  Safety Fax Number: 844-220-5303, 06-6233-2540

  Email address: ClinicalSAE@shionogi.com, ctsafetyinfo@shionogi.co.jp

SAE Reporting to sponsor/CRO via Paper SAE Form

- Facsimile transmission of the paper SAE form is the preferred method to transmit this information to the medical monitor/sponsor's safety group.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the paper SAE form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the paper SAE form within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the safety management plan and below:
- Safety Fax Number: 844-220-5303, 06-6233-2540

  Email address: ClinicalSAE@shionogi.com, ctsafetyinfo@shionogi.co.jp

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal (see definition below) unless permanently sterile.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP.

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented tubal ligation
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), discretion of the investigator/subinvestigator should be applied to determining study entry.

     Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     – A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than a single FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency Failure rate of < 1% per year when used consistently and correctly
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] PLUS an additional barrier method • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion • Vasectomized partner (*Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)* • Combined (estrogen- and progestogen-containing) hormonal contraception[c] associated with inhibition of ovulation (eg, oral, intravaginal, transdermal, injectable) PLUS an additional barrier method • Progestogen-only hormone contraceptive[c] associated with inhibition of ovulation: oral, injectable PLUS an additional barrier method
Highly Effective Methods[b] That Are User Dependent Failure rate of < 1% per year when used consistently and correctly
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a Contraceptive use by men or women should be consistent with regulations regarding the methods of contraception for those participating in clinical studies. b Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c S-217622 may lead to an increase or decrease of hormonal contraception levels. Therefore, hormonal contraception must not be used alone and must be combined with other barrier method. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

10.5 Appendix 5: Liver Safety: Actions and Suggested Follow-up Assessments

Liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Liver Chemistry Stopping Criteria and Follow-up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria - Liver Events Meeting the Stopping Criteria</th></tr>
<tr><td>Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)</td><td>ALT or AST ≥ 5 × upper limit of normal (ULN)</td></tr>
<tr><td>Duration of ALT or AST elevation</td><td>ALT or AST ≥ 3 × ULN persists for ≥ 4 weeks</td></tr>
<tr><td>Bilirubin[a,b]</td><td>ALT or AST ≥ 3 × ULN AND bilirubin ≥ 2 × ULN (> 35% direct bilirubin)</td></tr>
<tr><td>International normalized ratio (INR)[b]</td><td>ALT or AST ≥ 3 × ULN AND INR > 1.5, if INR obtained</td></tr>
<tr><td>Monitoring not possible</td><td>ALT or AST ≥ 3 × ULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptoms[c]</td><td>ALT or AST ≥ 3 × ULN with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required actions and monitoring and recommended follow-up</th></tr>
<tr><th>Actions</th><th>Follow-up assessments</th></tr>
<tr><td>• Immediately discontinue study intervention.
• Report the event to the sponsor within 24 hours.
• Complete the Liver Event Form, and also complete the serious adverse event “SAE” page if the event also meets the criteria for an SAE[b].
• Perform liver function follow-up assessments.
• Monitor the participant until liver function test abnormalities resolve, stabilize, or return to baseline (see MONITORING below).
• Do not restart/rechallenge participant with study intervention unless stipulated in the protocol and approved by the sponsor.
• If study intervention restart/rechallenge is not stipulated in the protocol or not approved, discontinue study intervention. Participants may remain in the study and continue to be followed for protocol specified follow-up assessments.
MONITORING:
If ALT or AST ≥ 3 × ULN AND bilirubin ≥ 2 × ULN or INR > 1.5:
• Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and</td><td>• Viral hepatitis serology[d]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend.
• If the participant is discontinued during the treatment period, collect blood for measurement of plasma concentrations to measure the plasma concentrations of S-217622[e].
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
• Fractionate bilirubin, if total bilirubin ≥ 2 × ULN
• Complete blood count with differential to assess eosinophilia.
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the adverse event (AE) of electronic case report form (eCRF)
• Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications of eCRF
• Record alcohol use in the Liver Event Form.</td></tr>
</table>

perform liver function follow-up assessments **within 24 hours**. • Monitor participants twice weekly until liver function abnormalities resolve, stabilize, or return to baseline • A specialist of hepatology consultation is recommended. **If ALT or AST ≥ 3 × ULN AND bilirubin < 2 × ULN and INR ≤ 1.5:** • Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver function follow-up assessments **within 24 to 72 hours.** • Monitor participants weekly until liver function abnormalities resolve, stabilize, or return to baseline.	**If ALT or AST ≥ 3 × ULN AND bilirubin ≥ 2 × ULN or INR > 1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week) [19]) • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete the Liver Event Form.

a Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT or AST ≥ 3 × ULN **AND** bilirubin ≥ 2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

b **All** events of ALT or AST ≥ 3 × ULN **AND** bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT or AST ≥ 3 × ULN **AND** INR > 1.5 may indicate severe liver injury (possible "Hy's Law") and **must be reported as an SAE**. The INR stated threshold value will not apply to participants receiving anticoagulants.

c New or worsening symptoms believed to be related to liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, and jaundice) or believed to be related to hypersensitivity (eg, fever, rash, and eosinophilia).

d Includes: Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen (HBsAg) and HBcAb; hepatitis C (HCV) RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

e Samples for drug concentration may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the blood sampling for drug concentration measurement on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a sample for drug concentration measurement cannot be collected in the time period indicated above, do not obtain a sample for drug concentration measurement. Procedures for handling and shipping of samples will be specified in a separate written procedure.

Liver Event Monitoring Escalation Criteria While Continuing Study Intervention

Criteria for escalating monitoring and actions for continued treatment after the onset of liver events	
Criteria	**Actions**
• 3 × upper limit of normal (ULN) ≤ alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 5 × ULN AND bilirubin < 2 × ULN without symptoms believed to be related to liver injury or hypersensitivity, AND can be monitored weekly for 4 weeks.	• Notify the sponsor within 24 hours of learning of the event to discuss participant safety. • Participants may continue study intervention. • Participants must return weekly for repeat liver function tests (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to baseline. • If a participant meets the liver chemistry stopping criteria, the procedures outlined in Section 7.1.1 will be followed. • If, after 4 weeks of monitoring, ALT or AST < 3 × ULN and bilirubin < 2 × ULN, monitor participants twice monthly until liver function tests resolve, stabilize, or return to baseline.

10.6 Appendix 6: COVID-19 Symptoms and Definition of Symptoms Onset

COVID-19 Symptoms

The 14 COVID-19 symptoms in this study are defined below:

- Fever (defined as body temperature ≥ 38.0°C per tympanic or rectal thermometer or ≥ 37.5°C per axillary, oral, or forehead/temporal thermometer; as defined in Section 8.2.3)
- Shortness of breath or difficulty breathing
- Cough
- Sore throat
- Nasal congestion (stuffy nose) or runny nose
- Chills
- Fatigue (lower energy or tiredness)
- Body or muscle pain or aches
- Headache
- Nausea (feeling like want to throw up)
- Vomiting (throwing up)
- Diarrhea (loose or watery stools)
- Change in sense of taste
- Change in sense of smell

COVID-19 Symptoms Onset in Study Participants

COVID-19 symptoms onset in study participants 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.

10.7 Appendix 7: 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)

10.8 Appendix 8: Household Members of Participant Questionnaire

Example questions in the Household Members of Participant Questionnaire are provided below.

On Day 1 (Screening Visit): Only 1 participant in a household will be asked about the number of people living with him or her in his or her household and rooms in his or her house.

- How many people living with you in your household who are not participating in this study?
- How many rooms are in your house (including bedroom, kitchen, and living room excluding bathroom, toilet, and garage)?

On Days 3, 6, 10, 15, 21, and 28: Only 1 participant in a household will be asked about any new COVID-19-positive people in his or her household who are not participating in this study.

- Has anyone in your household who is not participating in this study been newly diagnosed with COVID-19 (including a PCR-positive test or self-test) or have COVID-19-like symptoms since your last visit?
- If yes, how many people meet these criteria?

10.9 Appendix 9: Participant Exposure Questionnaire

Example questions in the Participant Exposure Questionnaire are provided below.

