This is the translated version of the protocol originally written in Japanese Version 10 (Amendment 9), issued on 20 Sep 2022.

CLINICAL STUDY PROTOCOL

Protocol Title	**: A Phase 2/3 Study of S-217622 in Participants Infected with SARS-CoV-2**
Protocol Number	**: 2108T1221**
Amendment Number	**: Version 10 (Amendment 9)**
Compound	**: S-217622**
Study Phase	**: Phase 2/3**
Short Title	**: A Phase 2/3 Study of S-217622**
Acronym	**: SCORPIO-SR**
Sponsor Name	**: Shionogi & Co., Ltd.**
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Regulatory Agency Identifying Number(s)	**: N/A**
Issue Date	**: 20 Sep 2022**

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:	A Phase 2/3 Study of S-217622 in Participants Infected with SARS-CoV-2
Protocol Number:	2108T1221
Compound Number:	S-217622
Short Title:	A Phase 2/3 Study of S-217622
Rationale:	S-217622 is a 3CL protease inhibitor created by Shionogi & Co., Ltd. and currently being developed as a therapeutic drug for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In the nonclinical study using a mouse model of SARS-CoV-2 infection, lung viral titers decreased in a dose-dependent manner by S-217622. Decreasing of viral titers is expected even in participants with SARS-CoV-2 infection. This study is designed as a phase 2/3 placebo-controlled study of 5-day administration of S-217622 consisting of four parts: Phase 2a Part whose primary objective is to confirm the antiviral effect in participants with mild/moderate or asymptomatic SARS-CoV-2 infection, Phase 2b Part whose primary objective is to confirm the early improvement effect on clinical symptoms and the antiviral effect against SARS-CoV-2 in participants with mild/moderate SARS-CoV-2 infection, Phase 3 Part whose primary objective is to verify the efficacy in participants with mild/moderate SARS-CoV-2 infection, and Phase 2b/3 Part whose primary objective is to verify the efficacy in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection. This study will be initiated after confirming the safety and tolerability of 5-day administration once-daily: 750 mg of the loading dose (Day 1) and 250 mg of the maintenance dose (Day 2 or later), until 5 days after the last study drug administration, in ongoing Phase 1 study of S-217622 in healthy adult participants (2102T1211).
Objectives and Endpoints:	The objectives and endpoints of Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part are shown in Table 1-1, Table 1-2, Table 1-3, and Table 1-4, respectively.

Table 1-1 Objectives and Endpoints (Phase 2a Part, Participants with Mild/Moderate or Asymptomatic SARS-CoV-2 Infection)

Objectives	Endpoints
Primary	
Common to participants with mild/moderate and with asymptomatic SARS-CoV-2 infection[a]	
• To investigate the antiviral effect of 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Change from baseline in SARS-CoV-2 viral titer at each time point
Secondary	
Common to participants with mild/moderate and with asymptomatic SARS-CoV-2 infection[a]	
• To investigate the antiviral effect of 5-day administration of S-217622 other than the primary endpoint in participants with SARS-CoV-2 infection.	• The following items concerning SARS-CoV-2 viral titer – Time to the first negative SARS-CoV-2 viral titer – Time to negative SARS-CoV-2 viral titer at 2 consecutive time points – Time to sustained negative SARS-CoV-2 viral titer – Proportion of participants with positive SARS-CoV-2 viral titer at each time point – SARS-CoV-2 viral titer at each time point – Relative change rate from baseline in SARS-CoV-2 viral titer at each time point – AUC of change in SARS-CoV-2 viral titer • The following items concerning RT-PCR testing (nasopharyngeal swabs) – Time to the first negative RT-PCR result – Time to negative RT-PCR results at 2 consecutive time points – Time to sustained negative RT-PCR results – Proportion of participants with positive RT-PCR result at each time point – Amount of SARS-CoV-2 viral RNA at each time point – Change from baseline in amount of SARS-CoV-2 viral RNA at each time point – Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point – AUC of change in amount of SARS-CoV-2 viral RNA

Objectives	Endpoints
• To investigate the effect in preventing aggravation following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Proportion of participants with the following or higher scores on 8-Point Ordinal Scale and time from the first dose of study intervention – Symptomatic, no limitation of activities (Score 1) – Symptomatic, limitation of activities (Score 2) – Hospitalized, no oxygen therapy (Score 3) – Hospitalized, with oxygen therapy (< 5 L/min) (Score 4) – Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) – Hospitalized, with ventilation (Score 6) – Death (Score 7) • SpO_2 at each time point
• To investigate QOL following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Change from baseline in EQ-5D-5L
• To confirm the pharmacokinetics following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Plasma concentration of S-217622 (Days 2, 6)
• To investigate the safety and tolerability following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Adverse events, laboratory tests, and vital signs (systolic/diastolic blood pressure, pulse rate, respiratory rate), ECG
Participants with mild/moderate SARS-CoV-2 infection[a]	
• To investigate the effect in improving clinical symptoms following 5-day administration of S-217622 in participants with mild/moderate SARS-CoV-2 infection.	• Time to improvement of COVID-19 symptoms[b, c] • Time to improvement of COVID-19 symptoms (duration of recovery, 72 hours [3 days] or longer)[b, c, d] • Time to improvement of COVID-19 symptoms (duration of recovery, 120 hours [5 days] or longer)[b, c, d] • Time to improvement of each COVID-19 symptom[b, c] • Change from baseline in total score of COVID-19 symptoms at each time point[b] • Proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point[b, c] • Proportion of participants with taste disorder or smell disorder at each time point • Time to resolution of fever (< 37.0°C)
Participants with asymptomatic SARS-CoV-2 infection[a]	
• To investigate the preventive effect of 5-day administration of S-217622 in participants with asymptomatic SARS-CoV-2 infection.	• Proportion of participants with development of COVID-19 symptoms[e, f]

Objectives	Endpoints
	• Proportion of participants with development of COVID-19 symptoms with fever (≥ 37.0°C)[e, f]
Exploratory	
Common to participants with mild/moderate and with asymptomatic SARS-CoV-2 infection[a]	
• To evaluate the amino acid substitutions in 3CL protease (nsp5) cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) cleavage site following drug administration
• To evaluate immunity in participants with SARS-CoV-2 infection.	• Geometric mean titer for SARS-CoV-2 neutralizing antibody titer (Days 1, 28)
• To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection.	• Change from baseline in aggravation markers[g]
• To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Proportion of participants with post-acute COVID-19 syndrome at each time point

Table 1-2 Objectives and Endpoints (Phase 2b Part, Participants with Mild/Moderate SARS-CoV-2 Infection)

Objectives	Endpoints
Primary	
• To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection, based on the time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6).	• Time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6)[b]
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection, based on the change from baseline on Day 4 in SARS-CoV-2 viral titer.	• Change from baseline on Day 4 in SARS-CoV-2 viral titer
Secondary	
• To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Time to improvement of COVID-19 symptoms[b, c] • Time to improvement of COVID-19 symptoms (duration of recovery, 72 hours [3 days] or longer)[b, c, d] • Time to improvement of COVID-19 symptoms (duration of recovery, 120 hours [5 days] or longer)[b, c, d]

Objectives	Endpoints
• To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Time to improvement of each COVID-19 symptom[b, c] • Change from baseline in total score of COVID-19 symptoms at each time point[b] • Proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point[b, c] • Proportion of participants with taste disorder or smell disorder at each time point • Time to resolution of fever (< 37.0°C) • The following items concerning SARS-CoV-2 viral titer – Time to the first negative SARS-CoV-2 viral titer – Time to negative SARS-CoV-2 viral titer at 2 consecutive time points – Time to sustained negative SARS-CoV-2 viral titer – Proportion of participants with positive SARS-CoV-2 viral titer at each time point – SARS-CoV-2 viral titer at each time point – Change from baseline in SARS-CoV-2 viral titer at each time point – Relative change rate from baseline in SARS-CoV-2 viral titer at each time point – AUC of change in SARS-CoV-2 viral titer • The following items concerning RT-PCR testing (nasopharyngeal swabs) – Time to the first negative RT-PCR result – Time to negative RT-PCR results at 2 consecutive time points – Time to sustained negative RT-PCR results – Proportion of participants with positive RT-PCR result at each time point – Amount of SARS-CoV-2 viral RNA at each time point – Change from baseline in amount of SARS-CoV-2 viral RNA at each time point – Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point – AUC of change in amount of SARS-CoV-2 viral RNA

Objectives	Endpoints
• To compare the effect to prevent aggravation following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Proportion of participants with the following or higher scores on 8-Point Ordinal Scale and time from the first dose of study intervention – Symptomatic, no limitation of activities (Score 1) – Symptomatic, limitation of activities (Score 2) – Hospitalized, no oxygen therapy (Score 3) – Hospitalized, with oxygen therapy (< 5 L/min) (Score 4) – Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) – Hospitalized, with ventilation (Score 6) – Death (Score 7) • SpO_2 at each time point
• To compare QOL following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Change from baseline in EQ-5D-5L
• To confirm the pharmacokinetics following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• S-217622: Plasma concentration (Days 2, 6)
• To compare the safety and tolerability following 5-day administration of S-217622 with those of placebo in participants with SARS-CoV-2 infection.	• Adverse events, laboratory tests, and vital signs (systolic/diastolic blood pressure, pulse rate, and respiratory rate)
Exploratory	
• To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infection.	• Spike gene sequence of SARS-CoV-2
• To perform polymorphism analysis of 3CL protease (nsp5) for participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) of SARS-CoV-2
• To evaluate the amino acid substitutions in 3CL protease (nsp5) and its cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) and its cleavage site following drug administration
• To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participant's specimen.	• EC_{50} of S-217622 on SARS-CoV-2 isolated from baseline sample
• To evaluate immunity in participants with SARS-CoV-2 infection.	• Geometric mean titer for SARS-CoV-2 neutralizing antibody titer (Days 1, 28)
• To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection.	• Change from baseline in aggravation markers[g]
• To investigate the effect on post-acute COVID-19 syndrome following 5-day	• Proportion of participants with post-acute COVID-19 syndrome at each time point

Objectives	Endpoints
administration of S-217622 in participants with SARS-CoV-2 infection.	

Table 1-3 Objectives and Endpoints (Phase 3 Part, Participants with Mild/Moderate SARS-CoV-2 Infection)

Objectives	Endpoints
Primary	
• To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection[n], based on the time to resolution of 5 COVID-19 symptoms.	• Time to resolution of 5 COVID-19 symptoms[h,o]
Key Secondary	
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection[n], based on the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA.	• Change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA
• To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection[n], based on time to the first negative SARS-CoV-2 viral titer.	• Time to the first negative SARS-CoV-2 viral titer
Other Secondary	
• To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Time to resolution of 5 COVID-19 symptoms without recurrence (duration of resolution: 48 hours [2 days] or longer)[h,o,p] • Time to resolution of 12 COVID-19 symptoms and COVID-19 symptom groups [b,h,q] • Time to resolution of 14 COVID-19 symptoms including taste disorder and smell disorder[e,k] • Time to resolution of each of the 5 COVID-19 symptoms[h,o] • Proportion of participants with taste disorder or smell disorder at each time point • Time to resolution of fever (< 37.0°C) • Proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration[b,i]
• To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• The following items concerning SARS-CoV-2 viral titer – Time to sustained negative SARS-CoV-2 viral titer

Objectives	Endpoints
	– Proportion of participants with positive SARS-CoV-2 viral titer at each time point – SARS-CoV-2 viral titer at each time point – Change from baseline in SARS-CoV-2 viral titer at each time point – Relative change rate from baseline in SARS-CoV-2 viral titer at each time point – AUC of change in SARS-CoV-2 viral titer • The following items concerning RT-PCR testing (nasopharyngeal swabs) – Proportion of participants with positive RT-PCR result at each time point – Amount of SARS-CoV-2 viral RNA at each time point – Change from baseline in amount of SARS-CoV-2 viral RNA at each time point – Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point – AUC of change in amount of SARS-CoV-2 viral RNA
• To compare the effect to prevent aggravation following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Proportion of participants with the following or higher scores on 8-Point Ordinal Scale and time from the first dose of study intervention – Symptomatic, no limitation of activities (Score 1) – Symptomatic, limitation of activities (Score 2) – Hospitalized, no oxygen therapy (Score 3) – Hospitalized, with oxygen therapy (< 5 L/min) (Score 4) – Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) – Hospitalized, with ventilation (Score 6) – Death (Score 7) • SpO_2 at each time point
• To compare QOL following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Change from baseline in EQ-5D-5L
• To confirm the pharmacokinetics following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• S-217622: Plasma concentration (Days 2, 6)
• To compare the safety and tolerability following 5-day administration of S-217622 with those of placebo in participants with SARS-CoV-2 infection.	• Adverse events, laboratory tests, and vital signs (systolic/diastolic blood pressure, pulse rate, and respiratory rate)

Objectives	Endpoints
Exploratory	
• To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infection.	• Spike gene sequence of SARS-CoV-2
• To perform polymorphism analysis of 3CL protease (nsp5) for participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) of SARS-CoV-2
• To evaluate the amino acid substitutions in 3CL protease (nsp5) and its cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) and its cleavage site following drug administration
• To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participant's specimen.	• EC_{50} of S-217622 on SARS-CoV-2 isolated from baseline sample
• To evaluate immunity in participants with SARS-CoV-2 infection.	• Geometric mean titer for SARS-CoV-2 neutralizing antibody titer (Days 1, 28)
• To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection.	• Change from baseline in aggravation markers[g] • Amount of viral antigen (spike, nucleocapsid), antiviral antigen antibody, and viral RNA in blood at each time point
• To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Proportion of participants with post-acute COVID-19 syndrome at each time point
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Time to the viral RNA <LLOQ and the negative RT-PCR result • Time to the first viral RNA <$LLOD_{95}$

Table 1-4 Objectives and Endpoints (Phase 2b/3 Part, Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection)

Objectives	Endpoints
Primary	
• To compare the effect of 5-day administration of S-217622 on preventing development or worsening of symptoms with that of placebo in participants with SARS-CoV-2 infection.	• Proportion of participants with development /worsening of COVID-19 symptoms[e,m]
Key secondary	
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection, based on the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA.	• Change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA
• To compare the antiviral effect of 5-day administration of S-217622 with that of	• Time to the first negative SARS-CoV-2 viral titer

Objectives	Endpoints
placebo in participants with SARS-CoV-2 infection, based on time to the first negative SARS-CoV-2 viral titer.	
Other secondary	
• To investigate the preventive effect of 5-day administration of S-217622 in participants with asymptomatic SARS-CoV-2 infection.	• Proportion of participants with development of COVID-19 symptoms [e, f] • Proportion of participants with development of COVID-19 symptoms with fever (≥ 37.0°C)[e, f]
• To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• The following items concerning SARS-CoV-2 viral titer – Time to sustained negative SARS-CoV-2 viral titer – Proportion of participants with positive SARS-CoV-2 viral titer at each time point – SARS-CoV-2 viral titer at each time point – Change from baseline in SARS-CoV-2 viral titer at each time point – Relative change rate from baseline in SARS-CoV-2 viral titer at each time point – AUC of change in SARS-CoV-2 viral titer • The following items concerning RT-PCR testing (nasopharyngeal swabs) – Proportion of participants with positive RT-PCR result at each time point – Amount of SARS-CoV-2 viral RNA at each time point – Change from baseline in amount of SARS-CoV-2 viral RNA at each time point – Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point – AUC of change in amount of SARS-CoV-2 viral RNA
• To compare the effect to prevent aggravation following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Proportion of participants with the following or higher scores on 8-Point Ordinal Scale and time from the first dose of study intervention – Symptomatic, no limitation of activities (Score 1) – Symptomatic, limitation of activities (Score 2) – Hospitalized, no oxygen therapy (Score 3) – Hospitalized, with oxygen therapy (< 5 L/min) (Score 4) – Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) – Hospitalized, with ventilation (Score 6)

Objectives	Endpoints
	– Death (Score 7) • SpO_2 at each time point
• To compare QOL following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Change from baseline in EQ-5D-5L
• To confirm the pharmacokinetics following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• S-217622: Plasma concentration (Days 2, 6)
• To compare the safety and tolerability following 5-day administration of S-217622 with those of placebo in participants with SARS-CoV-2 infection.	• Adverse events, laboratory tests, and vital signs (systolic/diastolic blood pressure, pulse rate, and respiratory rate)
Exploratory	
• To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infection.	• Spike gene sequence of SARS-CoV-2
• To perform polymorphism analysis of 3CL protease (nsp5) for participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) of SARS-CoV-2
• To evaluate the amino acid substitutions in 3CL protease (nsp5) and its cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) and its cleavage site following drug administration
• To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participant's specimen.	• EC_{50} of S-217622 on SARS-CoV-2 isolated from baseline sample
• To evaluate immunity in participants with SARS-CoV-2 infection.	• Geometric mean titer for SARS-CoV-2 neutralizing antibody titer (Days 1, 28)
• To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection.	• Change from baseline in aggravation markers[g]
• To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Proportion of participants with post-acute COVID-19 syndrome at each time point
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Time to the viral RNA <LLOQ and the negative RT-PCR result • Time to the first viral RNA $<LLOD_{95}$

ALT = alanine aminotransferase, AUC = area under curve, CCL = C-C motif ligand, CK = creatine kinase, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, EC_{50} = half maximal effective concentration, ECG = electrocardiography, EQ-5D-5L = EuroQol 5 dimensions 5-level [redacted], INR = international normalized ratio, [redacted], LDH = lactate dehydrogenase, $LLOD_{95}$ = lower limit of detection with a positivity rate greater than 95%, LLOQ = lower limit of quantitation, PT = prothrombin time, RNA = ribonucleic acid, RT-PCR = reverse transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SpO_2 = saturation of percutaneous oxygen, [redacted]

a Participants who meet inclusion criterion #2 to #4 in Section 5.1.1 but do not meet exclusion criterion #1 to #5 in Section 5.2.1 are defined as participants with mild/moderate SARS-CoV-2 infection; participants who meet inclusion criterion #2 and #3 in Section 5.1.2 but do not meet exclusion criterion #1 to #5 in Section 5.2.2 are defined as participants with asymptomatic/mild symptoms only SARS-CoV-2 infection.

b The following 12 symptoms will be evaluated: low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath (difficulty breathing), nausea, vomiting, and diarrhea.

c The 12 symptoms of COVID-19 will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). The time to improvement of COVID-19 symptoms is defined as the time from the start of study intervention to when all of the symptoms meet the following criteria.

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have remained improved to moderate or better, or moderate symptoms at baseline have remained improved to mild or better for 24 hours.
- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have remained severe or better, or moderate symptoms at baseline have remained or improved moderate or better for 24 hours.
- Symptoms other than the above (Symptoms that have not occurred before the onset of COVID-19, occur after baseline [pre-treatment examination]): Mild or better condition has remained for 24 hours.

d As for the definition of the time to improvement of COVID-19 symptoms described in c, the duration should be read as 72 hours or longer, or 120 hours or longer.

e Taste disorder and smell disorder are added to the 12 symptoms of low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath (difficulty breathing), nausea, vomiting, and diarrhea. These 14 symptoms will be evaluated.

f Of the 14 symptoms in COVID-19, taste disorder and smell disorder will be evaluated on a 3-point scale of 0 to 2 (0, The same as usual; 1, Less than usual; 2, No sense of smell/taste). The other 12 symptoms will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). Participants with development of any COVID-19 symptoms are defined as participants who have symptoms meeting the following criteria.

- The scores for taste disorder and smell disorder have worsened from 0 (The same as usual) to 1 (Less than usual) or 2 (No sense of smell/taste).
- Feeling hot or feverish, cough, shortness of breath (difficulty breathing): Severity of none at baseline has worsened to mild or worse, mild symptoms at baseline have worsened to moderate or worse, or moderate symptoms at baseline have worsened to severe on either symptom (severe symptoms at baseline will be excluded from the onset judgement of COVID-19 symptoms).
- Low energy or tiredness, muscle or body aches, headache, chills or shivering, stuffy or runny nose, sore throat, nausea, vomiting, and diarrhea: Severity of none at baseline has worsened to mild or worse, mild symptoms at baseline have worsened to moderate or worse, or moderate symptoms at baseline have worsened to severe on 2 or more symptoms at the same point (severe symptoms at baseline will be excluded from the onset judgement of COVID-19 symptoms).

g [redacted]

h The 12 symptoms of COVID-19 will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). The time to resolution of COVID-19 symptoms is defined as the time from the start of study intervention to when all of the symptoms meet the following criteria.

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the

participant to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have remained improved to moderate or better, moderate symptoms at baseline have remained improved to mild or better, and mild symptoms at baseline have remained mild or better for 24 hours.

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have remained severe or improved, moderate symptoms at baseline have remained moderate or improved, and mild symptoms at baseline have remained mild or improved for 24 hours.
- Symptoms other than the above (symptoms that have not occurred before the onset of COVID-19, and occurred after baseline [pre-treatment examination]): The condition with no symptoms has remained for 24 hours.

i The 12 symptoms of COVID-19 will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). The proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration is defined as the proportion of participants with one or more 12 COVID-19 symptoms which have not resolved at the final evaluation point after 3 weeks of administration, that is, on or after Day 18 (after 432 hours [18 days] from initiation of administration) taking into account the time allowance of Day 21 (Table 1-9). Resolution of COVID-19 symptoms at the final evaluation point is assessed according to the following rules:

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have improved to moderate or better, moderate symptoms at baseline have improved to mild or better, and mild symptoms at baseline have remained mild or improved better at the final evaluation point.
- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have remained severe or improved, moderate symptoms at baseline have remained moderate or improved, and mild symptoms at baseline have remained mild or improved at the final evaluation point.
- Symptoms other than the above (symptoms that have not occurred before the onset of COVID-19, and occurred after baseline [pre-treatment examination]): No symptoms have been observed at the final evaluation point.

k Of the 14 symptoms in COVID-19, taste disorder and smell disorder will be evaluated on a 3-point scale of 0 to 2 (0, The same as usual; 1, Less than usual; 2, No sense of smell/taste). The other 12 symptoms will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). The time to resolution of COVID-19 symptoms including taste disorder and smell disorder is defined as the time from the start of study intervention to when all of the symptoms meet the following criteria.

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination): As for taste disorder and smell disorder, 2 (No sense of smell/taste) has remained improved to 1 (Less than usual) or better, or 1 (Less than usual) has remained 1 (Less than usual) or better for 24 hours; and as for the other 12 symptoms, severe symptoms at baseline have remained improved to moderate or better, or moderate symptoms at baseline have remained improved to mild or better, or mild symptoms at baseline have remained mild or better for 24 hours.
- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination): As for taste disorder and smell disorder, 2 (No sense of smell/taste) has remained 2 (No sense of smell/taste) or improved, or 1 (Less than usual) has remained 1 (Less than usual) or improved for 24 hours; and as for the other 12 symptoms, severe symptoms at baseline have remained severe or improved, or moderate symptoms at baseline have remained moderate or improved, or mild symptoms at baseline have remained mild or improved for 24 hours.
- Symptoms other than the above (symptoms that have not occurred before the onset of COVID-19,

and occurred after baseline [pre-treatment examination]): 0 (The same as usual) as for taste disorder and smell disorder and the condition with no symptoms as for the other 12 symptoms have remained for 24 hours.

m Of the 14 symptoms in COVID-19, taste disorder and smell disorder will be evaluated on a 3-point scale of 0 to 2 (0, The same as usual; 1, Less than usual; 2, No sense of smell/taste). The other 12 symptoms will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). Participants with development/worsening of any COVID-19 symptoms are defined as participants who have symptoms meeting the following criteria.

- The scores for taste disorder and smell disorder have worsened from 0 (The same as usual) to 1 (Less than usual) or 2 (No sense of smell/taste), or from 1 (Less than usual) to 2 (No sense of smell/taste) (the baseline score of 2 [No sense of smell/taste] will be excluded from the onset/worsening judgement of COVID-19 symptoms).
- Feeling hot or feverish, cough, shortness of breath (difficulty breathing): Severity of none at baseline has worsened to mild or worse, mild symptoms at baseline have worsened to moderate or worse, or moderate symptoms at baseline have worsened to severe on either symptom (severe symptoms at baseline will be excluded from the onset/worsening judgement of COVID-19 symptoms).
- Low energy or tiredness, muscle or body aches, headache, chills or shivering, stuffy or runny nose, sore throat, nausea, vomiting, and diarrhea: Severity of none at baseline has worsened to mild or worse, mild symptoms at baseline have worsened to moderate or worse, or moderate symptoms at baseline have worsened to severe which are maintained for 24 hours on 2 or more symptoms at the same point (severe symptoms at baseline will be excluded from the onset/worsening judgement of COVID-19 symptoms).

n While the primary analysis population is defined as a population with < 72 hours of time from the onset of COVID-19 to randomization out of the ITT population or mITT population, the evaluation will be performed in the ITT population or mITT population as well.

o The following 5 symptoms will be evaluated: stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness.

p Recurrence will be judged if any symptom meets the following criteria after the resolution of evaluated COVID-19 symptoms (duration of resolution: 48 hours [2 days] or longer).

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have become severe, moderate or mild symptoms at baseline have become moderate or worse, and have remained so for 48 hours.
- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination): Moderate symptoms at baseline have become severe, and mild symptoms at baseline have become moderate or worse, and have remained so for 48 hours (symptoms with the severity of severe at baseline will not be evaluated as recurrence).
- Symptoms other than above (symptoms that have not occurred before the onset of COVID-19, and occurred after baseline [pre-treatment examination]): The symptoms have become moderate or worse and remained so for 48 hours.

q COVID-19 symptom groups to be evaluated include the following 3 categories:

- Respiratory symptoms: stuffy or runny nose, sore throat, cough, and shortness of breath (difficulty breathing)
- General symptoms: low energy or tiredness, muscle or body aches, headache, chills or shivering, and feeling hot or feverish
- Gastrointestinal symptoms: nausea, vomiting, and diarrhea

Overall Design:

This study consists of four parts: Phase 2a Part in participants with mild/moderate or asymptomatic SARS-CoV-2 infection, Phase 2b Part and Phase 3 Part in participants with mild/moderate SARS-CoV-2 infection (cohort to evaluate time to improvement: cohort A), and Phase 2b/3 Part in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B). This study is a multicenter, randomized, double-blind, placebo-controlled study, and consists of 3 groups: S-217622 125 mg group, S-217622 250 mg group, and placebo group.

The primary objective of Phase 2a Part is to confirm the antiviral effect at an early stage. Therefore, analysis including viral titers and viral ribonucleic acid (RNA) level will be performed as needed for all participants with mild/moderate or asymptomatic SARS-CoV-2 infection. At this time, given that the measurement of viral titers and amount of viral RNA would reveal blindedness of the study, they will be measured by anonymizing the participants. In addition, measurement and analysis of the drug concentration may be performed as needed for S-217622 125 mg group and S-217622 250 mg group only in Phase 2a Part. At this time, information of the drug concentration will be treated under blind. In addition, unblind interim evaluations may be performed several times in Phase 2a Part to confirm efficacy and safety of S-217622 at an early stage. It will be performed based on the results collected by when all participants have been observed on Day 9, by approximately 4 weeks after the initiation of Phase 2a Part. Since interim evaluations will be performed unblinded, the manual of interim evaluations will be prepared and finalized before the first one is performed. The manual will define folders that stores unblinding information and results of interim evaluations, and people who can access them.

After enrollment of Phase 2a Part is completed, Phase 2b Part and Phase 3 Part will be conducted in participants with mild/moderate SARS-CoV-2 infection (cohort to evaluate time to improvement: cohort A), and Phase 2b/3 Part will be conducted in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B). After enrollment of Phase 2b Part is completed, enrollment of Phase 3 Part will be initiated.

The primary objective of Phase 2b Part is to evaluate the early improvement effect on clinical symptoms by Day 6 and the early antiviral effect against SARS-CoV-2 on Day 4 in participants with mild/moderate SARS-CoV-2 infection (cohort to evaluate time to improvement: cohort A). In Phase 2b Part, unblinding will be performed at the time when all participants have been observed on Day 6, and the efficacy and safety of S-217622 up to Day 6 will be evaluated at an early stage based on the results collected. Data will be continuously collected even after Day 7 and an exploratory evaluation of the efficacy and safety will be performed.

The primary objective of Phase 3 Part is to verify the efficacy in participants with mild/moderate SARS-CoV-2 infection, and the primary objective of Phase 2b/3 Part is to verify the efficacy in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection. In Phase 2b/3 Part in participants with asymptomatic/mild symptoms only

SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B), an interim analysis of the primary endpoint and the two key secondary endpoints will be performed for the participant populations with mild/moderate SARS-CoV-2 infection (cohort to evaluate time to improvement: cohort A) and with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B) by the Independent Data Monitoring Committee (IDMC) for the purpose of stopping for efficacy when the follow-up is completed in 50% of the target participants. It will be judged whether the interim analysis is to be performed or not depending on the enrollment rate, and if the enrollment of the target sample size is expected to be almost completed at the time of obtaining the interim analysis result, the interim analysis will not be performed. The timing to judge whether to perform the interim analysis or not, criteria to perform the interim analysis including enrollment rates, and criteria to judge stopping for efficacy are to be stipulated in the standard operation procedures of the IDMC in advance and will be finalized before performing the interim analysis.

Number of Participants:

Phase 2a Part (participants with mild/moderate or asymptomatic SARS-CoV-2 infection)

Each intervention group will enroll 23 participants with mild/moderate or asymptomatic SARS-CoV-2 infection per group for a total of 69 participants in 3 groups.

Phase 2b Part (participants with mild/moderate SARS-CoV-2 infection)

Each intervention group will enroll 145 participants with mild/moderate SARS-CoV-2 infection per group for a total of 435 participants in 3 groups. The number of participants to be enrolled may be changed based on the proportion of participants with the detection of SARS-CoV-2 viral titer at Visit 1 (pre-intervention) calculated during the study period.

Phase 3 Part (participants with mild/moderate SARS-CoV-2 infection)

Each intervention group will enroll 530 participants with mild/moderate SARS-CoV-2 infection per group for a total of 1590 participants in 3 groups, and 260 participants with mild/moderate SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization per group for a total of 780 participants in 3 groups.

Phase 2b/3 Part (participants with asymptomatic/mild symptoms only SARS-CoV-2 infection)

Each intervention group will enroll 200 participants with asymptomatic/mild symptoms only SARS-CoV-2 infection per group for a total of 600 participants in 3 groups. In case it is judged that no interim analysis is to be performed for the purpose of stopping for efficacy based on the expected enrollment rate in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B), 570 participants who have been confirmed to be eligible will be randomly assigned to each of these intervention groups (190 participants per group).

Along with the change of dose used to verify efficacy, the following will be re-set.

Each intervention group will enroll 165 participants with asymptomatic/mild symptoms only SARS-CoV-2 infection per group for a total of 495 participants in 3 groups. In case it is judged that no interim analysis is to be performed for the purpose of stopping for efficacy based on the expected enrollment rate in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B), each intervention group will enroll 160 participants with asymptomatic/mild symptoms only SARS-CoV-2 infection per group for a total of 480 participants in 3 groups by the time of final analysis.

Intervention Groups and Duration:

Phase 2a Part

A total of 69 participants with mild/moderate or asymptomatic SARS-CoV-2 infection who are confirmed to be eligible will be randomly assigned to S-217622 125 mg group (23 participants), S-217622 250 mg group (23 participants), and placebo group (23 participants). The population of mild/moderate or asymptomatic in each group is not set.

Phase 2a Part consists of the intervention period (Days 1 to 5), the follow-up period (Days 6 to 28), and exploratory period (Days 29 to 337). Participants are considered to have completed the study if he/she has completed the follow-up period. Only participants who agree to participate in the exploratory period will be evaluated in the period. After the manufacturing and marketing approval of S-217622, it is possible to change to post-marketing clinical trials and continue the exploratory period. Participants will receive 5-day oral administration of S-217622 or placebo once daily. The loading dose will be administered only for the first study intervention (Day 1) (see Table 1-5).

Table 1-5 Dose and Breakdown of Number of Participants in the Study (Phase 2a Part)

Arm	Dose		Study participants	Number of participants	Total
	Loading dose (Day 1)	Maintenance dose (Days 2–5)			
S-217622 125 mg group	375 mg	125 mg	Participants with mild/moderate or asymptomatic SARS-CoV-2 infection	23	69
S-217622 250 mg group	750 mg	250 mg	Participants with mild/moderate or asymptomatic SARS-CoV-2 infection	23	
Placebo group	---	---	Participants with mild/moderate or asymptomatic SARS-CoV-2 infection	23	

Phase 2b Part

A total of 435 participants with mild/moderate SARS-CoV-2 infection who have at least 1 moderate symptoms and have been confirmed to be eligible will be randomly assigned to S-217622 125 mg group (145 participants), S-217622 250 mg group (145 participants), and placebo group (145 participants).

Phase 2b Part consists 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 are considered to have completed the study if he/she has completed the follow-up period. Only participants who agree to participate in the exploratory period will be evaluated in the period. After the manufacturing and marketing approval of S-217622, it is possible to change to post-marketing clinical trials and continue the exploratory period. Participants will receive 5-day oral administration of S-217622 or placebo once daily. The loading dose will be administered only for the first study intervention (Day 1) (see Table 1-6).

Table 1-6 Dose and Breakdown of Number of Participants in the Study (Phase 2b Part)

Arm	Dose		Study participants	Number of participants	Total
	Loading dose (Day 1)	Maintenance dose (Days 2–5)			
S-217622 125 mg group	375 mg	125 mg	Participants with mild/moderate SARS-CoV-2 infection	145	435
S-217622 250 mg group	750 mg	250 mg	Participants with mild/moderate SARS-CoV-2 infection	145	
Placebo group	---	---	Participants with mild/moderate SARS-CoV-2 infection	145	

Phase 3 Part

A total of 1590 participants with mild/moderate SARS-CoV-2 infection and have been confirmed to be eligible will be randomly assigned to S-217622 125 mg group (530 participants), S-217622 250 mg group (530 participants), and placebo group (530 participants).

Of these, 780 participants who have been confirmed to be eligible as participants with mild/moderate SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization will be randomly assigned to S-217622 125 mg group (260 participants), S-217622 250 mg group (260 participants), and placebo group (260 participants).

The study period and doses are the same as in Phase 2b Part (see Table 1-7).

Table 1-7 Dose and Breakdown of Number of Participants in the Study (Phase 3 Part)

Arm	Dose		Study participants*	Number of participants	Total
	Loading dose (Day 1)	Maintenance dose (Days 2–5)			
S-217622 125 mg group	375 mg	125 mg	Participants with mild/moderate SARS-CoV-2 infection	260	780
S-217622 250 mg group	750 mg	250 mg	Participants with mild/moderate SARS-CoV-2 infection	260	
Placebo group	---	---	Participants with mild/moderate SARS-CoV-2 infection	260	

* With < 72 hours from the onset of COVID-19 to randomization.

Phase 2b/3 Part

A total of 600 participants with asymptomatic/mild symptoms only SARS-CoV-2 infection who have been confirmed to be eligible will be randomly assigned to S-217622 125 mg group (200 participants), S-217622 250 mg group (200 participants), and placebo group (200 participants). In case it is judged that no interim analysis is to be performed for the purpose of stopping for efficacy, 570 participants who have been confirmed to be eligible will be randomly assigned to each of these intervention groups (190 participants per group).

Along with the change of dose used to verify efficacy, the following will be re-set.

Four hundred and ninety-five participants who have been confirmed to be eligible as participants with asymptomatic/mild symptoms only SARS-CoV-2 infection will be randomly assigned to S-217622 125 mg group (165 participants), S-217622 250 mg group (165 participants), and placebo group (165 participants). In case it is judged that no interim analysis is to be performed for the purpose of stopping for efficacy, 480 participants who have been confirmed to be eligible will be randomly assigned to each of these intervention groups (160 participants per group).

The study period and doses are the same as in Phase 2b Part (see Table 1-8).

Table 1-8 Dose and Breakdown of Number of Participants in the Study (Phase 2b/3 Part)

Arm	Dose		Study participants	Number of participants*	Total*
	Loading dose (Day 1)	Maintenance dose (Days 2–5)			
S-217622 125 mg group	375 mg	125 mg	Participants with asymptomatic/mild symptoms only SARS-CoV-2 infection	165 [160]	495 [480]
S-217622 250 mg group	750 mg	250 mg	Participants with asymptomatic/mild symptoms only SARS-CoV-2 infection	165 [160]	
Placebo group	---	---	Participants with asymptomatic/mild symptoms only SARS-CoV-2 infection	165 [160]	

* [ ] indicates the number of participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in case no interim analysis is to be performed.

Data and Safety Monitoring Board / Independent Data Monitoring Committee: Yes

1.2 Schema

Figure 1-1 Study Schematic (Common for Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part)

Screening	Intervention Period					Follow-up Period					Exploratory Period**		
	V1	V2	Op V1	V3	Op V2	V4	V5	V6	V7	V8	V9	V10	V11
	Day 1	Day 2	Day 3*	Day 4	Day 5*	Day 6	Day 9	Day 14	Day 21	Day 28	Day 85	Day 169	Day 337
	↑	↑	↑	↑	↑								
	Randomization/ 5-day administration												

* Visits for Day 3 and Day 5 are optional (however, administration of study intervention and entry of participant diary should be conducted).