On Day 1 (Screening Visit): The participant will be asked about the duration of time that the study participant spent together with the index patient or other COVID-19 infected household members before and after the onset of COVID-19 symptoms in the index patient or other COVID-19 infected household members.

- How many hours did you spend together with the index patient or other COVID-19 infected household members 24 hours before the onset of the index patient's COVID-19 symptoms (< 3 hours, 3 to 6 hours, > 6 hours)
- How many hours did you spend together with the index patient or other COVID-19 infected household members 24 hours after the onset of the index patient's symptoms (< 3 hours, 3 to 6 hours, > 6 hours)

On Day 15: The participant will be asked about his/her lifestyle during both his/her usual life before the COVID-19 symptomatic period of the index patient or other COVID-19 infected household members and during the COVID-19 symptomatic period of the index patient in this study.

- Did you eat meals with the index patient or other COVID-19 infected household members? (Yes/No)
- Did you share the bedroom with the index patient or other COVID-19 infected household members? (Yes/No)
- Did you share bathroom with the index patient or other COVID-19 infected household members? (Yes/No)
- Did you wear a mask in your house? (Yes/No)
- Did you often wash your hands and gargle? (Yes/No)
- Did you often ventilate a room? (Yes/No)
- Did you often disinfect doorknobs and other common areas? (Yes/No)
- Did you wear gloves and masks when handling soiled linens and clothing? (Yes/No/Not applicable*)
  - * If the participants did not have a chance to handle soiled linens and clothing, "Not applicable" is selected.
- Did you seal and dispose of the index patient or other COVID-19 infected household members garbage? (Yes/No/Not applicable*)
  - * If the participants did not have a chance to handle index patient or other COVID-19 infected household members garbage, "Not applicable" is selected.

10.10 Appendix 10: EuroQol 5 Dimensions 5 Levels (EQ-5D-5L)

Quality of Life Questionnaires (EQ-5D-5L)

Site name	
Participant identification code	
Visit	
Date	

Under each heading, please check **the ONE box that best describes your health TODAY.**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(eg, work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN/DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY/DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

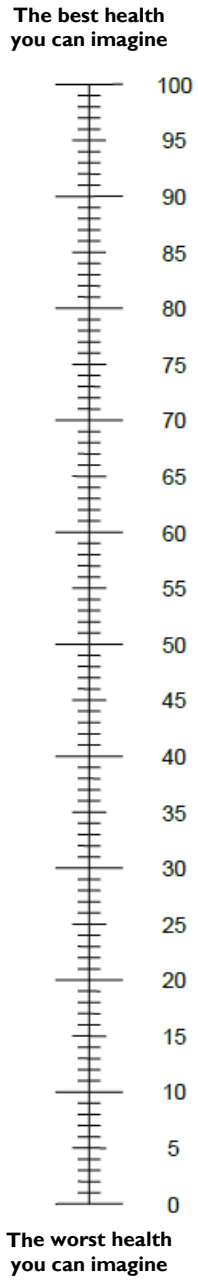
2

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- **We would like to know how good or bad your health is <u>TODAY</u>.**
- **This scale is numbered from 0 to 100.**
- **100 means the <u>best</u> health you can imagine.**

  0 means the <u>worst</u> health you can imagine.
- **Mark an "X" on the scale to indicate how good or bad your health is TODAY.**
- **Now, please the write the number you marked on the scale in the box below.**

YOUR HEALTH TODAY = ☐



3

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10.11 Appendix 11: Abbreviations and Definitions

3CL	3C-like
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
C_{24}	plasma concentration at 24 hours after first administration
C_{192}	plasma concentration at 192 hours after first administration
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CSR	clinical study report
C_{trough}	plasma trough concentrations
CV	coefficient of variation
CYP	cytochrome P450
DAIDS	Division of AIDS
DDI	drug-drug interaction
DSMB	data safety monitoring board
EC_{90}	90% effective concentration
ECG	electrocardiograph(y)
eCRF	electronic case report form
EDC	electronic data capture
EQ	EuroQol
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EUA	emergency use authorization
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GEE	generalized estimating equations