** To be performed only for participants who agree/assent to participate in the exploratory period.

1.3 Schedule of Activities

Table 1-9 Schedule of Activities (Common for Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part)

Procedure	Intervention Period						Follow-up Period					Exploratory Period			Disconti -nuation
Day	1		2	3	4	5	6	9	14	21	28	85	169	337	
Acceptable time window	−1	-	+1	-	+1	-	+1	±1	±2	±3	±3	±14	±14	±14	+3
Visit	V1		V2	Op V1	V3	Op V2	V4	V5	V6	V7	V8	V9	V10	V11	
	pre-dose	post-dose													
Informed consent/Assent	X														
Inclusion and exclusion criteria	X														
Randomization	X														
Study intervention		X	X	X	X	X									
Medical examination	X		X		X		X	X	X	X	X				X
Participant background	X														
Pregnancy test	X										X				X
SARS-CoV-2 nasopharyngeal swab collection	X		X	X	X	X	X	X	X	X					X
Participant diary	X	Twice daily							Once daily						
8-Point Ordinal Scale	X		X		X		X	X	X	X	X				X
Laboratory assessments	X						X		X		X				X
Vital signs	X		X		X		X	X	X	X	X				X
ECG	X	X	X		X		X								
AE review	X	← X →													X
Concomitant medication review	X		X		X		X	X	X	X	X				X
Blood sampling for drug concentration measurement			X				X								X
Blood sampling for immunity assessment	X										X				X
Post-acute COVID-19 syndrome												X	X	X	

AE = adverse event, ECG = electrocardiograph(y), eCRF = electronic case report form, EQ-5D-5L = EuroQol 5 dimensions 5-level, Op V = optional visit, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SpO_2 = saturation of percutaneous oxygen, V = visit

Annotation	
---	Visits for Day 3 (Op V1) and Day 5 (Op V2) are optional (however, administration of study intervention and entry of participant diary should be conducted). Tests, etc. to be performed before intervention on Day 1 (V1) may be performed on Day -1. Visits for Day 85 (V9), Day 169 (V10), and Day 337 (V11) will be performed only for participants who agree/assent to participate in the exploratory period. For participants who are at home or on accommodation treatment, each visit may be conducted through home-visit medical care, telemedicine or home-visit nursing.
Discontinuation	If a participant is discontinued from the study, tests at discontinuation will be performed as much as possible. If a participant is discontinued during the exploratory period, tests at discontinuation will not be performed.
Informed consent/Assent	Informed consent/Assent may be obtained by remotely explaining the study via online medical examination system.
Inclusion and exclusion criteria	---
Randomization	---
Study intervention	Administer once daily on Days 1 to 5. Administer loading dose only on Day 1 and maintenance dose on Days 2 to 5. No time window is accepted for administration of study intervention. The study intervention for Days 2 to 5 will be handed to participants on Day 1.
Medical examination	---
Participant background	---
Pregnancy test	To be performed on Day 1 (before study intervention) and Day 28 for women of childbearing potential only. The test will be performed as necessary at the discretion of the investigator/subinvestigator.
SARS-CoV-2 nasopharyngeal swab collection	To be performed on Day 1 (before study intervention) and Days 2 to 6, 9, 14, and 21. Visits for Day 3 (Op V1) and Day 5 (Op V2) are optional.
Participant diary	The participant himself/herself will evaluate him/her COVID-19 symptom scores and EQ-5D-5L* and measure SpO_2 and body temperature twice daily (morning and evening) from before the first dose of study intervention on Day 1 to Day 9 and once daily (evening) from Day 10 to Day 21 at the same time whenever possible. Then the participant will enter the results in the participant diary. The first time of Day 1 will be performed before the first study intervention. When acetaminophen is taken for the purpose of antipyretic/analgesic, COVID-19 symptom score is not evaluated, and body temperature is not measured until 4 hours after taking it.
8-Point Ordinal Scale	To be assessed on Day 1 (before study intervention) and Days 2, 4, 6, 14, 21, and 28. If the score changes (except for the changes between Score 0 and Score 2), the date when the event occurred and the score should be recorded on eCRF.
Laboratory assessments	To be performed on Day 1 (before study intervention) and Days 6, 14, and 28.
Vital signs	Vital signs to be measured include systolic/diastolic blood pressure, pulse rate, and respiratory rate. The measurement will be performed on Day 1 (before study intervention) and Days 2, 4, 6, 14, 21, and 28.
ECG	Only in Phase 2a Part, to be performed with 2-lead or more ECG (It is possible to be performed by the participant himself/herself). Not to be performed immediately after blood sampling.

Annotation	
	To be performed on Day 1 (before study intervention, 1 to 8 hours after the study intervention), Days 2, 4, and 6. If the result is abnormal judged by portable ECG in the measurement on Day 1 (1 to 8 hours after the study intervention), the participant has to inform the investigator/subinvestigator or the designee.
AE review	---
Concomitant medication review	On Day 1 (before study intervention), review will be made including prior treatment.
Blood sampling for drug concentration measurement	To be performed on Days 2 and 6. To be performed at discontinuation if the participant discontinues the study by Day 5.
Blood sampling for immunity assessment	To be performed on Day 1 (before study intervention) and Day 28.
Post-acute COVID-19 syndrome	To be performed only for participants who agree/assent to participate in the exploratory period. The participant himself/herself will evaluate his/her post-acute COVID-19 syndrome on Days 85, 169, and 337. Then the participant will enter the results in the participant diary.

2. INTRODUCTION

S-217622 is a 3CL protease inhibitor created by Shionogi & Co., Ltd. and currently being developed as a therapeutic drug for coronavirus disease 2019 (COVID-19).

2.1 Study Rationale

In the nonclinical study using a mouse model of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, lung viral titers decreased in a dose-dependent manner by S-217622 [1]. Decreasing of viral titers is expected even in SARS-CoV-2-infected people. The study is designed as a phase 2/3 placebo-controlled study of 5-day administration of S-217622 consisting of four parts: Phase 2a Part whose primary objective is to confirm the antiviral effect following administration of S-217622 in the early stage in participants with mild/moderate and asymptomatic SARS-CoV-2 infection, Phase 2b Part whose primary objective is to confirm the early improvement effect on clinical symptoms and the early antiviral effect against SARS-CoV-2 in participants with mild/moderate SARS-CoV-2 infection, Phase 3 Part whose primary objective is to verify the efficacy in participants with mild/moderate SARS-CoV-2 infection, and Phase 2b/3 Part whose primary objective is to verify the efficacy in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection.

This study will be initiated after confirming the safety and tolerability of 5-day administration once-daily: 750 mg of the loading dose (Day 1) and 250 mg of the maintenance dose (Day 2 or later), until 5 days after the last study drug administration, following lower dose part, in ongoing Phase 1 study of S-217622 in healthy adult participants (2102T1211).

2.2 Background

2.2.1 Novel Coronavirus (SARS-CoV-2)

From the 1960’s to 2018, 6 types of coronaviruses have been reported. Of these, 4 types (OC43, 229E, NL63, HKU1) cause mild symptoms such as common cold symptoms and gastrointestinal symptoms. However, severe acute respiratory syndrome coronavirus (SARS-CoV) infection that occurred in Asia and Canada between 2002 and 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) infection that has been developing in the Middle East area since 2012 cause significant public health concerns due to their nature as zoonotic diseases as well as their high infectivity and high lethality in humans [2].

In December 2019, outbreaks of pneumonia of unknown cause were reported in several areas in Wuhan City, Hubei Province, People's Republic of China. Epidemiological studies confirmed that this pneumonia was caused by novel coronavirus, and the causative virus was named SARS-CoV-2 [2].

SARS-CoV-2, as same as SARS-CoV does, enters the host cell by specific binding of spike protein on its outer shell surface to angiotensin converting enzyme 2 (ACE2) expressed on the cell membrane surface of the target host cell. ACE2 is expressed in nasal mucosal epithelial cells, alveolar epithelial cells, intestinal epithelial cells in the small intestine, etc. [2, 3].

2.2.2 Coronavirus Disease 2019 (COVID-19)

The infection with SARS-CoV-2 was named COVID-19, and the World Health Organization (WHO) declared on January 30, 2020 "Public Health Emergency of International Concern (PHEIC)" on COVID-19. Later, on March 11, 2020, WHO expressed that COVID-19 could be characterized as a pandemic (global epidemic) because of the situation of its worldwide spread as well as its severity [4]. SARS-CoV-2 was originally thought to be transmitted exclusively from animals to humans, but has been shown to be transmitted from infected individuals with symptoms to humans, as well as from infected individuals with no symptoms [2]. Of these infected individuals, at least one-third are believed to be asymptomatic [5].

Common symptoms with COVID-19 include fever, cough, runny nose, stuffy nose, sore throat, muscle pain, and diarrhea, which are similar to common cold. In addition, other symptoms including loss of taste and sense of smell have been reported. High-risk patients with advanced age, cardiovascular disease, respiratory disease, renal disease, diabetes mellitus, obesity, or immunodeficiency are more likely to become severe. Such patients experience rapidly progressing pneumonia, resulting in shortness of breath, dyspnea, etc., and may require treatments with oxygen inhalation, ventilator, or extracorporeal membrane oxygenation (ECMO). This has led to the tightening and collapse of healthcare systems worldwide [2]. In some patients, COVID-19 symptoms may persist after recovery, with varying duration and symptoms, which is known to affect short-term and long-term health (post-acute COVID-19 syndrome) [6].

As of August 2022, remdesivir and molnupiravir, which are RNA polymerase inhibitors, nirmatrelvir/ritonavir, which is a 3CL protease inhibitor, casirivimab and imdevimab, sotrovimab which are anti-SARS-CoV-2 monoclonal antibody, dexamethasone and baricitinib, which are immunomodulators/immunosuppressors, and tocilizumab, which is a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody, have been approved as therapeutic drugs against SARS-CoV-2 infection in Japan. However, no therapeutic approach has been established for asymptomatic patients and patients who are at a low risk of becoming severe, and the development of a novel therapeutic drug has been awaited.

2.2.3 Characteristics of S-217622

S-217622 is a candidate compound for therapeutic drug against SARS-CoV-2 infection, generated by Shionogi & Co., Ltd. S-217622 is an inhibitor against SARS-CoV-2 3CL

protease which is essential for processing of complex protein coded by SARS-CoV-2 gene and for viral replication.

2.3 Benefit/Risk Assessment

S-217622 has been developed as a therapeutic drug against SARS-CoV-2 infection. In the nonclinical study using a mouse model of SARS-CoV-2 infection, lung viral titers decreased in a dose-dependent manner [1]. Decreasing of viral titers by S-217622 is also expected in people with mild/moderate and asymptomatic/mild symptoms only SARS-CoV-2 infection, who are the subjects of this study. As of August 2022, the safety and tolerability of S-217622 5-day administration of 750 mg as the loading dose and 250 mg as the maintenance dose has been confirmed in Phase 1 study of S-217622 in healthy adult participants (2102T1211) and in Phase 2a Part and Phase 2b Part of this study. Risks anticipated from the results of nonclinical studies are presented in the Investigator's Brochure [1].

3. OBJECTIVES AND ENDPOINTS

The primary objective and secondary objectives of Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3Part are shown in Table 3-1, Table 3-2, Table 3-3, and Table 3-4, respectively.

Table 3-1 Objectives and Endpoints (Phase 2a Part, Participants with Mild/Moderate or Asymptomatic SARS-CoV-2 Infection)

Objectives	Endpoints
Primary	
Common to participants with mild/moderate and with asymptomatic SARS-CoV-2 infection[a]	
• To investigate the antiviral effect of 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Change from baseline in SARS-CoV-2 viral titer at each time point
Secondary	
Common to participants with mild/moderate and with asymptomatic SARS-CoV-2 infection[a]	
• To investigate the antiviral effect of 5-day administration of S-217622 other than the primary endpoint in participants with SARS-CoV-2 infection.	• The following items concerning SARS-CoV-2 viral titer – Time to the first negative SARS-CoV-2 viral titer – Time to negative SARS-CoV-2 viral titer at 2 consecutive time points – Time to sustained negative SARS-CoV-2 viral titer – Proportion of participants with positive SARS-CoV-2 viral titer at each time point – SARS-CoV-2 viral titer at each time point

Objectives	Endpoints
	– Relative change rate from baseline in SARS-CoV-2 viral titer at each time point – AUC of change in SARS-CoV-2 viral titer • The following items concerning RT-PCR testing (nasopharyngeal swabs) – Time to the first negative RT-PCR result – Time to negative RT-PCR results at 2 consecutive time points – Time to sustained negative RT-PCR results – Proportion of participants with positive RT-PCR result at each time point – Amount of SARS-CoV-2 viral RNA at each time point – Change from baseline in amount of SARS-CoV-2 viral RNA at each time point – Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point – AUC of change in amount of SARS-CoV-2 viral RNA
• To investigate the effect in preventing aggravation following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Proportion of participants with the following or higher scores on 8-Point Ordinal Scale and time from the first dose of study intervention – Symptomatic, no limitation of activities (Score 1) – Symptomatic, limitation of activities (Score 2) – Hospitalized, no oxygen therapy (Score 3) – Hospitalized, with oxygen therapy (< 5 L/min) (Score 4) – Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) – Hospitalized, with ventilation (Score 6) – Death (Score 7) • SpO_2 at each time point
• To investigate QOL following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Change from baseline in EQ-5D-5L
• To confirm the pharmacokinetics following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Plasma concentration of S-217622 (Days 2, 6)
• To investigate the safety and tolerability following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Adverse events, laboratory tests, and vital signs (systolic/diastolic blood pressure, pulse rate, respiratory rate), ECG
Participants with mild/moderate SARS-CoV-2 infection[a]	
• To investigate the effect in improving clinical symptoms following 5-day administration of	• Time to improvement of COVID-19 symptoms[b, c]

Objectives	Endpoints
S-217622 in participants with mild/moderate SARS-CoV-2 infection.	• Time to improvement of COVID-19 symptoms (duration of recovery, 72 hours [3 days] or longer)[b, c, d] • Time to improvement of COVID-19 symptoms (duration of recovery, 120 hours [5 days] or longer)[b, c, d] • Time to improvement of each COVID-19 symptom[b, c] • Change from baseline in total score of COVID-19 symptoms at each time point[b] • Proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point[b, c] • Proportion of participants with taste disorder or smell disorder at each time point • Time to resolution of fever (< 37.0°C)
Participants with asymptomatic SARS-CoV-2 infection[a]	
• To investigate the preventive effect of 5-day administration of S-217622 in participants with asymptomatic SARS-CoV-2 infection.	• Proportion of participants with development of COVID-19 symptoms[e, f] • Proportion of participants with development of COVID-19 symptoms with fever (≥ 37.0°C)[e, f]
Exploratory	
Common for participants with mild/moderate and asymptomatic SARS-CoV-2 infection[a]	
• To evaluate the amino acid substitutions in 3CL protease (nsp5) cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection. • To evaluate immunity in participants with SARS-CoV-2 infection. • To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection. • To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) cleavage site following drug administration • Geometric mean titer for SARS-CoV-2 neutralizing antibody titer (Days 1, 28) • Change from baseline in aggravation markers[g] • Proportion of participants with post-acute COVID-19 syndrome at each time point

Table 3-2 Objectives and Endpoints (Phase 2b Part, Participants with Mild/Moderate SARS-CoV-2 Infection)

Objectives	Endpoints
Primary	
• To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection, based on the	• Time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6)[b]

Objectives	Endpoints
time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6).	
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection, based on the change from baseline on Day 4 in SARS-CoV-2 viral titer.	• Change from baseline on Day 4 in SARS-CoV-2 viral titer
Secondary	
• To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Time to improvement of COVID-19 symptoms[b, c] • Time to improvement of COVID-19 symptoms (duration of recovery, 72 hours [3 days] or longer)[b, c, d] • Time to improvement of COVID-19 symptoms (duration of recovery, 120 hours [5 days] or longer)[b, c, d] • Time to improvement of each COVID-19 symptom[b, c] • Change from baseline in total score of COVID-19 symptoms at each time point[b] • Proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point[b, c] • Proportion of participants with taste disorder or smell disorder at each time point • Time to resolution of fever (< 37.0°C)
• To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• The following items concerning SARS-CoV-2 viral titer – Time to the first negative SARS-CoV-2 viral titer – Time to negative SARS-CoV-2 viral titer at 2 consecutive time points – Time to sustained negative SARS-CoV-2 viral titer – Proportion of participants with positive SARS-CoV-2 viral titer at each time point – SARS-CoV-2 viral titer at each time point – Change from baseline in SARS-CoV-2 viral titer at each time point – Relative change rate from baseline in SARS-CoV-2 viral titer at each time point – AUC of change in SARS-CoV-2 viral titer • The following items concerning RT-PCR testing (nasopharyngeal swabs) – Time to the first negative RT-PCR result

Objectives	Endpoints
	– Time to negative RT-PCR results at 2 consecutive time points – Time to sustained negative RT-PCR results – Proportion of participants with positive RT-PCR result at each time point – Amount of SARS-CoV-2 viral RNA at each time point – Change from baseline in amount of SARS-CoV-2 viral RNA at each time point – Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point – AUC of change in amount of SARS-CoV-2 viral RNA
• To compare the effect to prevent aggravation following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Proportion of participants with the following or higher scores on 8-Point Ordinal Scale and time from the first dose of study intervention – Symptomatic, no limitation of activities (Score 1) – Symptomatic, limitation of activities (Score 2) – Hospitalized, no oxygen therapy (Score 3) – Hospitalized, with oxygen therapy (< 5 L/min) (Score 4) – Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) – Hospitalized, with ventilation (Score 6) – Death (Score 7) • SpO_2 at each time point
• To compare QOL following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Change from baseline in EQ-5D-5L
• To confirm the pharmacokinetics following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• S-217622: Plasma concentration (Days 2, 6)
• To compare the safety and tolerability following 5-day administration of S-217622 with those of placebo in participants with SARS-CoV-2 infection.	• Adverse events, laboratory tests, and vital signs (systolic/diastolic blood pressure, pulse rate, and respiratory rate)
Exploratory	
• To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infection.	• Spike gene sequence of SARS-CoV-2
• To perform polymorphism analysis of 3CL protease (nsp5) for participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) of SARS-CoV-2

Objectives	Endpoints
• To evaluate the amino acid substitutions in 3CL protease (nsp5) and its cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) and its cleavage site following drug administration
• To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participant's specimen.	• EC_{50} of S-217622 on SARS-CoV-2 isolated from baseline sample
• To evaluate immunity in participants with SARS-CoV-2 infection.	• Geometric mean titer for SARS-CoV-2 neutralizing antibody titer (Days 1, 28)
• To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection.	• Change from baseline in aggravation markers[g]
• To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Proportion of participants with post-acute COVID-19 syndrome at each time point

Table 3-3 Objectives and Endpoints (Phase 3 Part, Participants with Mild/Moderate SARS-CoV-2 Infection)

Objectives	Endpoints
Primary	
• To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection[n], based on the time to resolution of 5 COVID-19 symptoms.	• Time to resolution of 5 COVID-19 symptoms[h,o]
Key Secondary	
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection[n], based on the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA.	• Change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA
• To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection[n], based on time to the first negative SARS-CoV-2 viral titer.	• Time to the first negative SARS-CoV-2 viral titer
Other Secondary	
• To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Time to resolution of 5 COVID-19 symptoms without recurrence (duration of resolution: 48 hours [2 days] or longer)[h,o,p] • Time to resolution of 12 COVID-19 symptoms and COVID-19 symptom groups[b,h,q]

Objectives	Endpoints
	• Time to resolution of 14 COVID-19 symptoms including taste disorder and smell disorder[e,k] • Time to resolution of each of the 5 COVID-19 symptoms[h,o] • Proportion of participants with taste disorder or smell disorder at each time point • Time to resolution of fever (< 37.0°C) • Proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration[b,i]
• To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• The following items concerning SARS-CoV-2 viral titer – Time to sustained negative SARS-CoV-2 viral titer – Proportion of participants with positive SARS-CoV-2 viral titer at each time point – SARS-CoV-2 viral titer at each time point – Change from baseline in SARS-CoV-2 viral titer at each time point – Relative change rate from baseline in SARS-CoV-2 viral titer at each time point – AUC of change in SARS-CoV-2 viral titer • The following items concerning RT-PCR testing (nasopharyngeal swabs) – Proportion of participants with positive RT-PCR result at each time point – Amount of SARS-CoV-2 viral RNA at each time point – Change from baseline in amount of SARS-CoV-2 viral RNA at each time point – Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point – AUC of change in amount of SARS-CoV-2 viral RNA
• To compare the effect to prevent aggravation following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Proportion of participants with the following or higher scores on 8-Point Ordinal Scale and time from the first dose of study intervention – Symptomatic, no limitation of activities (Score 1) – Symptomatic, limitation of activities (Score 2) – Hospitalized, no oxygen therapy (Score 3)

Objectives	Endpoints
	– Hospitalized, with oxygen therapy (< 5 L/min) (Score 4) – Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) – Hospitalized, with ventilation (Score 6) – Death (Score 7) • SpO_2 at each time point
• To compare QOL following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Change from baseline in EQ-5D-5L
• To confirm the pharmacokinetics following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• S-217622: Plasma concentration (Days 2, 6)
• To compare the safety and tolerability following 5-day administration of S-217622 with those of placebo in participants with SARS-CoV-2 infection.	• Adverse events, laboratory tests, and vital signs (systolic/diastolic blood pressure, pulse rate, and respiratory rate)
Exploratory	
• To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infection.	• Spike gene sequence of SARS-CoV-2
• To perform polymorphism analysis of 3CL protease (nsp5) for participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) of SARS-CoV-2
• To evaluate the amino acid substitutions in 3CL protease (nsp5) and its cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) and its cleavage site following drug administration
• To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participant's specimen.	• EC_{50} of S-217622 on SARS-CoV-2 isolated from baseline sample
• To evaluate immunity in participants with SARS-CoV-2 infection.	• Geometric mean titer for SARS-CoV-2 neutralizing antibody titer (Days 1, 28)
• To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection.	• Change from baseline in aggravation markers[g] • Amount of viral antigen (spike, nucleocapsid), antiviral antigen antibody, and viral RNA in blood at each time point
• To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Proportion of participants with post-acute COVID-19 syndrome at each time point
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Time to the viral RNA <LLOQ and the negative RT-PCR result • Time to the first viral RNA $<LLOD_{95}$

Table 3-4 Objectives and Endpoints (Phase 2b/3 Part, Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection)

Objectives	Endpoints
Primary	
• To compare the effect of 5-day administration of S-217622 on preventing development or worsening of symptoms with that of placebo in participants with SARS-CoV-2 infection.	• Proportion of participants with development /worsening of COVID-19 symptoms[e,m]
Key secondary	
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection, based on the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA. • To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection, based on time to the first negative SARS-CoV-2 viral titer.	• Change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA • Time to the first negative SARS-CoV-2 viral titer
Other secondary	
• To investigate the preventive effect of 5-day administration of S-217622 in participants with asymptomatic SARS-CoV-2 infection. • To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Proportion of participants with development of COVID-19 symptoms [e, f] • Proportion of participants with development of COVID-19 symptoms with fever (≥ 37.0°C)[e, f] • The following items concerning SARS-CoV-2 viral titer – Time to sustained negative SARS-CoV-2 viral titer – Proportion of participants with positive SARS-CoV-2 viral titer at each time point – SARS-CoV-2 viral titer at each time point – Change from baseline in SARS-CoV-2 viral titer at each time point – Relative change rate from baseline in SARS-CoV-2 viral titer at each time point – AUC of change in SARS-CoV-2 viral titer • The following items concerning RT-PCR testing (nasopharyngeal swabs) – Proportion of participants with positive RT-PCR result at each time point – Amount of SARS-CoV-2 viral RNA at each time point – Change from baseline in amount of SARS-CoV-2 viral RNA at each time point

Objectives	Endpoints
	– Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point – AUC of change in amount of SARS-CoV-2 viral RNA
• To compare the effect to prevent aggravation following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Proportion of participants with the following or higher scores on 8-Point Ordinal Scale and time from the first dose of study intervention – Symptomatic, no limitation of activities (Score 1) – Symptomatic, limitation of activities (Score 2) – Hospitalized, no oxygen therapy (Score 3) – Hospitalized, with oxygen therapy (< 5 L/min) (Score 4) – Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) – Hospitalized, with ventilation (Score 6) – Death (Score 7) • SpO_2 at each time point
• To compare QOL following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Change from baseline in EQ-5D-5L
• To confirm the pharmacokinetics following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• S-217622: Plasma concentration (Days 2, 6)
• To compare the safety and tolerability following 5-day administration of S-217622 with those of placebo in participants with SARS-CoV-2 infection.	• Adverse events, laboratory tests, and vital signs (systolic/diastolic blood pressure, pulse rate, and respiratory rate)
Exploratory	
• To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infection.	• Spike gene sequence of SARS-CoV-2
• To perform polymorphism analysis of 3CL protease (nsp5) for participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) of SARS-CoV-2
• To evaluate the amino acid substitutions in 3CL protease (nsp5) and its cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) and its cleavage site following drug administration
• To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participant's specimen.	• EC_{50} of S-217622 on SARS-CoV-2 isolated from baseline sample
• To evaluate immunity in participants with SARS-CoV-2 infection.	• Geometric mean titer for SARS-CoV-2 neutralizing antibody titer (Days 1, 28)

Objectives	Endpoints
• To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection.	• Change from baseline in aggravation markers[g]
• To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Proportion of participants with post-acute COVID-19 syndrome at each time point
• To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.	• Time to the viral RNA <LLOQ and the negative RT-PCR result • Time to the first viral RNA <$LLOD_{95}$

ALT = alanine aminotransferase, AUC = area under curve, CCL = C-C motif ligand, CK = creatine kinase, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, EC_{50} = half maximal effective concentration, ECG = electrocardiography, EQ-5D-5L = EuroQol 5 dimensions 5-level [redacted] INR = international normalized ratio, [redacted] LDH = lactate dehydrogenase, $LLOD_{95}$ = lower limit of detection with a positivity rate greater than 95%, LLOQ = lower limit of quantitation, PT = prothrombin time, RNA = ribonucleic acid, RT-PCR = reverse transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SpO_2 = saturation of percutaneous oxygen, [redacted]

a Participants who meet inclusion criterion #2 to #4 in Section 5.1.1 but do not meet exclusion criterion #1 to #5 in Section 5.2.1 are defined as participants with mild/moderate SARS-CoV-2 infection; participants who meet inclusion criterion #2 and #3 in Section 5.1.2 but do not meet exclusion criterion #1 to #5 in Section 5.2.2 are defined as participants with asymptomatic/mild symptoms only SARS-CoV-2 infection.

b The following 12 symptoms will be evaluated: low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath (difficulty breathing), nausea, vomiting, and diarrhea.

c The 12 symptoms of COVID-19 will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). The time to improvement of COVID-19 symptoms is defined as the time from the start of study intervention to when all of the symptoms meet the following criteria.

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have remained improved to moderate or better, or moderate symptoms at baseline have remained improved to mild or better for 24 hours.
- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have remained severe or better, or moderate symptoms at baseline have remained or improved moderate or better for 24 hours.
- Symptoms other than the above (Symptoms that have not occurred before the onset of COVID-19, occur after baseline [pre-treatment examination]): Mild or better condition has remained for 24 hours.

d As for the definition of the time to improvement of COVID-19 symptoms described in c, the duration should be read as 72 hours or longer, or 120 hours or longer.

e Taste disorder and smell disorder are added to the 12 symptoms of low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath (difficulty breathing), nausea, vomiting, and diarrhea. These 14 symptoms will be evaluated.

f Of the 14 symptoms in COVID-19, taste disorder and smell disorder will be evaluated on a 3-point scale of 0 to 2 (0, The same as usual; 1, Less than usual; 2, No sense of smell/taste). The other 12

symptoms will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). Participants with development of any COVID-19 symptoms are defined as participants who have symptoms meeting the following criteria.

- The scores for taste disorder and smell disorder have worsened from 0 (The same as usual) to 1 (Less than usual) or 2 (No sense of smell/taste).
- Feeling hot or feverish, cough, shortness of breath (difficulty breathing): Severity of none at baseline has worsened to mild or worse, mild symptoms at baseline have worsened to moderate or worse, or moderate symptoms at baseline have worsened to severe on either symptom (severe symptoms at baseline will be excluded from the onset judgement of COVID-19 symptoms).
- Low energy or tiredness, muscle or body aches, headache, chills or shivering, stuffy or runny nose, sore throat, nausea, vomiting, and diarrhea: Severity of none at baseline has worsened to mild or worse, mild symptoms at baseline have worsened to moderate or worse, or moderate symptoms at baseline have worsened to severe on 2 or more symptoms at the same point (severe symptoms at baseline will be excluded from the onset judgement of COVID-19 symptoms).

g [redacted]

h The 12 symptoms of COVID-19 will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). The time to resolution of COVID-19 symptoms is defined as the time from the start of study intervention to when all of the symptoms meet the following criteria.

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have remained improved to moderate or better, moderate symptoms at baseline have remained improved to mild or better, and mild symptoms at baseline have remained mild or better for 24 hours.
- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have remained severe or improved, moderate symptoms at baseline have remained moderate or improved, and mild symptoms at baseline have remained mild or improved for 24 hours.
- Symptoms other than the above (symptoms that have not occurred before the onset of COVID-19, and occurred after baseline [pre-treatment examination]): The condition with no symptoms has remained for 24 hours.

i The 12 symptoms of COVID-19 will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). The proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration is defined as the proportion of participants with one or more 12 COVID-19 symptoms which have not resolved at the final evaluation point after 3 weeks of administration, that is, on or after Day 18 (after 432 hours [18 days] from initiation of administration) taking into account the time allowance of Day 21 (Table 1-9). Resolution of COVID-19 symptoms at the final evaluation point is assessed according to the following rules:

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have improved to moderate or better, moderate symptoms at baseline have improved to mild or better, and mild symptoms at baseline have remained mild or improved better at the final evaluation point.
- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have remained severe or improved, moderate symptoms at baseline have remained moderate or improved, and mild symptoms at baseline have remained mild or improved at the final evaluation point.
- Symptoms other than the above (symptoms that have not occurred before the onset of COVID-19, and occurred after baseline [pre-treatment examination]): No symptoms have been observed at the

final evaluation point.

k Of the 14 symptoms in COVID-19, taste disorder and smell disorder will be evaluated on a 3-point scale of 0 to 2 (0, The same as usual; 1, Less than usual; 2, No sense of smell/taste). The other 12 symptoms will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). The time to resolution of COVID-19 symptoms including taste disorder and smell disorder is defined as the time from the start of study intervention to when all of the symptoms meet the following criteria.

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination): As for taste disorder and smell disorder, 2 (No sense of smell/taste) has remained improved to 1 (Less than usual) or better, or 1 (Less than usual) has remained 1 (Less than usual) or better for 24 hours; and as for the other 12 symptoms, severe symptoms at baseline have remained improved to moderate or better, or moderate symptoms at baseline have remained improved to mild or better, or mild symptoms at baseline have remained mild or better for 24 hours.
- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination): As for taste disorder and smell disorder, 2 (No sense of smell/taste) has remained 2 (No sense of smell/taste) or improved, or 1 (Less than usual) has remained 1 (Less than usual) or improved for 24 hours; and as for the other 12 symptoms, severe symptoms at baseline have remained severe or improved, or moderate symptoms at baseline have remained moderate or improved, or mild symptoms at baseline have remained mild or improved for 24 hours.
- Symptoms other than the above (symptoms that have not occurred before the onset of COVID-19, and occurred after baseline [pre-treatment examination]): 0 (The same as usual) as for taste disorder and smell disorder and the condition with no symptoms as for the other 12 symptoms have remained for 24 hours.

m Of the 14 symptoms in COVID-19, taste disorder and smell disorder will be evaluated on a 3-point scale of 0 to 2 (0, The same as usual; 1, Less than usual; 2, No sense of smell/taste). The other 12 symptoms will be evaluated on a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe). Participants with development/worsening of any COVID-19 symptoms are defined as participants who have symptoms meeting the following criteria.

- The scores for taste disorder and smell disorder have worsened from 0 (The same as usual) to 1 (Less than usual) or 2 (No sense of smell/taste), or from 1 (Less than usual) to 2 (No sense of smell/taste) (the baseline score of 2 [No sense of smell/taste] will be excluded from the onset/worsening judgement of COVID-19 symptoms).
- Feeling hot or feverish, cough, shortness of breath (difficulty breathing): Severity of none at baseline has worsened to mild or worse, mild symptoms at baseline have worsened to moderate or worse, or moderate symptoms at baseline have worsened to severe on either symptom (severe symptoms at baseline will be excluded from the onset/worsening judgement of COVID-19 symptoms).
- Low energy or tiredness, muscle or body aches, headache, chills or shivering, stuffy or runny nose, sore throat, nausea, vomiting, and diarrhea: Severity of none at baseline has worsened to mild or worse, mild symptoms at baseline have worsened to moderate or worse, or moderate symptoms at baseline have worsened to severe which are maintained for 24 hours on 2 or more symptoms at the same point (severe symptoms at baseline will be excluded from the onset/worsening judgement of COVID-19 symptoms).

n While the primary analysis population is defined as a population with < 72 hours of time from the onset of COVID-19 to randomization out of the ITT population or mITT population, the evaluation will be performed in the ITT population or mITT population as well.

o The following 5 symptoms will be evaluated: stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness.

p Recurrence will be judged if any symptom meets the following criteria after the resolution of evaluated COVID-19 symptoms (duration of resolution: 48 hours [2 days] or longer).

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the

participant to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline have become severe, moderate or mild symptoms at baseline have become moderate or worse, and have remained so for 48 hours.

- Pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination): Moderate symptoms at baseline have become severe, and mild symptoms at baseline have become moderate or worse, and have remained so for 48 hours (symptoms with the severity of severe at baseline will not be evaluated as recurrence).
- Symptoms other than above (symptoms that have not occurred before the onset of COVID-19, and occurred after baseline [pre-treatment examination]): The symptoms have become moderate or worse and remained so for 48 hours.

q COVID-19 symptom groups to be evaluated include the following 3 categories:

- Respiratory symptoms: stuffy or runny nose, sore throat, cough, and shortness of breath (difficulty breathing)
- General symptoms: low energy or tiredness, muscle or body aches, headache, chills or shivering, and feeling hot or feverish
- Gastrointestinal symptoms: nausea, vomiting, and diarrhea

4. STUDY DESIGN

4.1 Overall Design

This study consists of 4 parts: Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part. Phase 2a Part is for participants with mild/moderate or asymptomatic SARS-CoV-2 infection. Phase 2b Part and Phase 3 Part are for participants with mild/moderate SARS-CoV-2 infection (cohort to evaluate time to improvement: cohort A), and Phase 2b/3 Part is for participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B), respectively. This study is a multicenter, randomized, double-blind, placebo-controlled study. The participants may be those at home, those at accommodation facilities, or those in a hospital.

In each part, eligible participants will be randomly assigned to S-217622 125 mg group, S-217622 250 mg group, and placebo group.

- S-217622 125 mg group (5-day administration once-daily):
  As a loading dose, S-217622 375 mg will be administrated only for the first study intervention. Thereafter, S-217622 125 mg will be administered on Days 2 to 5.
- S-217622 250 mg group (5-day administration once-daily):
  As a loading dose, S-217622 750 mg will be administrated only for the first study intervention. Thereafter, S-217622 250 mg will be administered on Days 2 to 5.
- Placebo group
  Placebo will be administered once daily for 5 days.

Each Part consists of the intervention period (Days 1 to 5), the follow-up period (Days 6 to 28), and the exploratory period (Days 29 to 337), which is common for all Parts. Participants are considered to have completed the study if he/she has completed the follow-up period. Only participants who agree to participate in the exploratory period will be evaluated in the period. After the manufacturing and marketing approval of S-217622, it is possible to change to post-marketing clinical trials and continue the exploratory period. The Study Schematic and the Schedule of Activities (SoA) are presented in Section 1.2 and Section 1.3, respectively.

- Intervention Period (Days 1 to 5):

  After obtaining informed consent/assent, screening tests will be performed to confirm the participant's eligibility to participate in the study. Participants determined to be eligible by screening tests will be randomized to either group on the day of the initiation of study intervention (Day 1).

  The study intervention (S-217622 or placebo) will be administered once daily for 5 days.

  The specified investigations and examinations will be performed on Days 1 to 5. For participants who are recuperating at home or accommodation facilities, measurements, blood sampling, etc. at each visit will be performed by a visiting physician or nurse, and medical examinations can also be performed through home-visit medical care or telemedicine. Visits for Day 3 and Day 5

are optional (however, administration of study intervention and entry of participant diary should be conducted).

– Follow-up Period (Days 6 to 28):

  The specified investigations and examinations will be performed on Days 6, 14, 21, and 28. Measurements, blood sampling, etc. will be performed by a visiting physician or nurse, and medical examinations can also be performed through home-visit medical care or telemedicine.

– Exploratory Period (Days 29 to 337) (Only participants who agree to participate in the exploratory period):

  The specified examinations will be performed to evaluate post-acute COVID-19 syndrome on Days 85, 169, 337.

4.1.1 Phase 2a Part: Participants with Mild/Moderate or Asymptomatic SARS-CoV-2 Infection

As for participants with mild/moderate or asymptomatic SARS-CoV-2 infection, 69 eligible participants will be randomly assigned to the S-217622 125 mg group (23 participants), S-217622 250 mg group (23 participants), or the placebo group (23 participants).

The primary objective of Phase 2a Part is to confirm the antiviral effect at an early stage. Therefore, analysis including viral titers and viral ribonucleic acid (RNA) level will be performed as needed for all participants with mild/moderate or asymptomatic SARS-CoV-2 infection. At this time, given that the measurement of viral titers and amount of viral RNA would reveal blindedness of the study, they will be measured by anonymizing the participants. In addition, measurement and analysis of the drug concentration may be performed as needed for S-217622 125 mg group and S-217622 250 mg group only in Phase 2a Part. At this time, information of the drug concentration will be treated under blind. In addition, unblind interim evaluations may be performed several times in Phase 2a Part to confirm efficacy and safety of S-217622 at an early stage. It will be performed based on the results collected by when all participants have been observed on Day 9, by approximately 4 weeks after the initiation of Phase 2a Part. Since interim evaluations will be performed unblinded, the manual of interim evaluations will be prepared and finalized before the first one is performed. The manual will define folders that stores unblinding information and results of interim evaluations, and people who can access them.

4.1.2 Phase 2b Part: Participants with Mild/Moderate SARS-CoV-2 Infection

As soon as enrollment of Phase 2a Part is completed, enrollment of Phase 2b Part will be initiated.

A total of 435 participants with mild/moderate SARS-CoV-2 infection who have been confirmed to be eligible will be randomly assigned to S-217622 125 mg group (145 participants), S-217622 250 mg group (145 participants), and placebo group (145

participants). The number of participants to be enrolled may be changed based on the proportion of participants with the detection of SARS-CoV-2 viral titer at Visit 1 (pre-intervention) calculated during the study period.

The primary objective of Phase 2b Part is to evaluate the early improvement effect on clinical symptoms by Day 6 and the early antiviral effect against SARS-CoV-2 on Day 4 in participants with mild/moderate SARS-CoV-2 infection (cohort to evaluate time to improvement: cohort A). In Phase 2b Part, unblinding will be performed at the time when all participants have been observed on Day 6, and the efficacy and safety of S-217622 up to Day 6 will be evaluated at an early stage based on the results collected. Data will be continuously collected even after Day 7 and an exploratory evaluation of the efficacy and safety will be performed by the end of the study.

4.1.3 Phase 3 Part: Participants with Mild/Moderate SARS-CoV-2 Infection

As soon as enrollment of Phase 2b Part is completed, enrollment of Phase 3 Part will be initiated.

A total of 1590 participants with mild/moderate SARS-CoV-2 infection and have been confirmed to be eligible will be randomly assigned to S-217622 125 mg group (530 participants), S-217622 250 mg group (530 participants), and placebo group (530 participants).

The required sample size of the population with < 72 hours from the onset of COVID-19 to randomization will be selected as described below.

Seven hundred and eighty participants who have been confirmed to be eligible as participants with mild/moderate SARS-CoV-2 infection and with < 72 hours from the onset of COVID-19 to randomization will be randomly assigned to S-217622 125 mg group (260 participants), S-217622 250 mg group (260 participants), and placebo group (260 participants).

4.1.4 Phase 2b/3 Part: Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection

As soon as enrollment of Phase 2a Part is completed, enrollment of Phase 2b/3 Part will be initiated.

On the premise that an interim analysis is performed for the purpose of stopping for efficacy, a total of 600 participants with asymptomatic/mild symptoms only SARS-CoV-2 infection who have been confirmed to be eligible will be randomly assigned to S-217622 125 mg group (200 participants), S-217622 250 mg group (200 participants), and placebo group (200 participants). In case it is judged that no interim analysis is to be

performed for the purpose of stopping for efficacy, 570 participants who have been confirmed to be eligible will be randomly assigned to each of these intervention groups (190 participants per group).