HDL-C	high-density lipoprotein cholesterol
HIPAA	Health Information Portability and Accountability Act
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
ITT	intention-to-treat
IV	intravenous
IWRS	interactive web response system
LAR	legally authorized representative
mAb	monoclonal antibody
MATE	multidrug and toxin extrusion
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
N	number
NOAEL	no-observed adverse effect level
NP	nasopharyngeal
NSAID	nonsteroidal inflammatory drug
NSP5	nonstructural protein 5
OAT3	organic anion transporter 3
OATP	organic anion transporter polypeptide
OCT	organic cation transporter
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
QTL	quality tolerance limits
RdRp	RNA-dependent RNA polymerase
RMST	restricted mean survival time
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)

SCORPIO-PEP	Stopping COVID-19 pRogression with early Protease InhibitOr treatment – Post Exposure Prophylaxis
SD	standard deviation
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WHODD	World Health Organization Drug Dictionary
WOCBP	woman of childbearing potential

10.12 Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Version 4 (Amendment 3): (03 Nov 2023)

Overall Rationale for the Amendment:

The primary purpose of this protocol amendment was to add a data safety monitoring board (DSMB), include changes consistent with the country-specific amendment (2.1 – EU), and to make study clarifications.

A high-level description of the changes and brief rationale are outlined in the following table. Minor editorial changes such as word changes, consistency additions, or formatting revisions are not summarized.

Section # and Name	Description of Change	Brief Rationale
Title page	Updated street address to 400 Campus Drive for Shionogi Inc.	Administrative change
1.1 Synopsis, 10.1.5 Committee Structure	Added a DSMB	To review ongoing safety data
Table 1-1, Table 3-1, 9.3.2.1 Primary Endpoint	For the supplemental analyses for the primary endpoint, clarified analyses will be conducted for the proportion of participants who are infected with SARS-CoV-2 and have COVID-19 symptoms onset through Days 10, 15, 21, and 28.	To clarify that supplemental analyses for related endpoints will be conducted for the timepoints throughout the study until Day 28
Table 1-1 and Table 3-1	Changed exploratory endpoints from “through Day 10” to “through Day 28”	To extend the duration of these analyses to include all study timepoints
Table 1-1, Table 3-1, 8.1.7 Viral RNA/Symptom Rebound, 9.3.2.3 Exploratory Endpoints	Added exploratory objective to investigate SARS-CoV-2 RNA and/or COVID-19 symptom rebound during the study	To evaluate SARS-CoV-2 RNA and/or COVID-19 symptom rebound during the study
Figure 1-2 (footnote c) and Figure 1-4 (footnote a)	Clarified that after an initial Event-driven Visit, additional Event-driven Visits will occur if new symptom(s) meet the criteria of symptom onset definition after all other COVID-19 symptoms resolved.	Clarification
Figure 1-3 (footnote a)	Clarified SARS-CoV-2 sample must be collected ≤ 72 hours prior to randomization of the participant and within 72 hours	Clarification

Section # and Name	Description of Change	Brief Rationale
	from the index patient ICF signature	
Figure 1-4 (footnote f)	Added footnote to clarify that NP swabs for Day 1 (Screening Visit) should be performed before the administration of the first dose of study intervention.	Clarification
Figure 1-4 (footnote g)	Changed positive to negative for home rapid antigen diagnostic test	Typographical error
2.3.1 Risk Assessment	For the clinical safety data, updated with current clinical data	Updated clinical data with the current version of the Investigator's Brochure (Edition 06, issued 11 Jul 2023).
	For the postmarketing data, updated with risk of anaphylaxis	Updated postmarketing data with current version of the Investigator's Brochure (Edition 06, issued 11 Jul 2023).
5.1 Inclusion Criteria	Moved introductory paragraph to Inclusion 2c	Formatting change
5.2 Exclusion Criteria	Criterion 3: deleted immunosuppressive agents	Participants with underlying disease requiring immunosuppressive agents are allowed in the study.
	Criterion 7: changed exclusion of anti-SARS-CoV-2 mAbs from 6 months to 3 months	Updated to allow enrollment of study participants with anti-SARS-CoV-2 mAbs administered more than 3 months
6.8.1 Prohibited and Precautionary Medications	Corrections made to list of sensitive CYP3A substrates with narrow therapeutic index and CYP3A substrates	Corrected for consistency with DDI tool
8 Study Assessments and Procedures	Added approximate volume of blood to be collected during the study	Added blood sample volume information; referenced pediatric guidance
10.1.1 Regulatory and Ethical Considerations	Clarified that good clinical practice procedures apply to all parties involved in the study	Additional detail added in alignment with European regulation 536/2014 Annex I Section D No. 17 lit. a)
10.1.9 Study and Site Start and Closure	Added further details for reasons for study termination	Additional detail added in alignment with European regulation 536/2014 Annex I Section D No. 17 lit. p)