Along with the change of dose used to verify efficacy, the following will be re-set.

On the premise that an interim analysis is performed for the purpose of stopping for efficacy, 495 participants with asymptomatic/mild symptoms only SARS-CoV-2 infection who have been confirmed to be eligible will be randomly assigned to S-217622 125 mg group (165 participants), S-217622 250 mg group (165 participants), and placebo group (165 participants). In case it is judged that no interim analysis is to be performed for the purpose of stopping for efficacy, 480 participants who have been confirmed to be eligible will be randomly assigned to each of these intervention groups (160 participants per group).

In Phase 2b/3 Part, an interim analysis of the primary endpoint and the two key secondary endpoints will be performed for the participant population with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B) for the purpose of stopping for efficacy when the follow-up has been completed in 50% of the target participants. It will be judged whether the interim analysis is to be performed or not depending on the enrollment rate, and if the enrollment of the target sample size is expected to be almost completed at the time of obtaining the interim analysis result, the interim analysis will not be performed. The timing to judge to perform the interim analysis, criteria to perform the interim analysis including enrollment rates, and the stopping criteria for efficacy are to be stipulated in the standard operation procedures of IDMC (see Section 9.8). If the interim analysis is performed, the number of analyses shall be 2 in total including the final analysis (1 interim analysis), and as the criteria for stopping for efficacy based on the α-spending function, the O'Brien–Fleming boundary will be adopted to the primary analysis for the primary endpoint and the Pocock boundary will be adopted to the primary analysis for each of the two key secondary endpoints.

If both the above-mentioned interim analysis and dose selection are to be performed, the interim analysis shall be performed after the dose selection.

4.2 Scientific Rationale for Study Design

In the nonclinical study using a mouse model of SARS-CoV-2 infection, lung viral titers decreased after administration of S-217622 in a dose-dependent manner, and there were no major concerns on safety in humans [1], therefore administration to humans was initiated. Given these, this study is designed as a phase 2/3 placebo-controlled study of S-217622 consisting of four parts: Phase 2a Part whose primary objective is to confirm the antiviral effect at an early stage in participants with mild/moderate or asymptomatic SARS-CoV-2 infection, Phase 2b Part whose primary objective is to confirm the early improvement effect on clinical symptoms and the early antiviral effect against SARS-CoV-2 in participants with mild/moderate SARS-CoV-2 infection, Phase 3 Part

whose primary objective is to verify the efficacy in participants with mild/moderate SARS-CoV-2 infection, and Phase 2b/3 Part whose primary objective is to verify the efficacy in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection. This study evaluates a monotherapy for participants with mild/moderate SARS-CoV-2 infection and participants with asymptomatic/mild symptoms only SARS-CoV-2 infection. Because there are many common items such as selection of participants, management of study, and timing of study implementation, it was planned as one clinical study rather than separate studies for each population. In addition, dose of Phase 3 Part and Phase 2b/3 Part will be selected based on the analysis results of Phase 2a Part and Phase 2b Part. This study will be initiated after confirming the safety and tolerability of 5-day administration of S-217622 once-daily: 750 mg of the loading dose (Day 1) and 250 mg of the maintenance dose (Day 2 or later), until 5 days after the last study drug administration, following lower dose part, in ongoing Phase 1 study of S-217622 in healthy adult participants (2102T1211).

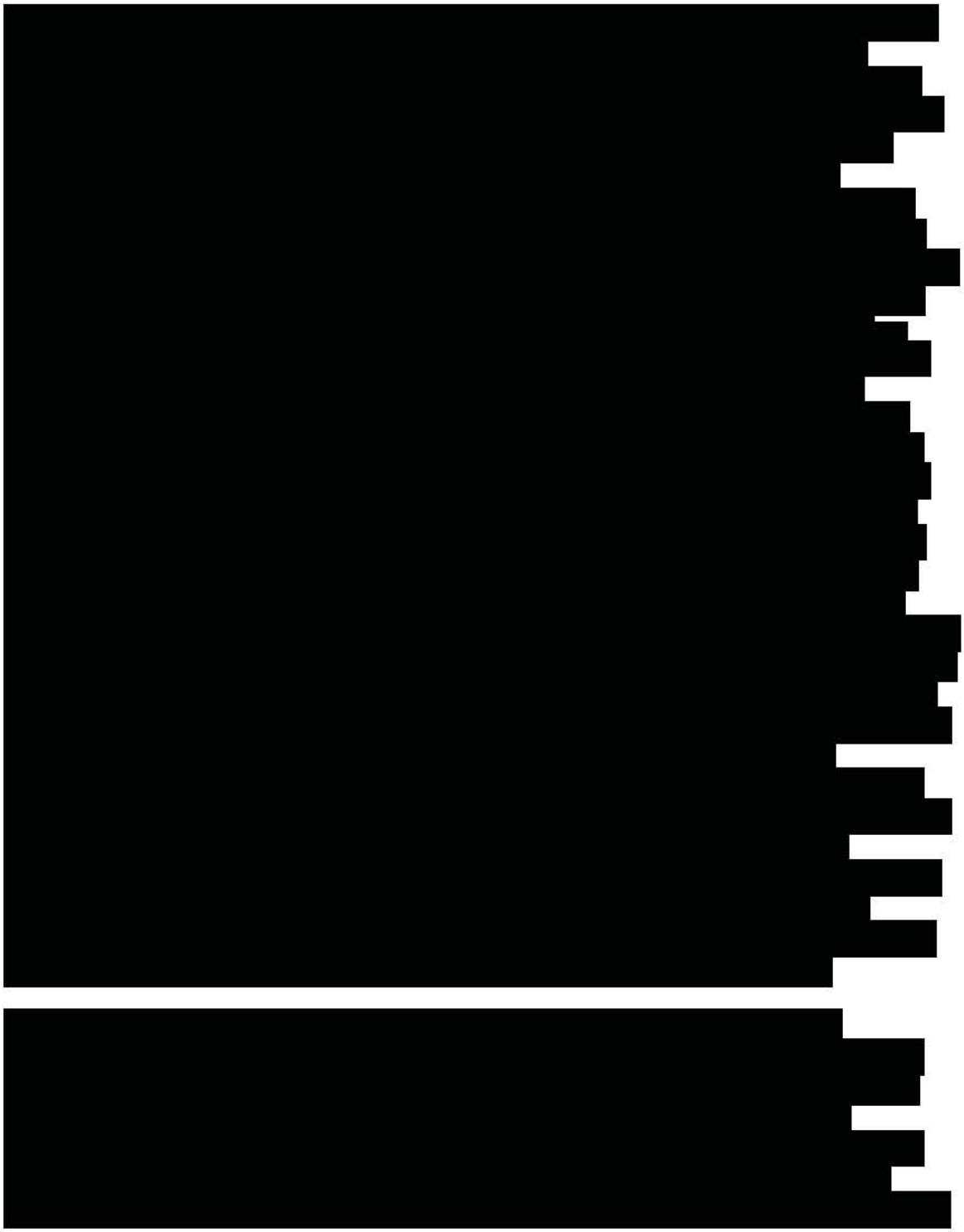
With reference to Phase 2a study of molnupiravir [7], the primary efficacy endpoints of Phase 2a Part were determined to be change from baseline in SARS-CoV-2 viral titer at each time point in participants with mild/moderate and asymptomatic SARS-CoV-2 infection to confirm the antiviral effect at an early stage. The primary efficacy endpoints of Phase 2b Part in participants with mild/moderate SARS-CoV-2 infection whose primary objective is to confirm the early improvement effect on clinical symptoms and the early antiviral effect against SARS-CoV-2 were determined to be time-weighted average change in total score of 12 COVID-19 symptoms by Day 6 and change from baseline on Day 4 in SARS-CoV-2 viral titer. With reference to the result of Phase 2b Part, the primary endpoints of Phase 3 Part in participants with mild/moderate SARS-CoV-2 infection and Phase 2b/3 Part in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection were determined to be time to resolution of 5 COVID-19 symptoms in participants with mild/moderate SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 symptom to randomization, and proportion of participants with development/worsening of COVID-19 symptoms in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection. In addition, the key secondary efficacy endpoints were determined to be change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA and time to the first negative SARS-CoV-2 viral titer in participants with mild/moderate and asymptomatic/mild symptoms only SARS-CoV-2 infection.

The stratification factors for randomization of this study are time from COVID-19 onset to randomization (< 72 hours/≥ 72 hours) and SARS-CoV-2 vaccination history for participants with mild/moderate SARS-CoV-2 infection, and SARS-CoV-2 vaccination history for participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, which may affect the clinical course and viral titer after intervention.

In addition, the exploratory period is set after the treatment period and the follow-up period in all of Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part. It will be performed only in participants who agree to participate in the exploratory period to confirm the long-term health effects of COVID-19, whose objective is to exploratorily

investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622.

4.3 Justification for Dose



In this study, participants aged 12 to < 18 years will be administered the same dosage as adults. It has been reported that expression levels of major drug-metabolizing enzymes and transporters do not differ significantly between pediatric (≥ 10 years of age) and adults, and also reported that renal function does not differ between pediatric (≥ 10 years of age) and adults [10]. It is considered that there is no significant difference in exposure between participants aged 12 to < 18 years and adults. Since chemotherapy inhibits the infectious and proliferative mechanisms of pathogenic microorganisms, the etiology of the disease and mechanism of action are similar in adults and pediatric [10]. S-217622 inhibits the virus growth mechanism, and the pharmacological action is considered to be similar in adults and pediatric. However, for participants under 18 years of age, the body weigh must be 40 kg or more to avoid the possible increase in exposure by carefully considering the safety.

4.4 End of Study Definition

A participant is considered to have completed the study as follow-up period completed case if he/she has completed the follow-up period including the scheduled procedure shown in the SoA (Section 1.3). A participant is considered to be exploratory period completed case if he/she participates in the exploratory period and has completed the exploratory period.

The end of the study is defined as the date of the last scheduled procedure (including the exploratory period) shown in the SoA for the last participant.

5. STUDY POPULATION

The study population will be in accordance with the inclusion and exclusion criteria described in this section. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

5.1.1 Participants with Mild/Moderate SARS-CoV-2 Infection (Phase 2a Part, Phase 2b Part, and Phase 3 Part)

Age

1. Participant must be 12 to < 70 years of age, at the time of signing the informed consent/assent.

Type of Participant and Disease Characteristics

2. Participants who were diagnosed as SARS-CoV-2 positive by any of the following tests within 120 hours before randomization.
   To note, within 120 hours from sample collection to randomization.
   - Nucleic acid detection test using nasopharyngeal swab, nasal swab, or saliva*[1]
     *[1]: Qualitative/quantitative reverse transcription polymerase chain reaction (RT-PCR) test or isothermal nucleic acid amplification method (eg, LAMP method or TMA method)
   - Antigen test (quantitative) using nasopharyngeal swab, nasal swab, or saliva
   - Antigen test (qualitative) using nasopharyngeal swab or nasal swab
3. Participants with time from COVID-19 onset*[2] to randomization of ≤ 120 hours.
   *[2]: Time point when at least one of 14 symptoms in COVID-19 occurs.
4. Participants who have at least one moderate (COVID-19 score: 2) or severe symptom among the following 12 COVID-19 symptoms at enrollment (excluding symptoms present prior to COVID-19 onset)
   Or participants who have at least one moderate (COVID-19 score: 2) or severe pre-existing symptom (symptoms present prior to COVID-19 onset) which was considered to have worsened at baseline:
   - General symptoms: Low energy or tiredness, muscle or body aches, headache, chills or shivering, and feeling hot or feverish
   - Respiratory symptoms: Stuffy or runny nose, sore throat, cough, and shortness of breath (difficulty breathing)
   - Gastrointestinal symptoms: Nausea, vomiting, and diarrhea

Sex

5. Male and female

a. Male participants:

Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 10 days after the last study drug administration:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception (see Section

10.4) as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
  - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

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 woman of childbearing potential (WOCBP)

OR

- All of the following apply:
  - Is a WOCBP and using a contraceptive method that is highly effective, with low user dependency and a failure rate of <1% per year, as described in Section 10.4 during the study intervention period and for at least 10 days after the last study drug administration. She must also agree not to donate her eggs (ova, oocytes) for the purpose of reproduction during the study.
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) 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 10.2.

The investigator/subinvestigator will review medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy and exclude the participant if she is of childbearing potential.

Informed consent

6. Participants capable of giving signed informed consent form (ICF)/assent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF/assent and in this protocol.

Body Weight

7. Body weight must be ≥ 40 kg (If participants are under 18 years of age at the time of assent).

5.1.2 Participants with Asymptomatic SARS-CoV-2 Infection (Phase 2a Part)
Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection (Phase 2b/3 Part)

Age

1. Participant must be 12 to < 70 years of age, at the time of signing the informed consent/assent.

Type of Participant and Disease Characteristics

2. Participants who were diagnosed as SARS-CoV-2 positive by any of the following tests within 120 hours before randomization.
   To note, within 120 hours from sample collection to randomization.
   - Nucleic acid detection test using nasopharyngeal swab, nasal swab, or saliva*
     *: Qualitative/quantitative RT-PCR test or isothermal nucleic acid amplification method (eg, LAMP method or TMA method)
   - Antigen test (quantitative) using nasopharyngeal swab, nasal swab, or saliva
   - Antigen test (qualitative) using nasopharyngeal swab or nasal swab
3. Phase 2a Part: Participants who have none of the following COVID-19 symptoms within 2 weeks before randomization

   To note, participants who have pre-existing symptoms that were present prior to SARS-CoV-2 infection and considered not to have worsened at baseline (pre-treatment examination) can be enrolled as participants with asymptomatic SARS-CoV-2 infection
   - General symptoms: Low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, taste disorder, and smell disorder
   - Respiratory symptoms: Stuffy or runny nose, sore throat, cough, and shortness of breath (difficulty breathing)
   - Gastrointestinal symptoms: Nausea, vomiting, and diarrhea

   Phase 2b/3 Part: Participants who do not have any symptoms of moderate (COVID-19 symptom score: 2) or severe out of the following 12 symptoms due to COVID-19 infection within 2 weeks before randomization (excluding symptoms present prior to COVID-19 onset).
   - General symptoms: Low energy or tiredness, muscle or body aches, headache, chills or shivering, and feeling hot or feverish
   - Respiratory symptoms: Stuffy or runny nose, sore throat, cough, and shortness of breath (difficulty breathing)
   - Gastrointestinal symptoms: Nausea, vomiting, and diarrhea

Sex

4. Male and female

a. Male participants:

Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 10 days after the last study drug administration:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception (see Section

10.4) as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
  - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

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 woman of childbearing potential (WOCBP)

OR

- All of the following apply:
  - Is a WOCBP and using a contraceptive method that is highly effective, with low user dependency and a failure rate of <1% per year, as described in Section 10.4 during the study intervention period and for at least 10 days after the last study drug administration. She must also agree not to donate her eggs (ova, oocytes) for the purpose of reproduction during the study.
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) 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 10.2.

The investigator/subinvestigator will review medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy and exclude the participant if she is of childbearing potential.

Informed consent

5. Participants capable of giving signed ICF/assent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF/assent and in this protocol.

Body Weight

6. Body weight must be ≥ 40 kg (If participants are under 18 years of age at the time of assent).

5.2 Exclusion Criteria

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

5.2.1 Participants with Mild/Moderate SARS-CoV-2 Infection (Phase 2a Part, Phase 2b Part, and Phase 3 Part)

Medical Conditions

1. Participants with SpO_2 during wakefulness of ≤ 93% (room air)

2. Participants who need oxygen administration
3. Participants who need a respirator
4. Participants who are strongly suspected to have worsening of symptoms SARS-CoV-2 infection within 48 hours after randomization, in the opinion of the investigator/subinvestigator
5. Participants with suspected active and systemic infections requiring treatment at the time of randomization (excluding SARS-CoV-2)
6. Current or chronic history of moderate or severe liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

   To note, moderate or higher is based on Grade 2 or higher of Common Terminology Criteria for Adverse Events [CTCAE] version 5.0 [11] (See Attachment 2).
7. Current or chronic history of moderate or severe kidney disease

   To note, moderate or higher is based on Grade 2 or higher of CTCAE version 5.0 [11] (See Attachment 2).

Prior/Concomitant Therapy

8. Participants who have used any of the following drugs within 7 days prior to randomization:
   - Approved drugs for the treatment of SARS-CoV-2 infection
   - Unapproved drugs for the treatment of SARS-CoV-2 infection (eg, interferon, convalescent plasma, monoclonal antibodies, immunoglobulins, antirheumatic drugs, corticosteroids [oral, injection, inhaled], ivermectin, favipiravir)

   Participants who have used any of the following drugs within 14 days prior to randomization:
   - Strong cytochrome P450 (CYP) 3A inhibitor
   - Strong CYP3A inducer
   - Products containing St. John's Wort

Prior/Concurrent Clinical Study Experience

9. Participants who have previously received S-217622
10. Participants who have donated ≥ 400 mL of blood within 12 weeks or ≥ 200 mL of blood within 4 weeks before signing the informed consent/assent
11. Exposure to 4 or more new chemical entities within 12 months prior to dosing
12. Current enrollment or past participation within the last 28 days before signing of consent/assent in any other clinical study involving an investigational study intervention or any other type of medical research

Other Exclusions

13. Participants who have difficulty entering the participant diary properly due to cognitive decline
14. Participants with drug abuse
15. Participants who are considered ineligible for the study by the investigator/subinvestigator due to sensitivity to any of the study interventions or

components thereof, drug allergy, or history of other allergy (except for seasonal allergies)

16. Participants who are considered ineligible for the study by the investigator/subinvestigator for any other reason

5.2.2 Participants with Asymptomatic SARS-CoV-2 Infection (Phase 2a Part) Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection (Phase 2b/3 Part)

Medical Conditions

1. Participants with (SpO_2) during wakefulness of ≤ 93% (room air)
2. Participants who need oxygen administration
3. Participants who need a respirator
4. Participants who are strongly suspected to have worsening of symptoms SARS-CoV-2 infection within 48 hours after randomization, in the opinion of the investigator/subinvestigator
5. Participants with suspected active and systemic infections requiring treatment at the time of randomization (excluding SARS-CoV-2)
6. Current or chronic history of moderate or severe liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

   To note, moderate or higher is based on Grade 2 or higher of CTCAE version 5.0 [11] (See Attachment 2).
7. Current or chronic history of moderate or severe kidney disease

   To note, moderate or higher is based on Grade 2 or higher of CTCAE version 5.0 [11] (See Attachment 2).

Prior/Concomitant Therapy

8. Participants who have used any of the following drugs within 7 days prior to randomization:
   - Approved drugs for the treatment of SARS-CoV-2 infection
   - Unapproved drugs for the treatment of SARS-CoV-2 infection (eg, interferon, convalescent plasma, monoclonal antibodies, immunoglobulins, antirheumatic drugs, corticosteroids [oral, injection, inhaled], ivermectin, favipiravir)

   Participants who have used any of the following drugs within 14 days prior to randomization:
   - Strong CYP3A inhibitor
   - Strong CYP3A inducer
   - Products containing St. John's Wort

Prior/Concurrent Clinical Study Experience

9. Participants who have previously received S-217622
10. Participants who have donated ≥ 400 mL of blood within 12 weeks or ≥ 200 mL of blood within 4 weeks before signing the informed consent/assent
11. Exposure to 4 or more new chemical entities within 12 months prior to dosing

12. Current enrollment or past participation within the last 28 days before signing of consent/assent in any other clinical study involving an investigational study intervention or any other type of medical research

Other Exclusions

13. Participants who have difficulty entering the participant diary properly due to cognitive decline
14. Participants with drug abuse
15. Participants who are considered ineligible for the study by the investigator/subinvestigator due to sensitivity to any of the study interventions or components thereof, drug allergy, or history of other allergy (except for seasonal allergies)
16. Participants who are considered ineligible for the study by the investigator/subinvestigator for any other reason

5.3 Lifestyle Considerations

1. Refrain from excessive eating or drinking from the time of informed consent/assent to the end of follow-up period (or completion of tests at discontinuation).
2. Use of tobacco and nicotine-containing products (including cigarette, electronic cigarette, pipe, cigar, chewing, nicotine patch, or nicotine gum) should be refrained during the study intervention period.
3. Refrain from consumption of grapefruit, Seville orange, or food and beverages containing them during the study intervention period.
4. Refrain from consumption of products containing St. John's Wort during the study intervention period.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are 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).

Screen failure participants may be rescreened. Rescreened participants should be assigned a participant number that is different from one for the initial screening.

6. STUDY INTERVENTION

Study intervention is defined as any test drug(s) or placebo intended to be administered to a study participant according to this study protocol.

6.1 Study Intervention(s) Administered

Table 6-1 Study Intervention

Study Intervention Name	S-217622 tablet 250 mg	S-217622 tablet 125 mg	S-217622 tablet Placebo-D	S-217622 tablet Placebo-B
Type	Drug	Drug	Drug	Drug
Dosage formulation	Tablet	Tablet	Tablet	Tablet
Unit dose strength(s)	Each tablet contains 250 mg of S-217622.	Each tablet contains 125 mg of S-217622.	Tablet that is indistinguishable in appearance from S-217622 250 mg tablet and contains no S-217622.	Tablet that is indistinguishable in appearance from S-217622 125 mg tablet and contains no S-217622.
Route of Administration	Oral	Oral	Oral	Oral
Use	Test drug	Test drug	Placebo	Placebo
Dosage level(s)	[S-217622 125 mg group] Oral administration once daily for 5 days on Days 1 to 5. Details of study intervention tablet to be taken at a time: Day 1 S-217622 tablet 125 mg × 3 tablets and S-217622 tablet Placebo-D × 3 tablets Days 2 to 5 S-217622 tablet 125 mg × 1 tablet and S-217622 tablet Placebo-D × 1 tablet [S-217622 250 mg group] Oral administration once daily for 5 days on Days 1 to 5. Details of study intervention tablet to be taken at a time: Day 1 S-217622 tablet 250 mg × 3 tablets and S-217622 tablet Placebo-B × 3 tablets Days 2 to 5 S-217622 tablet 250 mg × 1 tablet and S-217622 tablet Placebo-B × 1 tablet [Placebo group] Oral administration once daily for 5 days on Days 1 to 5. Details of study intervention tablet to be taken at a time: Day 1 S-217622 tablet Placebo-D × 3 tablets and S-217622 tablet Placebo-B × 3 tablet Days 2 to 5 S-217622 tablet Placebo-D × 1 tablet and S-217622 tablet Placebo-B × 1 tablet			
Sourcing	Provided centrally by the sponsor.			
Packaging and Labeling	Test drug and placebo will be supplied in the following containers: For Day 1, 1 tablet is packed in a PTP sheet, and 6 sheets are packed in an individual box. For Day 2 or later, 1 tablet is packed in a PTP sheet, and 2 sheets are packed in an individual box. The individual boxes will be labeled as required requirements in Japan.			
Dosing instructions	See Section 5.3.			

6.2 Preparation/Handling/Storage/Accountability of Study Intervention

1. The investigator/subinvestigator 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 may receive study intervention and only 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/subinvestigator and authorized site staff.
3. The investigator/subinvestigator, medical 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 handling and management of study intervention and final disposition of unused study intervention are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

As for Phase 2a Part, the participants determined to be eligible by screening tests will be randomly assigned to S-217622 125 mg group, S-217622 250 mg group, and placebo group at a ratio of 1:1:1 using the interactive response technology (IRT). As for Phase 2b Part and Phase 3 Part in participants with mild/moderate SARS-CoV-2 infection (cohort to evaluate time to improvement: cohort A), the participants determined to be eligible by screening tests will be randomly assigned to S-217622 125 mg group, S-217622 250 mg group, and placebo group at a ratio of 1:1:1 using the IRT. As for Phase 2b/3 Part in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B) as well, the participants determined to be eligible by screening tests will be randomly assigned to S-217622 125 mg group, S-217622 250 mg group, and placebo group at a ratio of 1:1:1 using the IRT (see Section 4.1). Randomization of participants with mild/moderate SARS-CoV-2 infection will be stratified by time from the onset of COVID-19 to randomization (< 72 hours/≥ 72 hours) and SARS-CoV-2 vaccination history. Randomization of participants with asymptomatic/mild symptoms only SARS-CoV-2 infection will be stratified by SARS-CoV-2 vaccination history. Vaccination history will be stratified by whether or not the first vaccination has been completed. The stratification factors for randomization, ie, time from COVID-19 onset to randomization (< 72 hours/≥ 72 hours) and SARS-CoV-2 vaccination history, will be based on the information entered in the IRT. To note, the common allocation table which is different from that in Phase 2a Part will be consecutively used in Phase 2b Part and Phase 3 Part for participants with mild/moderate SARS-CoV-2 infection (cohort to evaluate time to improvement: cohort A). For participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B) as well, the different allocation table will be used between Phase 2a Part and Phase 2b/3 Part.

Prior to study initiation, each site will be provided with information on how to log in and use the IRT.

6.3.2 Blinding

This study is a double-blind study using a placebo that is indistinguishable in appearance, labeling, and packaging. All relevant personnel, including the sponsor, participants, and investigator/subinvestigator, will remain blinded. In this study, the study intervention allocation table will be managed by the IRT. Some unblinded staffs will be assigned in the sponsor and the contract research organization (CRO) for statistical analyses.

After the interim evaluation of Phase 2a Part is performed (if performed) and after the follow-up periods of Phase 2a Part, Phase 3 Part and Phase 2b/3 Part are completed, all data in the electronic case report forms (eCRFs) for the applicable participant will be locked; and subsequently the study intervention allocation table will be obtained from the IRT. After Day 6 of all participants in Phase 2b Part has been completed, the interim database lock will be performed for applicable data in the eCRFs for the applicable participants; and subsequently the study intervention allocation table will be obtained from the IRT. In Phase 2a Part, analysis including viral titers and viral RNA level will be performed as needed. In this time, given that the measurement of viral titers and amount of viral RNA would reveal blindedness of the study, they will be measured by anonymizing the participants. If measurement and analysis of the drug concentration is performed in Phase 2a Part, information of the drug concentration will be treated under blind. In Phase 2b Part, unblinding will be performed at the time when all participants have been observed on Day 6 to evaluate the efficacy and safety of S-217622 up to Day 6 at an early stage.

In any Part in which enrollment and follow-up has completed first, unblinding will be permitted for the Part. If an interim analysis is performed, the study intervention allocation table will be submitted to the IDMC.

Unblinding by request of the investigator should occur only in the event of an emergency or adverse event (AE) for which it is necessary to know the study intervention to determine an appropriate course of therapy for the participant. If the investigator considers it necessary to reveal the allocation of a particular participant, the investigator may open the study intervention allocation table using the IRT in accordance with the specified procedure. Prior to unblinding, and if the situation allows it, the investigator should try to contact the sponsor in order to get additional information about the study intervention. If the sponsor cannot be contacted in advance, the sponsor should be informed of the unblinding as soon as possible. However, the allocation to study intervention will not be revealed at that time. The IRT will keep a record of the reason for unblinding, participant identification code, date and time of unblinding, and who unblinded. Detailed procedures for emergency unblinding will be provided in a separate protocol.

6.4 Study Intervention Compliance

The investigator/subinvestigator will assess compliance with study intervention at each visit and record it in the source document and the eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. Any deviation from the prescribed dosage regimen occur should be recorded in the eCRF with the start date and end date of intervention.

A record of the number of study intervention tablets dispensed to and taken by each participant must be maintained and reconciled with compliance records. If by any chance a participant forgot to take study intervention tablet, deviated from the specified dosage regimen, lost study intervention tablet, etc., the participant should promptly notify it to the investigator/subinvestigator or study collaborator.

6.5 Prior/Concomitant Therapy

Prior treatments (prior drugs/therapies) are defined as treatments (prescription drugs, over-the-counter drugs, and therapies other than drug therapy) performed within 7 days before randomization. Restrictions related to prior therapies are specified in exclusion criterion #8. Participants who meet the exclusion criteria cannot be enrolled in the study.

Concomitant treatments (concomitant drugs/therapies) are defined as treatments (prescription drugs, over-the-counter drugs, and therapies other than drug therapy) performed after the first administration of study intervention.

For medications (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) and/or vaccines that the participant is receiving at the time of enrollment or receives during the study, the following information must be recorded in eCRF. Medications that have been used continuously at a stable dosage regimen for at least 7 days prior to the first administration of study intervention should be continued at the same dosage regimen as much as possible until the end of the follow-up period. The sponsor should be contacted if there are any questions regarding prior or concomitant therapy.

- Reason for use
- Dates of administration including start and end dates
- Dosage information including route of administration

6.5.1 Prohibited Concomitant Therapy

Use of the following therapies is prohibited from the time of informed consent/assent to the completion of examinations on Day 28 or at the time of discontinuation. However, even if a prohibited concomitant therapy is used, the participant should continue the study procedures according to the specified SoA as much as possible.

- Approved drugs for the treatment of SARS-CoV-2 infection

- Unapproved drugs for the treatment of SARS-CoV-2 infection (eg, interferon, convalescent plasma, monoclonal antibodies, immunoglobulins, antirheumatic drugs, corticosteroids [oral, injection, inhaled], ivermectin, favipiravir)
- Antiviral, antibacterial, or antifungal drugs (excluding external use)
- Antipyretic analgesics other than acetaminophen
- Antitussives and expectorants
- Combination cold remedy
- Other study interventions

Use of the following therapies is prohibited from the time of informed consent/assent to the completion of examinations on Day 28. However, even if a prohibited concomitant therapy is used, the participant should continue the study procedures according to the specified SoA as much as possible.

- [redacted]

Use of the following therapies is prohibited from the time of informed consent/assent to 10 days after the last study drug administration or at the time of discontinuation. However, even if a prohibited concomitant therapy is used, the participant should continue the study procedures according to the specified SoA as much as possible.

- [redacted]

6.6 Dose Modification of Study Intervention

There will be no dose modifications in this study.

6.7 Intervention after the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

The investigator/subinvestigator 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 7.1.2), or meets any of the following conditions. Even if study intervention is discontinued, the participant should continue the study participation and continue the study procedures according to the specified SoA as much as possible.

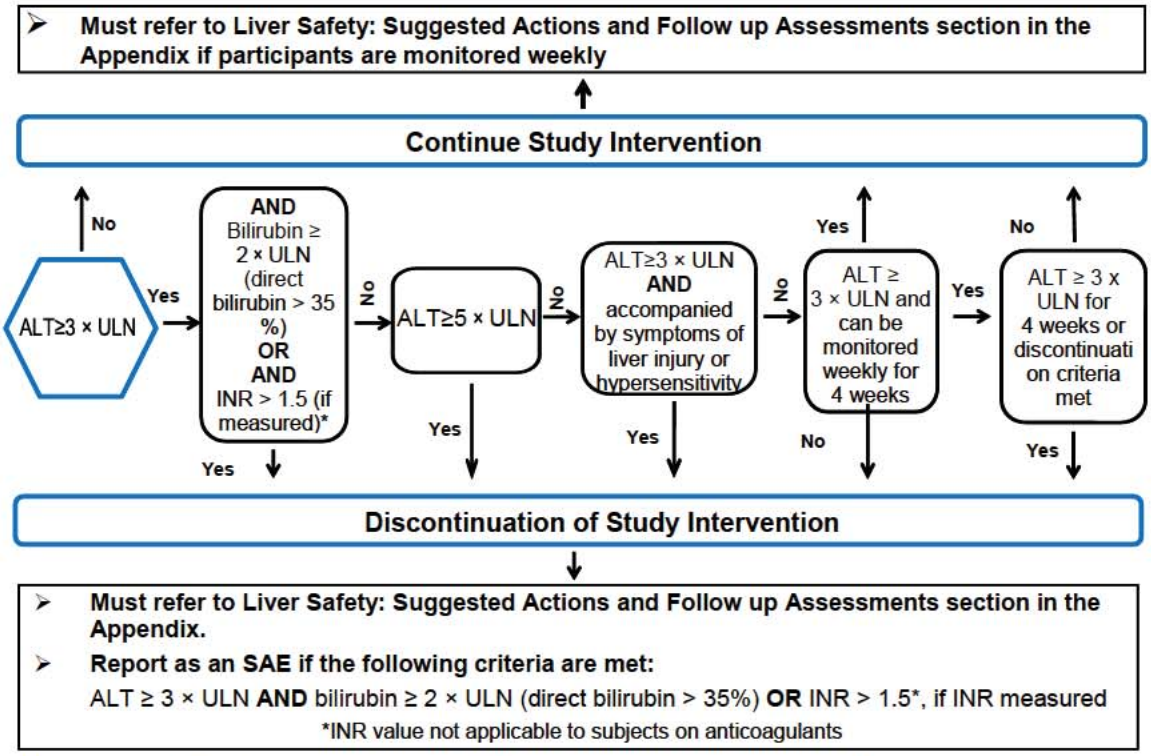
- If a participant experience worsening of the underlying disease (SARS-CoV-2 infection) and the investigator/subinvestigator determines that discontinuation of the study intervention is in the best interest of the participant.
- If a participant experiences a serious or intolerable AE and the investigator/subinvestigator determines that discontinuation of the study intervention is in the best interest of the participant.
- If a participant is found to be ineligible for the study.
- If a participant requests to discontinue the study intervention.
- If a participant is lost to follow-up.
- If the investigator/subinvestigator decides to discontinue the study intervention for any other reason.

7.1.1 Discontinuation of Study Intervention Based on Liver Chemistry

Discontinuation of study intervention for abnormal liver function should be considered by the investigator/subinvestigator when a participant meets one of the liver chemistry stopping criteria (see Figure 7-1) or if the investigator/subinvestigator believes that it is in best interest of the participant.

Liver Safety: Suggested Actions and Follow-up Assessments are shown in Section 10.5.

Figure 7-1 Liver Chemistry Stopping Criteria and Monitoring Enhancing Algorithm



Abbreviations: ALT = alanine aminotransferase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

7.1.2 Discontinuation of Study Intervention Due to Pregnancy

Refer to Section 8.3.5 and Section 10.4 for discontinuation of study intervention due to pregnancy and collection of pregnancy information.

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 withdrawn at any time at the discretion of the investigator/subinvestigator for safety, behavioral, compliance, or administrative reasons. However, unless there is a safety reason, the participant should only be withdrawn from study intervention, while continuing the study participation and continuing the study procedures according to the specified SoA as much as possible, in order to protect the integrity of the study and the participant's well-being.

If the participant withdraws consent/assent, 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/subinvestigator must document this in the site study records.

At the time of discontinuing from the study, if possible, the procedures to be conducted at discontinuation should be conducted, as shown in the SoA (Section 1.3). The participant will be permanently discontinued both from the study intervention and from the study participation at that time.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator/subinvestigator 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 withdrawn from the study.
- Discontinuation of specific sites or of the study as a whole are handled as part of 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.

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, 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.

Procedures conducted before signing of the ICF/assent may be utilized for baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Investigation of participant's background

The investigator/subinvestigator will investigate the following information in accordance with the SoA (Section 1.3). The investigator or his/her designee will record the results of the investigation in the eCRF.

- Baseline participant characteristic

  Date of ICF by participants or their legally acceptable representative, date of birth, age at the time of ICF (automatically calculated by the electronic data capture [EDC] system), sex, ethnicity, race

- Past and current medical conditions

  Medical history includes all ongoing complications at screening, diseases requiring hospitalization within 1 year prior to screening, and diseases requiring visits within 12 weeks prior to screening.

- Physical examination

  Date of measurement, height, body weight, body mass index (BMI) (automatically calculated by the EDC system)

- Lifestyle factors

  Alcohol consumption (yes/no), smoking cigarettes (yes/no), and details if yes

- SARS-CoV-2 Infection

  Date of pathogen test, name of test method, severity
  Time from the onset of COVID-19*[1] (participants with mild/moderate and mild symptoms only SARS-CoV-2 infection)
  *[1]: Time point when at least one of 14 symptoms in COVID-19 occurs.

  Days from the day of close contact*[2] with a person with SARS-CoV-2 infection (participants with asymptomatic SARS-CoV-2 infection
  *[2]: The definition of close contact is based on the Guideline for conducting an active epidemiological survey on patients with COVID-19 presented by National institute of infectious diseases [12].
    1. Those who live with or have been in contact with positive patients for a long time.
    2. Those who have been examining, nursing, or caring for positive patients without proper infection protection
    3. Those who are likely to touch directly with pollutants such as airway secretions or body fluids of positive patients
    4. Others: Those who have been in contact with a positive patient for 15 minutes or more at a hand-touchable distance without necessary infection prevention measures.

– SARS-CoV-2 vaccine

  Vaccination history (vaccinated/not vaccinated) and the name of the vaccine administered and all dates of vaccination if vaccinated

8.1 Efficacy Assessments

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

8.1.1 Virologic Examination

The investigator or his/her designee will take nasopharyngeal swab from participants according to the SoA (Section 1.3). The date of 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 specified in Section 10.1.5, SARS-CoV-2 virus titer and viral amount of viral RNA will be measured, and RT-PCR results (positive or negative) will be determined. For the purpose of bridging the virus titer measurement results between facilities, some samples of the nasopharyngeal swab collected in Phase 2a Part will be sent to [redacted] to measure the virus titer.

8.1.2 Participant Diary

Participants will assess their COVID-19 symptom scores (Section 8.1.2.1), SpO_2, temperature, and EuroQol 5 dimensions 5-level (EQ-5D-5L) according to the SoA (Section 1.3) and the results will be entered into the electronic patient-reported outcome (ePRO) system by the participant. Electronic data entered by each participant into the system will be used for the participant diary.

Before administration of study intervention on Day 1, the investigator/subinvestigator or study collaborator will explain the assessment and entry methods to the participants. Entry time is shown in Table 8-1.

When acetaminophen is taken for the purpose of antipyretic/analgesic, COVID-19 symptom score is not evaluated, and body temperature is not measured until 4 hours after taking it.

Table 8-1 Entry Time

Date of assessment	Evaluation point	Entry time
Day 1	Pre-dose	00:00 ~ 23:59
	Post-dose	12:00 ~ 23:59
Days 2 to 9	Morning	04:00 ~ 23:59
	Evening	12:00 ~ 23:59
Days 10 to 21	-	00:00 ~ 23:59

8.1.2.1 COVID-19 Symptom Score

Of the 14 symptoms in COVID-19 [13] shown below, participants will assess taste disorder and smell disorder themselves using a 3-point scale of 0 to 2 (0, The same as usual; 1, Less than usual; 2, No sense of smell/taste) and the other 12 symptoms using a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe) (see Section 10.6).

- General symptoms: Low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, taste disorder, smell disorder
- Respiratory symptoms: Stuffy or runny nose, sore throat, cough, and shortness of breath (difficulty breathing)
- Gastrointestinal symptoms: Nausea, vomiting, and diarrhea

Participants will assess COVID-19 symptoms twice daily (morning and evening) from before the first dose of study intervention on Day 1 to Day 9 and once daily (evening) from Day 10 to Day 21 at the same time whenever possible according to the SoA (Section 1.3) and enter the results of assessment in the participant diary.