Version 3 (Amendment 2): (19 Apr 2023)

Overall Rationale for the Amendment:

The primary purpose of this protocol amendment was to incorporate recommendations from the regulatory agency. Minor editorial changes such as word changes or formatting revisions are not summarized.

A high-level description of the change(s) and brief rationale for specific items are outlined in the following:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Table 1-1, 3 Objectives, Endpoints, and Estimands, Table 3-1	Primary analysis: population changed to participants with negative test at screening and using the mITT population Added key secondary analysis: same as the primary endpoint using the ITT population Added secondary endpoint of participants with positive test and COVID-19 symptoms onset through Days 15 or 28 Secondary endpoints changed from Day 15 to Day 28	The ITT population will be used to reflect real world clinical settings, and the secondary endpoints were added to explore additional analyses
1.1 Synopsis, Table 1-1, 1.3 Schedule of Activities (SoA), Figure 1-4, 3 Objectives, Endpoints, and Estimands, Table 3-1, 5.1 Inclusion Criteria (Criterion 2a), 9.3.2.1 Primary Endpoints, 9.3.2.2 Secondary Endpoints, 10.6 Appendix 6: COVID-19 Symptoms and Definition of Symptoms Onset	Replaced COVID-19 symptom of "feeling feverish" with "fever" Changed symptom onset to 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	To align the terms of the COVID-19 symptoms
1.1 Synopsis Overall Design and Number of Participants, 4.1 Overall Design, 9.5 Sample Size Determination	Changed the sample size from 2040 participants randomized to 2200 participants randomized	Due to change in assumption of secondary infection rate in the placebo group
1.2 Schema, Figure 1-2, Schedule of Activities (SoA), 8.1.3 Global Impression Questionnaire, 10.7 Appendix 7 Global Impression Questionnaire	Added visit on Day 21; last day of follow-up changed from Day 15 to Day 28; Event-driven visit changed to occur through Day 28; added collection of Global Impression Questionnaire	To obtain additional data through Day 28

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA), Figure 1-4, 8.2.2 Vital Signs	Added resting peripheral oxygen saturation (SpO_2) to vital signs	Clarification: previously SpO_2 collection was part of symptom-focused physical examination.
2.2 Background	Added number of cases based on February 2023	Previous version included information as of July 2022; updated with more recent information
2.3.1 Risk Assessment	Added Phase 3 Study 2018T1221 safety results	Updated with recent data
4.2 Scientific Rationale for Study Design	Rationale for Day 10 for primary endpoint added	Additional clarifications were added
4.2 Scientific Rationale for Study Design, 6.8.2 Rescue Medication	Revised the text to separate rescue medications for index patient and study participant	Clarification
4.3 Justification for Dose	Additional nonclinical results added	Additional clarifications were added
5.1 Inclusion Criteria, Index Patients	Clarified that only 1 index patient from each household will be enrolled Criterion 2a: Deleted requirement that the index patient be the first and only COVID-19 case in the household and added text that allows multiple members in the household with confirmed SARS-CoV-2 infection.	Additional clarifications were added
	Criterion 3: Added new criterion that the index patient must have a potential study participant who can participate in the study within 72 hours after onset of COVID-19 symptoms in an index patient.	Additional clarifications were added
5.1 Inclusion Criteria, Study Participants	Criterion 6a: Added contraceptive requirements for male participants	Requested by regulatory agency
5.2 Exclusion Criteria, Study Participants	Criterion 6: Changed exclusion criteria of receipt of convalescent plasma or anti-SARS-CoV-2 biologic products from 6 months to 3 months prior to Screening	Allowing additional level of flexibility to the eligibility criteria

Section # and Name	Description of Change	Brief Rationale
	Criterion 7: Added "in the last 6 months" for participants who have received anti-SARS-CoV-2 mAbs	To avoid any use with potential long-acting mAb combination
	Criterion 9: Clarified confirmation of symptomatic infection as "(positive SARS-CoV-2 test and meeting the study definition of COVID-19 symptoms onset)"	Clarification was added
	Criterion 14: Deleted exclusion criterion that participant cannot live with a SARS-CoV-2 infection person other than the index patient	Clarification to the study protocol criteria
5.1 Inclusion Criteria, Study Participant, 6.3 Measures to Minimize Bias: Randomization and Blinding	Added that randomization will be performed based at the study participant's level	Clarification was added
6.3 Measures to Minimize Bias: Randomization and Blinding	Added blinding of HDL-C	To maintain the study blind due to possible decrease in HDL-C
6.8.1 Prohibited and Precautionary Medications, 6.8.2 Rescue Medication	Added cautionary statement if Paxlovid is administered after treatment period of S-217622	Given potential increase of nirmatrelvir/ritonavir AUC and C_{max}, careful monitoring is recommended if Paxlovid is administered after discontinuation of S-217622
9 Statistical Considerations	Revised the statistical hypotheses based on modifications made to the endpoints	To accommodate a health authority's recommendation and the addition of a key secondary analysis
10.1.1 Regulatory and Ethical Considerations	Deleted "substantial" amendments to the protocol requiring health authority approval	All amendments to the protocol will require health authority approval prior to initiation
10.1.4 Data Protection, 10.1.4.1 Organizational Measures to Protect Personal Data	Added last bullet in Section 10.1.4 and added new Section 10.1.4.1	Additional text added to accommodate the data protection requirements of the Clinical Trial Regulation (CTR)

Version 2 (Amendment 1): (28 Oct 2022)

Overall Rationale for the Amendment:

The primary purpose of this protocol amendment was to add clarifications to improve study implementation. For example, the requirement for the amount of time from informed consent to randomization was changed from ≤ 96 hours to ≤ 72 hours. Unless otherwise noted, changes are noted with strikethrough for deletion of text and underline for added text. Minor editorial changes such as word changes or formatting revisions are not summarized.