8.1.2.2 SpO_2

Participants will measure SpO_2 using a pulse oximeter twice daily (morning and evening) from before the first dose of study intervention on Day 1 to Day 9 and once daily (evening) from Day 10 to Day 21 at the same time whenever possible according to the SoA (Section 1.3) and enter the measurement results in the participant diary.

Before administration of study intervention on Day 1, the investigator/subinvestigator or study collaborator will explain how to use the pulse oximeter and hand it to the participant. Handing of a pulse oximeter will be specified in a separate written procedure.

8.1.2.3 Body Temperature

Participants will measure axillary temperature twice daily (morning and evening) from before the first dose of study intervention on Day 1 to Day 9 and once daily (evening) from Day 10 to Day 21 at the same time whenever possible according to the SoA (Section 1.3) and enter the measurement results in the participant diary.

Before administration of study intervention on Day 1, the investigator/subinvestigator, or study collaborator will explain how to use thermometer and hand it to the participant. Handing of a thermometer will be specified in a separate written procedure.

8.1.2.4 EQ-5D-5L

Participants will assess EQ-5D-5L twice daily (morning and evening) from before the first dose of study intervention on Day 1 to Day 9 and once daily (evening) from Day 10 to Day 21 at the same time whenever possible according to the SoA (Section 1.3) and enter the assessment results in the participant diary.

8.1.3 8-Point Ordinal Scale

The investigator/subinvestigator will assess the participant's condition on a 8-point scale of 0 to 7 based on the 8-Point Ordinal Scale (see Section 10.7) according to the SoA (see Section 1.3). The investigator or his/her designee will record the assessment scores in the eCRF. If the score changes (except for the changes between Score 0 and Score 2), the date when the event occurred and the score should be recorded on eCRF.

The assessment of 8-Point Ordinal Scale will be made solely on the basis of the participant's medical condition and avoid the influence of the surrounding medical environment.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3). For participants who are recuperating at home or accommodation facilities, measurements, blood sampling, etc. will be performed by visiting nurses designated by the investigator, and medical examinations can also be performed through home-visit medical care or telemedicine. Details will be specified in a separate written procedure.

For any abnormalities in laboratory tests (hematology, blood chemistry, coagulation test, serology, urinalysis, other tests) or other safety assessments (physical examination, vital signs, ECG) that fluctuate from baseline, the investigator/subinvestigator will determine whether those abnormalities are clinically significant. Abnormal laboratory test results are defined as values outside the reference range. The investigator/subinvestigator will determine whether an abnormal value at baseline that worsens after the initiation of the study is clinically significant. Any test results which are considered to be clinically significant by the investigator/subinvestigator will be recorded as AEs. If abnormal laboratory finding is associated with disease or other conditions, the investigator should report only the disease or other conditions as an AE.

The investigator/subinvestigator will consider that those events that meet the following criteria are clinically significant. In other situations, the investigator/subinvestigator will determine whether the events are clinically significant at their own discretion.

- 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 of the study intervention
- 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 (Section 7.1 and Section 10.5)

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

8.2.1 Medical Examination

The investigator/subinvestigator will perform physical examination according to the SoA (Section 1.3). The investigator or his/her designee will record any clinically significant change as an AE on the eCRF.

8.2.2 Vital Signs

The investigator or his/her designee will measure blood pressure (systolic/diastolic), pulse rate, and respiratory rate according to the SoA (Section 1.3). If vital signs are scheduled at the same time as blood sampling, the blood sampling should occur at the scheduled time, and vital signs should be obtained as close to the scheduled time as possible prior to the blood sampling. Blood pressure and pulse rate will be measured twice using a sphygmomanometer after at least 3 minutes of rest. Respiratory rate will be measured visually by counting the number of vertical movements of the anterior chest or upper abdomen for 30 seconds. The mean value of blood pressure and pulse rate will be calculated from two measurements. The value twice the respiratory rate (breaths/min) for 30 seconds will be recorded.

The dates and results of vital signs taken after screening will be recorded in the eCRF. The investigator/subinvestigator will determine whether any abnormal changes from baseline (before administration of the study intervention) are clinically significant and record the clinically significant changes as AEs in the eCRF.

8.2.3 ECG

To be performed only in Phase 2a Part.

Two-lead or more ECG will be performed before the first study intervention, and 1 to 8 hours after the study intervention on Day 1, at medical examination on Days 2, 4, and 6 according to the SoA (Section 1.3) (It is possible to be performed by the participant himself/herself with portable ECG). Not to be performed immediately after blood sampling. If the result is judged abnormal by ECG in the measurement on Day 1 (1 to 8 hours after the study intervention), the participant has to inform the investigator/subinvestigator or the designee.

The investigator/subinvestigator will determine whether the ECG is normal or abnormal, and whether the ECG finding is clinically significant or not if it is determined to be abnormal. If it is determined to be clinically significant, the investigator/subinvestigator will determine whether it is related to medical history. The investigator or designee will record the date and interpretation (normal, abnormal but not clinically significant, or

abnormal and clinically significant) of the ECG, and related medical history if applicable, in the eCRF. Any abnormal ECG finding assessed as a clinically significant change will be recorded as an AE in the eCRF.

If a participant uses a portable ECG, before administration of study intervention on Day 1, the investigator/subinvestigator or study collaborator will explain how to use portable ECG and hand it to the participant. Handing of a portable ECG will be specified in a separate written procedure.

8.2.4 Laboratory Assessments

The investigator or his/her designee will perform all protocol-required laboratory assessments as defined in Section 10.2 in accordance with the Laboratory Manual and the SoA (Section 1.3).

The investigator/subinvestigator must review the laboratory test results, document this review, and record any clinically relevant changes occurring during the study as AEs in the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator/subinvestigator to be more severe than expected for the participant's condition (see Section 10.3). The laboratory reports must be filed with the source documents.

Clinically significant abnormal laboratory tests considered related to study intervention that are still persisting 14 days after the last study drug administration should be repeated until the values return to normal or baseline (prior to study intervention) or are considered not significant by the investigator/subinvestigator or sponsor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator/subinvestigator, the etiology should be investigated and the sponsor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory resulted treatment of the participant or are considered clinically significant by the investigator/subinvestigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3 Adverse Events and Serious Adverse Events

AEs reported by the participant must be captured in source documents.

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from the date of signing of the ICF/assent through the end of follow-up period at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or its designee immediately and under no circumstance should this exceed 24 hours of knowledge of occurrence, as indicated in Section 10.3. The investigator/subinvestigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigator/subinvestigator is not obligated to actively seek AEs or SAEs after conclusion of the follow-up period. However, if the investigator/subinvestigator learns of any SAE, including a death, at any time after a participant has completed follow-up period, and he/she considers the event to be reasonably related to the study intervention or study participation, he/she must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading 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/subinvestigator 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 Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator/subinvestigator to the 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 regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs), and investigator/subinvestigator.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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, if appropriate, according to requirements.

8.3.5 Pregnancy

All pregnancy information on female participants and female partners of male participants will be collected through the end of the follow-up period. Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

If a pregnancy is reported, the investigator/subinvestigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

No adverse events of special interest have been identified as of August 2022.

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 sponsor by the investigator using a Special Situations Report Form (paper form) established by the sponsor within 24 hours of knowledge of occurrence. If there are associated SAEs, the investigator must also complete and submit an SAE report as well.

- 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.
- Medication Error - Any unintended error in the prescribing, dispensing or administration of a study intervention(s) (including intercepted error).

8.4 Treatment of Overdose

For this study, any dose of study intervention greater than daily dose of study intervention within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific treatment for an overdose; however, the sponsor should take actions to assure the safety of participant.

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

1. Notify the sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities through the end of the follow-up period.
3. Obtain a plasma sample for pharmacokinetic analysis promptly if requested by the sponsor (determined on a case-by-case basis).
4. Record the overdose and the duration of the overdose on the Special Situations Report Form.

Decisions regarding dose interruptions or modifications will be made by the investigator/subinvestigator in consultation with the sponsor based on the clinical evaluation of the participant.

8.5 Pharmacokinetics

Drug concentrations will be determined using plasma samples according to the SoA (Section 1.3). The time of daily dosing, food condition (if taken within 2 hours of a meal), and date and time of each PK sample collection will be recorded in the eCRF. The time should be recorded in 24-hour clock.

The collected plasma samples will be shipped on dry ice to the bioanalytical laboratory shown in Section 10.1.5. For details of sampling, handling, and shipping methods, etc., refer to the separately specified written procedures.

Details of the pharmacokinetic analysis are provided in Section 9.4.3.

Samples for plasma drug concentration measurement may also be used for safety evaluation if further investigation becomes necessary during or after the follow-up period. In that case, an analysis plan and a report will be prepared separately from the clinical study report.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

8.8.1 Aggravation Markers

[redacted]

8.9 Immunogenicity Assessments

Immunogenicity will not be assessed in this study.

8.10 Health Economics

EQ-5D-5L will be evaluated as a Health Economics/Medical Resource Utilization and Health Economics parameter in this study.

EQ-5D-5L is a standardized questionnaire developed by the EuroQol Group to enable a simple evaluation of general health status for clinical and economic appraisal. EQ-5D-5L questionnaire consists of 2 pages: EQ-5D-5L descriptive questionnaire and EQ Visual Analog Scale (VAS). 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 visual analogue scale, where the best state is 100 and the worst state is 0. The EQ-5D-5L questionnaire is provided in Section 10.8.

8.11 Other Assessments

8.11.1 SARS-CoV-2 Lineage

Analysis of SARS-CoV-2 lineage will be performed for participants with SARS-CoV-2 infection in Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part.

Spike gene sequence analysis will be performed using nasopharyngeal swab collected on Day 1 at the measurement laboratory shown in Section 10.1.5 in accordance with the separately specified written procedure or protocol. A report will be prepared separately from the clinical study report. The similar analysis may be performed in Phase 2a Part.

8.11.2 Polymorphisms of 3CL Protease (nsp 5)

A polymorphism analysis of 3CL protease (nsp5) will be performed for participants with SARS-CoV-2 infection in Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part.

The nasopharyngeal swab collected on Day 1 will be used for a gene sequence analysis of 3CL protease (nsp5) in accordance with the separately specified written procedure or protocol at the measurement laboratory shown in Section 10.1.5. A report will be prepared separately from the clinical study report.

8.11.3 Amino Acid Substitution in 3CL Protease (nsp5) and its Cleavage Site

A gene sequence analysis of the 3CL protease (nsp5) (Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part) and its cleavage site (all Parts) will be performed to evaluate the drug-induced amino acid substitutions in participants with evaluable viruses, as needed. A gene sequence analysis of the 3CL protease (nsp5) is possibly performed also in Phase 2a Part.

The nasopharyngeal swab collected on Day 1 and at visits after administration of the study intervention with a minimum amount of viral RNA sufficient for genome analysis will be used for the evaluation of amino acid substitution in accordance with the separately specified written procedure or protocol at the measurement laboratory shown in Section 10.1.5. Access to data on the evaluation of amino acid substitution will be restricted. A report will be prepared separately from the clinical study report.

8.11.4 Drug Antiviral Activity

The antiviral activity of S-217622 against evaluable viruses collected at baseline will be evaluated in Phase 2b Part and Phase 3 Part. It will be evaluated in Phase 2b/3 Part, as needed.

The drug antiviral activity test will be performed using nasopharyngeal swab collected on Day 1 at the measurement laboratory shown in Section 10.1.5 in accordance with the

separately specified written procedure or protocol. A report will be prepared separately from the clinical study report.

8.11.5 Immunity

Participants' SARS-CoV-2 neutralizing antibody titers will be measured to evaluate the effect of the study intervention on acquisition of innate immunity from SARS-CoV-2 infection.

The investigator or his/her designee will collect blood for the measurement of SARS-CoV-2 neutralizing antibody titers according to the SoA (Section 1.3). The date of sample collection will be recorded in the eCRF. Procedures for collection, storage, and shipping of samples will be specified in a separate written procedure.

At the measurement laboratory shown in Section 10.1.5, SARS-CoV-2 neutralizing antibody titers will be measured in accordance with the separately specified written procedures or protocol. A report will be prepared separately from the clinical study report.

8.11.6 Post-acute COVID-19 Syndrome

Participants, who agree/assent to participate in the exploratory period, evaluate his/her post-acute COVID-19 syndrome [6] according to the SoA (Section 1.3), then, participants will enter the results on the patient diary. Detail of contents is shown in Attachment 3.

Post-acute COVID-19 syndrome will be evaluated during the exploratory period. After the manufacturing and marketing approval of S-217622, the study is possible to change to post-marketing clinical trials. In this case, a report will be prepared separately from the clinical study report.

8.11.7 Allergy Antigen Test (Cedar/cypress Allergy)

In Phase 3 Part, allergy antigen test (cedar/cypress allergy) will be performed using samples for the measurement of SARS-CoV-2 neutralizing antibody titers collected on Day 1 at the measurement laboratory shown in Section 10.1.5 in accordance with the separately specified written procedure or protocol. The test may be performed in other Parts, as needed.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Statistical hypothesis will be established for each of Phase 2b Part and Phase 3 Part with participants with mild/moderate SARS-CoV-2 infection and Phase 2b/3 Part with participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in this study. Since Phase 2a Part is exploratory, no statistical hypothesis will be established.

9.1.1 Statistical Hypothesis for Participants with Mild/Moderate SARS-CoV-2 Infection in Phase 2b Part

In Phase 2b Part, the 2 primary endpoints (time-weighted average change in the total score of the 12 COVID-19 symptoms from the initiation of administration [Day 1] up to 120 hours [Day 6], and change from baseline on Day 4 in SARS-CoV-2 viral titer) in the participants with mild/moderate SARS-CoV-2 infection will be treated as co-primary endpoints. Therefore, if comparisons of the S-217622 treatment group and the placebo group are statistically significant at a one-sided significance level of 0.025 in both primary endpoints, it is considered that the efficacy of the corresponding S-217622 treatment group has been confirmed. As a multiplicity adjustment method, a fixed sequence procedure will be applied to pairwise comparisons with the placebo group for the 2 primary endpoints. If only comparisons between the placebo group and the S-217622 125 mg group are statistically different at one-sided significance level of 0.025 in both primary endpoints, comparisons in the 2 primary endpoints between the placebo group and the S-217622 250 mg group will be performed at one-sided significance level of 0.025. Because the 2 primary endpoints are co-primary endpoints, the multiplicity adjustment for the comparisons in the 2 primary endpoints between the S-217622 treatment group and the placebo group will not be performed. For the secondary endpoints in Phase 2b Part, while pairwise comparisons between the S-217622 treatment group and the placebo group will be performed, multiplicity adjustment will not be performed.

9.1.2 Statistical Hypothesis for Participants with Mild/Moderate Symptoms SARS-CoV-2 Infection in Phase 3 Part

In the population with mild/moderate SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization and the population with SARS-CoV-2 infection in Phase 3 Part, for the primary endpoint (time to resolution of the 5 COVID-19 symptoms), and the two key secondary endpoints, that is, the key secondary endpoint 1 (change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA) and the key secondary endpoint 2 (time to the first negative SARS-CoV-2 viral titer), comparison of the S-217622 125 mg group and the placebo group will be performed at a one-sided significance level of 0.025 based on a statistical hypothesis test taking multiplicity adjustment into account. As a multiplicity adjustment method in Phase 3 Part, tests will be performed in the order of the primary endpoint, the key secondary endpoint 1 and the key secondary endpoint 2 in using a fixed sequence procedure in the population with SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization,

and subsequently in the same order in the population with SARS-CoV-2 infection. Details of the multiplicity adjustment procedure are provided in Section 9.4.1. Other secondary endpoints in Phase 3 Part will be compared between the S-217622 125 mg group and the placebo group without multiplicity adjustment. In addition, all efficacy endpoints including the primary endpoint and key secondary endpoints will also be compared between the S-217622 250 mg group and the placebo group without multiplicity adjustment.

9.1.3 Statistical Hypothesis for Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection in Phase 2b/3 Part

For the primary endpoint (proportion of participants with development/worsening of COVID-19 symptoms) and the two key secondary endpoints, that is, the key secondary endpoint 1 (change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA) and the key secondary endpoint 2 (time to the first negative SARS-CoV-2 viral titer), comparison of the S-217622 125 mg group and the placebo group will be performed for participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in Phase 2b/3 Part at a one-sided significance level of 0.025 based on a statistical hypothesis test taking multiplicity adjustment. As a multiplicity adjustment method in Phase 2b/3 Part, tests will be performed in the order of the primary endpoint, the key secondary endpoint 1 and the key secondary endpoint 2 using a fixed sequence procedure. Details of the multiplicity adjustment procedure are provided in Section 9.4.1. Other secondary endpoints in Phase 2b/3 Part will be compared between the S-217622 125 mg group and the placebo group without multiplicity adjustment. In addition, all efficacy endpoints including the primary endpoint and key secondary endpoints will also be compared between the S-217622 250 mg group and the placebo group without multiplicity adjustment.

In addition, for the participant population with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: cohort B) in the Phase 2b/3 Part, an interim analysis of the primary endpoint and the two key secondary endpoints will be performed for the purpose of stopping for efficacy when the follow-up has been completed in 50% of the target sample size.

It will be judged whether the interim analysis is to be performed or not depending on the enrollment rate, and if the enrollment of the target sample size is expected to be almost completed at the time of obtaining the interim analysis result, the interim analysis will not be performed. If the interim analysis is to be performed, the number of analyses shall be 2 in total including the final analysis (1 interim analysis), and the criteria for stopping for efficacy based on the α-spending function will be the O'Brien–Fleming boundary for the primary analysis of the primary endpoint and the Pocock boundary for the primary analyses of the two key secondary endpoints. Based on the significance level allocated to comparison between the S-217622 125 mg group and the placebo group and the information fraction of each endpoint at the time of interim analysis, the nominal significance level which corresponds to the rejection region of each comparison performed in the interim analysis and final analysis will be calculated in order to control the type 1 error rate.

9.2 Sample Size Determination

9.2.1 Determination of Sample Size in Phase 2a Part

The required number of participants in Phase 2a Part was set at 11 per group where participants with mild/moderate or asymptomatic SARS-CoV-2 infection who are positive SARS-CoV-2 viral titer at baseline. Since the viral titer was detected in 44% (74/170) of participants whose viral titer could be measured at baseline in Phase 2a study of molnupiravir [7], assuming that the proportion of participants who were positive RT-PCR result and had the viral titer detected at baseline is approximately 50% of enrolled participants of the study, the number of participants to be enrolled in Phase 2a Part was calculated to be 69 (23 participants/group) of all participants with mild/moderate or asymptomatic SARS-CoV-2 infection.

The required sample size of 11 participants per group is equivalent to the sample size that provides 82.3% power under the condition that the difference between each S-217622 treatment group and the placebo group is 2.5 log, the standard deviation common to each group is 2.2 log, and the significance level is two-sided 10% when the change from baseline in SARS-CoV-2 viral titer is compared between the 2 groups.

9.2.2 Determination of Sample Size for Participants with Mild/Moderate SARS-CoV-2 Infection in Phase 2b Part

One of the primary analyses for primary endpoints in Phase 2b Part is an intergroup comparison of time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6). Referring the result of interim evaluation in Phase 2a Part, the intergroup difference of this change was assumed to be −1, and the standard deviation was assumed to be 2.6. With one-sided significant level of 0.025 under this assumption, the required number of participants to detect this intergroup difference with 80% power in a 2-sample t-test was calculated to be 108 per group. Assuming that dropout rate due to detection failure of virus titer is 25% referring the detection rate of SARS-CoV-2 virus titer on Visit 1 (pre-intervention) in Phase 2a Part, the number of participants to be enrolled was calculated to be 435 (145 participants/group). It is noted that the power to detect the difference in the other primary endpoint, the change from baseline on Day 4 in SARS-CoV-2 viral titer, by the 2-sample t-test was calculated to be 99.9%, assuming that the intergroup difference is −0.5 $\log_{10}$ $TCID_{50}$/mL, the standard deviation is 0.7, and the number of participants per group is 108.
The number of participants to be enrolled may be changed based on the proportion of participants with the detection of SARS-CoV-2 viral titer at Visit 1 (pre-intervention) calculated during the study period.