A high-level description of the changes and brief rationale for specific items are outlined in the following:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Table 1-1, 3 Objectives, Endpoints, and Estimands, Table 3-1, 9.3.2.2 Secondary Endpoints	Added secondary endpoints: • Proportion of participants with sustained resolution of the 4 key COVID-19 symptoms (nasal congestion or runny nose, sore throat, cough, fever and fatigue) • Change in total score of the 4 key COVID-19 symptoms at each timepoint • AUC of the daily total symptom score for the 4 key COVID-19 symptoms over time from onset of the 4 key COVID-19 symptoms through Day 15	Added endpoint for the objective comparing S-217622 with placebo in resolution and improvement of COVID-19 symptoms
1.1 Synopsis, Table 1-1 (footnote a), 1.2 Schema, Figure 1-2 (footnote c), 1.3 Schedule of Activities (SoA), Figure 1-4 (footnote a), 3 Objectives, Endpoints, and Estimands, Table 3-1 (footnote a), 9.3.2.1 Primary Endpoint, 10.6 Appendix 6: COVID-19 Symptoms and Definition of Symptoms Onset	Changed the second bullet in the definition of COVID-19 symptoms onset: • Occurrence (or worsening in the case of preexisting COVID-19-related symptoms) of at least 2 of ~~all other~~ the following 7 COVID-19 symptoms for at least 24 hours: (1) nasal congestion or runny nose, (2) sore throat, (3) cough, (4) fever, (5) fatigue, (6) loss of taste, and (7) loss of smell.	Changed definition from “all other” COVID-19 symptoms to be more specific to include 7 symptoms that are based on the Phase 3 study data.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema , Figure 1-1 (footnote a), Figure 1-2 (footnote a), 1.3 Schedule of Activities (SoA), Figure 1-3 (footnote a), Figure 1-4 (footnotes b and l), 5.1 Inclusion Criteria, Index Patients (Criterion 2c), Study Participants (Criteria 7a and 8)	Changed requirement for informed consent and randomization from ≤ 96 hours to ≤ 72 hours from onset of COVID-19 symptoms	It was determined that ≤ 72 hours is a more appropriate and adequate amount of time to evaluate the efficacy of S-217622.
1.3 Schedule of Activities (SoA), Figure 1-3	Added collection of body temperature at Screening Visit	Added staff-collected body temperature to Screening Visit as it is part of the inclusion symptoms criteria
1.3 Schedule of Activities (SoA), Figure 1-3 (footnote a)	Added: Any documentation of positive SARS-CoV-2 viral testing (such as nucleic acid amplification test or antigen test) within 24 hours from the index patient ICF signature time is acceptable.	Clarification
1.3 Schedule of Activities (SoA), Figure 1-3	Divided Screening Visit assessments into before and after randomization	Clarification
1.3 Schedule of Activities (SoA), Figure 1-4 (Vital signs)	Added collection of vital signs at Day 6	Added vital signs after completion of study intervention (ie, first visit in Follow-up Period)
1.3 Schedule of Activities (SoA), Figure 1-4 (Staff-collected body temperature), 8.2.3 Body Temperature	Removed requirement for body temperature to be collected by site staff after the Screening Visit	Body temperature will be measured twice daily by the participant; therefore, the requirement for site staff to collect body temperature during the Study Intervention and Follow-up Periods was removed.
1.1 Synopsis, Table 1-1, 3 Objectives, Endpoints, and Estimands, Table 3-1, 8.1.1 Nasopharyngeal Swabs (Virology Test), 8.10.4 Antiviral Activity Against SARS-CoV-2 Clinical Isolates, 9.3.2.2 Secondary Endpoints	Deleted endpoints associated with viral titer	RT-PCR is adequate to investigate the primary endpoint and a standard method globally to detect the virus for the SARS-CoV-2 infection. Furthermore, viral titer is not mandatory based on the FDA guidance.
2.3.1 Risk Assessment, Clinical Data	Corrected and updated clinical data for Study 2102T1211	One of the ongoing studies has now been completed. All data described in Section 2.3.1 are provided in the Investigator's Brochure Edition 04 issued on 30 Jun 2022.
4.3 Justification for Dose	Deleted old text and replaced with new text.	Text rewritten for clarity, although justification and dose remain as in previous version of the protocol.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria, Index Patients, Criteria 2	Modified text: a. Be the first case of COVID-19 in the household in the last 6 months from time of informed consent. No other household members had positive COVID-19 test (a nucleic acid amplification test or antigen test) from any respiratory tract specimen (eg, oropharyngeal, NP or nasal swab, or saliva) in the last 6 months. b. Have at least 1 COVID-19 symptom as listed below within 24 hours of the index patient providing informed consent. c. Must have positive SARS-CoV-2 test (a nucleic acid amplification test or antigen test ~~RT-PCR or rapid antigen~~) from any respiratory tract specimen (eg, oropharyngeal, NP, or nasal swab, or saliva) from a sample collected ≤ ~~96~~72 hours prior to randomization of the participant	Clarification
5.1 Inclusion Criteria, Study Participants, Criterion 2	Modified text: Has a negative screening SARS-CoV-2 infection, as determined by ~~RT-PCR~~ SARS-CoV-2 test (a nucleic acid amplification test or ~~rapid~~ antigen test) from any respiratory tract specimen (eg, oropharyngeal, NP or nasal swab, or saliva).	Clarification
5.1 Inclusion Criteria, Study Participants, Criterion 4b	Modified text: b. No COVID-19 symptoms at screening (~~unless symptoms are caused by comorbidities~~ if a participant has COVID-19-like preexisting	Clarification

Section # and Name	Description of Change	Brief Rationale
	symptoms caused by comorbidities, only 1 preexisting symptom is allowed.)	
5.1 Inclusion Criteria, Study Participants, Criterion 6b	Contraceptive methods in females should be used for at least 14 days after last study intervention administration. Donation of eggs should not occur until 14 days after last study intervention administration.	Changed 10 days to 14 days based on current guidance for S-217622
5.1 Inclusion Criteria, Study Participants, Criterion 7	Corrected "index patient" to "participant" For participants under the legal age, written informed consent must be obtained from the parent(s)/legal guardian/or other LAR of the ~~index patient~~ participant. Written informed assent must also be provided in the case of participants ≥ 12 years.	Typographical error
5.2 Exclusion Criteria, Index Patients and Study Participants, Criterion 1	Added exclusion criterion for index patients and study participants to exclude documented respiratory infection (eg, flu virus infection) within 14 days prior to Screening Visit	Index patients and study participants with documented respiratory infection (eg, flu virus) should not be enrolled in the study.
5.2 Exclusion Criteria, Study Participants, Criterion 10	Deleted exclusion of strong cytochrome P450 (CYP) 3A inhibitor 14 days prior to enrollment	Typographical error
5.2 Exclusion Criteria, Study Participants, Criterion 9	Added that the use of S-217622 (if commercially available) is not allowed.	Given that S-217622 could be commercially available in some local regions, clarified that the use of S-217622 (other than investigational use during the study) is excluded.
5.2 Exclusion Criteria, Study Participants, Criterion 14	Modified text to clarify that participants can only live with 1 person with confirmed SARS-CoV-2 infection or COVID-like symptoms	Clarification
5.4 Screen Failures	Modified text to allow index patients and study participants to be rescreened once	Index patients or study participants who do not meet the criteria for participation in the study, may be rescreened once at the discretion of the investigator.

Section # and Name	Description of Change	Brief Rationale
6.8.1 Prohibited and Precautionary Medications	Additional prohibited CYP3A substrates added: anamorelin, azelnidipine, blonanserin, dihydroergotamine, ergometrine, ergotamine, finerenone, ivabradine, methylergometrine, quinidine, riociguat, suvorexant, and venetoclax Added prohibited strong CYP3A inducers: apalutamide, carbemezpine, enzalutamide, mitotane, phosphenytoin, and St. John's wort	Additional contraindicated medications were added.
8.3.6 Adverse Events of Special Interest	Deleted "rash" as an adverse event of special interest (AESI) in this study.	Rash events will be entered as AEs and they are no longer reported as AESIs
9.3.2.2 Secondary Endpoints	Description of analyses were rewritten	Clarification
9.3.2.4 Subgroup Analyses of Efficacy Endpoints	Added subgroup analysis of index patients with COVID-19 upper respiratory symptoms at baseline	Additional analysis added
9.5 Sample Size Determination	Sample size remains the same, but the description of determination of sample size was rewritten	Clarification
10.3 Appendix 3, 10.3.4 Reporting of SAEs	Added facsimile number and e-mail address for safety contacts in Japan	Additional details added for safety contacts in Japan
10.5 Appendix 5: Liver Safety: Actions and Suggested Follow-up Assessments	Criteria for escalating monitoring and actions for continued treatment after the onset of liver events was changed for AST from ≤ 5 × ULN to < 5 × ULN	Typographical error (removed equal sign)
10.7 Appendix 7: Household Members of Participant Questionnaire	Added Household Members of Participant Questionnaire as an appendix.	Clarification
10.9 Appendix 9: EuroQol 5 Dimensions 5-Levels (EQ5D-5L)	Added EQ-5D-5L questionnaire as an appendix.	Clarification

10.13 Appendix 13: Investigator's Signature

Study Title:	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
Study Number:	2206T1331
Date of Original:	25 Aug 2022
Date of Latest Amendment:	08 Jul 2024

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

[enter name and credentials]
[enter title]
[enter affiliation]

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the sponsor.

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Final Approval	[redacted] 08-Jul-2024 15:37:35 GMT+0000

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