9.2.3 Determination of Sample Size for Participants with Mild/Moderate SARS-CoV-2 Infection in Phase 3 Part

In the protocol (version 9), as for the participants with mild/moderate SARS-CoV-2 infection in Phase 3 Part, the primary analysis for the primary endpoint was a comparison

of time to resolution of 12 COVID-19 symptoms between groups, and the sample size was calculated as described below.

In Phase 2b Part, the median of time to resolution of COVID-19 symptoms was 10.1 days in the placebo group, 7.1 days in the S-217622 125 mg group, and 6.4 days in the S-217622 250 mg group. Although almost all of the participants in Phase 2b Part were enrolled in Japan, considering that the enrollment will be expanded to other Asian regions in Phase 3 Part, the median in each S-217622 treatment group was conservatively assumed to be 8 days while the median in the placebo group was assumed to be 10 days. Accordingly, as for the time to resolution of COVID-19 symptoms, the difference which would be detected in each S-217622 treatment group was assumed to be 0.8 (= 8/10 days) as the hazard ratio to placebo group.

Since multiplicity adjustment by the Bonferroni's method is planned, the sample size required to detect these differences with 80% power using log-rank test at a one-sided significance level of 0.0125 was calculated to be a total of 1428 participants (476 per group) for the 3 groups of participants with mild/moderate SARS-CoV-2 infection. Assuming that the dropout rate due to a negative RT-PCR result in the test immediately before enrollment would be 10%, the sample size of participants to be enrolled was calculated to be 1590 participants (530 per group).

In this study, the dose of Phase 3 Part may be selected based on the analysis of Phase 2a Part and Phase 2b Part. To determine the sample size in the case where the dose of Phase 3 Part is selected, the sample size required to detect the same difference as above with 80% power was calculated using a log-rank test at a one-sided significance level of 0.025. As a result, the sample size of participants with mild/moderate SARS-CoV-2 infection required was calculated to be 393 participants per group. With the assumed dropout rate mentioned above, the sample size of participants to be enrolled was calculated to be 880 participants (440 participants each for the selected dose group and placebo group).

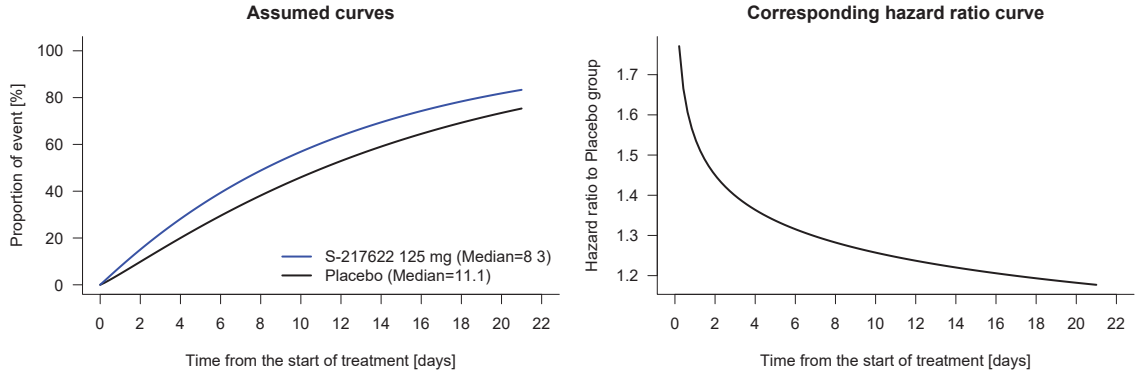
The number of participants to be enrolled may be changed based on the proportion of participants with a positive RT-PCR result at Visit 1 (pre-intervention) calculated during the study period.

In this protocol (version 10), along with the changes of primary analysis population, primary endpoint, and dose to verify efficacy, the method for primary analysis was also changed from the stratified log-rank test to the Peto-Prentice's stratified generalized Wilcoxon test. The required sample size for participants with mild/moderate SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization was reconsidered as described below.

As for participants with mild/moderate SARS-CoV-2 infection in Phase 3 Part, the population with SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization will be the primary analysis population. For this population, the required sample size was calculated to compare the time to resolution of the 5 COVID-19 symptoms between the S-217622 125 mg group and the placebo group.

The comparison between the S-217622 125 mg group and the placebo group in the time to resolution of the 5 COVID-19 symptoms will be conducted at first. In the population with < 72 hours from the onset of COVID-19 to randomization in Phase 2b Part, by referring the Kaplan-Meier curve of time to resolution of the 5 COVID-19 symptoms and considering a possibility that a conservative effect may be observed in the active drug group, a Weibull distribution in Figure 9-1 was assumed. In this distribution, the assumed medians are 8.3 days for the S-217622 125 mg group and 11.1 days for the placebo group.

Figure 9-1 Weibull Distributions and Corresponding Hazard Ratio Curve, Assumed for Calculation of Required Sample Size for Phase 3 Part with Regard to Time to Resolution of 5 COVID-19 Symptoms



The required sample size to detect this difference with 80% power using the Peto-Prentice generalized Wilcoxon test at a one-sided significance level of 0.025 was calculated to be 230 per group as the sample size required for the population with < 72 hours from the onset of COVID-19 to randomization. Based on this, assuming that the drop-out rate due to a negative RT-PCR result in the test immediately before enrollment would be approximately 10%, the required number of enrolled participants with < 72 hours from the onset of COVID-19 to randomization was calculated to be a total of 780 participants (260 per group) for the 3 groups.

9.2.4 Determination of Sample Size for Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection in Phase 2b/3 Part

The protocol (version 9) described that 600 participants who have been confirmed to be eligible as participants with asymptomatic/mild symptoms only SARS-CoV-2 infection would be randomly assigned to S-217622 125 mg group (200 participants), S-217622 250 mg group (200 participants), and placebo group (200 participants), and that in case it is judged that no interim analysis is to be performed for the purpose of stopping for

efficacy, 570 participants who have been confirmed to be eligible would be randomly assigned to each of these intervention groups (190 participants per group).

In this protocol (version 10), along with the changes of dose used to verify efficacy, a one-sided significance level for comparison in the primary analysis was changed from 0.0125 to 0.025, and the required sample size was reconsidered as described below.

Proportion of participants who were positive RT-PCR and completed the follow-up period without symptoms of SARS-CoV-2 was reported approximately 70% [5]. Therefore, the proportion of participants with development/worsening of COVID-19 symptoms in the placebo group in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in Phase 2b/3 Part was conservatively estimated to be 20%. The proportion of participants with development/worsening of COVID-19 symptoms in the S-217622 125 mg group was assumed to be 8% (risk ratio of 0.4 for S-217622 125 mg to placebo).

[In case of performing an interim analysis]

In case of performing an interim analysis for the purpose of stopping for efficacy, the number of participants required at the time of final analysis was calculated to be 146 participants with asymptomatic/mild symptoms only SARS-CoV-2 infection per group assuming the information fraction for the primary endpoint is 50% at the time of interim analysis and that the criteria for stopping for efficacy are adopted using the O'Brien–Fleming boundary based on α-spending function. The nominal significance level calculated from the significance level (one-sided 0.025) allocated to a comparison with the placebo group for the S-217622 125 mg group was used in order to detect these differences with the power of 80% in Wald test for the risk ratio. Based on this, assuming that the drop-out rate due to a negative RT-PCR result in the test immediately before enrollment would be approximately 10%, the required number of enrolled participants with asymptomatic/mild symptoms only SARS-CoV-2 infection was calculated to be a total of 495 participants (165 per group) for the 3 groups.

[In case of not performing an interim analysis]

Since multiplicity adjustment by the Bonferroni method is planned, the sample size required to detect differences between the S-217622 125 mg group and the placebo group with 80% power using a Fisher's exact test at a one-sided significance level of 0.025 was calculated to be 143 participants with asymptomatic/mild symptoms only SARS-CoV-2 infection per group. Based on this, assuming that the dropout rate due to a negative RT-PCR result in the test immediately before enrollment would be approximately 10%, the required number of enrolled participants with asymptomatic/mild symptoms only SARS-CoV-2 infection was calculated to be a total of 480 participants (160 per group) for the 3 groups.

The number of participants to be enrolled may be changed based on the proportion of participants with a positive RT-PCR result at Visit 1 (pre-intervention) calculated during the study period.

9.3 Populations for Analyses

Consisting of participants in whom the study has been conducted in compliance with Good Clinical Practice (GCP), the populations by part are defined as follows. The definition of the population is the same for Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part.

Population	Description
Enrolled	All participants who sign on the ICF and are enrolled in this study.
All Randomized	All participants randomly assigned to the study intervention.
Intention-To-Treat (ITT) Population	All participants who were randomly assigned to the study intervention and had a SARS-CoV-2 infection. The infection with SARS-CoV-2 will be confirmed by RT-PCR result based on nasopharyngeal swab sample on Visit 1 (pre-intervention). Participants will be analyzed according to the assigned study intervention.
Intention-To-Treat 1 (ITT1) Population	All participants randomly assigned to the study intervention with SARS-CoV-2 viral titer detected at baseline. The detection of SARS-CoV-2 viral titer will be confirmed by viral titer assessment based on nasopharyngeal swab sample. Participants will be analyzed according to the assigned study intervention.
Modified Intention-To-Treat (mITT) Population	All participants randomly assigned to the study intervention with RT-PCR positivity confirmed on Visit 1 (pre-intervention) and with SARS-CoV-2 viral titer detected at baseline. The infection with SARS-CoV-2 and detection of SARS-CoV-2 viral titer will be confirmed by RT-PCR result and viral titer assessment based on nasopharyngeal swab sample. Baseline will be defined as the last value obtained before receiving the first dose of study intervention. Participants will be analyzed according to the assigned study intervention.
Per Protocol Set (PPS)	Per Protocol Set (PPS) includes all participants in the ITT or ITT1 population and without any major protocol deviations.
Safety Population	All participants randomly assigned to study intervention and who received at least one dose of study intervention. Participants will be analyzed according to the initial intervention they actually received.
PK Concentration Population	All participants who received at least one dose of study intervention with at least one evaluable plasma concentration value. This population will be used for the drug concentration listing and graphical presentations.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized for Phase 2a Part, Phase 2b Part, and Phase 3 Part prior to the unblinding of each of these Parts, and for Phase 2b/3 Part prior to the unblinding of the final analysis. 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 including primary and key secondary endpoints.

9.4.1 General Considerations

Statistical analysis and pharmacokinetic analysis will be outsourced by the sponsor to a CRO. 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 particularly imputed. All statistical tests will be performed at a two-sided significance level of 0.05 unless otherwise specified. Baseline will be defined as the last value obtained before receiving the first dose. All participant data (including data not tabulated) will be presented in listings by participant.

In Phase 3 Part for participants with mild/moderate SARS-CoV-2 infection, while the primary comparison will be conducted between the S-217622 125 mg group and the placebo group, comparison between the S-217622 250 mg group and the placebo group will also be conducted in the same fashion as a secondary positioning. In addition, in Phase 3 Part, the primary analysis population will be the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population. In general, all other efficacy analyses will be conducted in the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population as the primary analysis population, and will also be conducted in the ITT population. The details will be described in the SAP. Each primary analysis of the primary endpoint and the key secondary endpoints will be conducted in the population with < 72 hours from the onset of COVID-19 to randomization. If any significant difference is observed in this population, the same analysis as each primary analysis will be subsequently conducted in the ITT population or the mITT population.

In Phase 2b Part and Phase 3 Part for participants with mild/moderate SARS-CoV-2 infection and in Phase 2b/3 Part for participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, in the primary analysis of each primary endpoint (all for these 3 Parts) and the primary analysis of the several key secondary endpoints (Phase 3 Part and Phase 2b/3 Part only), the type 1 error rate control will be applied. The type 1 error rate control will not be applied for the analyses in all endpoints in Phase 2a Part, secondary endpoints in Phase 2b Part, or other secondary endpoints in Phase 3 Part and Phase 2b/3 Part. All analyses and tabulation of listings will be performed using SAS version 9.4 (or higher).

[Type 1 Error Rate Control in Phase 2b Part: participants with mild/moderate SARS-CoV-2 infection]

For participants with mild/moderate SARS-CoV-2 infection, the following comparisons with placebo will be performed based on the fixed sequence procedure, to maintain the type 1 error rate control in the primary analyses of primary endpoints. The sequence of pairwise comparisons is shown below.

1. Primary analysis of primary endpoints: Each of the 2 primary endpoints, ie., time-weighted average change in total score of 12 COVID-19 symptoms from

initiation of administration (Day 1) up to 120 hours (Day 6) and change from baseline on Day 4 in SARS-CoV-2 viral titer will be compared between S-217622 125 mg group and placebo group.

2. Primary analysis of primary endpoints: the same comparisons as in 1. above to be performed between S-217622 250 mg group and placebo group.

If only significance differences are observed at a one-sided significance level of 0.025 in both of the 2 primary endpoints in 1. above, comparisons in the 2 primary endpoints in 2. above will be performed. Because the 2 primary endpoints are co-primary endpoints, the multiplicity adjustment for the comparisons in the 2 primary endpoints in each of 1. and 2. above will not be performed.

[Type 1 Error Rate Control in Phase 3 Part: participants with mild/moderate SARS-CoV-2 infection]

In each primary analysis and key secondary analyses of the primary endpoint, the key secondary endpoint 1 and the key secondary endpoint 2 in the population with mild/moderate SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization and in the whole analysis population in Phase 3 Part, type 1 error rate control using a fixed sequence procedure for comparisons between the S-217622 125 mg group and the placebo group will be performed. Multiplicity-adjusted comparisons in participants with mild/moderate SAR-CoV-2 infection are as follows:

1. Primary analysis of the primary endpoint: In the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population, the time to resolution of the 5 COVID-19 symptoms will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

2. Primary analysis of the key secondary endpoint 1: In the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #1, the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

3. Primary analysis of the key secondary endpoint 2: In the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #2, the time to the first negative SARS-CoV-2 viral titer will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

4. Key secondary analysis of the primary endpoint: In the ITT population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #3, the time to resolution of the 5 COVID-19

symptoms will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

5. Key secondary analysis of the key secondary endpoint 1: In the ITT population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #4, the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

6. Key secondary analysis of the key secondary endpoint 2: In the mITT population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #5, the time to the first negative SARS-CoV-2 viral titer will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

[Type 1 Error Rate Control in Final Analysis of Phase 2b/3 Part: participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (in case of performing an interim analysis for the purpose of stopping for efficacy)]

When performing an interim analysis for the purpose of stopping for efficacy, with respect to the primary analyses of the primary endpoint, the key secondary endpoint 1 and the key secondary endpoint 2 in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection for the comparison between the S-217622 125 mg group and the placebo group in the interim analysis and the final analysis, the same procedures are used for type 1 error rate control as when not performing the interim analysis for stopping for efficacy as described below. This will be done following the fixed sequence procedure. For the nominal significance level utilized in each comparison, the O'Brien–Fleming boundary will be adopted for the primary analysis of the primary endpoint and the Pocock boundary will be adopted for the primary analysis of the key secondary endpoint 1 and the key secondary endpoint 2 for the criteria for stopping for efficacy based on α-spending function. The significance level (one-sided 0.025) allocated to the comparison between the S-217622 125 mg group and the placebo group and those calculated based on the information fraction for each endpoint at the time of interim analysis will be used.

[Type 1 Error Rate Control in Final Analysis of Phase 2b/3 Part: participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (in case of not performing an interim analysis for the purpose of stopping for efficacy)]

In the primary analysis of the primary endpoint, the key secondary endpoint 1 and the key secondary endpoint 2 in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in Phase 2b/3 Part, type 1 error rate control using a fixed sequence procedure for comparisons between endpoints will be performed. Multiplicity-adjusted comparisons in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection are as follows:

1. Primary analysis of the primary endpoint: In the ITT population, the proportion of participants with development/worsening of COVID-19 symptoms will be compared

between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

2. Primary analysis of the key secondary endpoint 1: In the ITT population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #1, the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

3. Primary analysis of the key secondary endpoint 2: In the mITT population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #2, the time to the first negative SARS-CoV-2 viral titer will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

9.4.2 Efficacy Analyses

All efficacy analyses will be based on the ITT population (Phase 2a Part, Phase 2b/3 Part), ITT1 population (Phase 2b Part), mITT population (Phase 2a Part, Phase 2b/3 Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of ITT population or mITT population (Phase 3 Part) as defined in Section 9.3. For Phase 3 Part, in principle, efficacy analyses will also be based on the ITT population or the mITT population. As for the primary endpoints of Phase 2a Part and Phase 2b Part, only the primary analyses will be performed based on the PPS population instead of ITT and ITT1 population, respectively, and based on the PPS population and that with positive SARS-CoV-2 viral titer at baseline instead of mITT population. In Phase 3 Part and Phase 2b/3 Part, the primary analyses and key secondary analyses of the primary endpoint and the key secondary endpoint 1 (Phase 3 Part only) will be performed based on the ITT1 population and the PPS population instead of the ITT population and primary analysis and key secondary analysis of the key secondary endpoint 2 (Phase 3 Part only) will be performed based on the ITT1 population and the PPS population and that with positive SARS-CoV-2 viral titer at baseline instead of the mITT population. In Phase 2b/3 Part, of participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, the analysis for the population of participants with asymptomatic SARS-CoV-2 infection and with mild symptoms only SARS-CoV-2 infection will be performed, and the details will be described in the SAP.

Efficacy analyses in this section will be summarized by treatment group in principle.

9.4.2.1 Primary Efficacy Endpoints

9.4.2.1.1 Primary Efficacy Endpoint in Phase 2a Part: Participants with Mild/Moderate or Asymptomatic SARS-CoV-2 Infection

The primary efficacy endpoint in participants with mild/moderate or asymptomatic SARS-CoV-2 infection is the change from baseline in SARS-CoV-2 viral titer at each time point.

The change from baseline in SARS-CoV-2 viral titer at each time point is defined as the absolute change from baseline in SARS-CoV-2 viral titer at each time point. Summary statistics for the change from baseline in SARS-CoV-2 viral titer at each time point will be calculated using the mITT population for the mild/moderate SARS-CoV-2 infection population, the asymptomatic SARS-CoV-2 infection population, and the combined population separately. In addition, the van Elteren test will be applied in the combined population of mild/moderate and asymptomatic SARS-CoV-2 infection populations to perform a pairwise comparison of SARS-CoV-2 viral titer at each time point between each S-217622 treatment group and the placebo group at a two-sided significance level of 0.05. As stratification factors for van Elteren test, the mild/moderate SARS-CoV-2 infection population and the asymptomatic SARS-CoV-2 infection population will be used. No multiplicity adjustment will be performed in these pairwise comparisons.

9.4.2.1.2 Primary Efficacy Endpoint in Phase 2b Part: Participants with Mild/Moderate SARS-CoV-2 Infection

The primary efficacy endpoint in participants with mild/moderate SARS-CoV-2 infection in Phase 2b Part is the time-weighted average change in total score of 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6) and the change from baseline on Day 4 in SARS-CoV-2 viral titer.

The total score of 12 symptoms of COVID-19 is the total of 4-point scale (0, None; 1, Mild; 2, Moderate; 3, Severe) of 12 symptoms of COVID-19 (low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath (difficulty breathing), nausea, vomiting, and diarrhea) using participant diary. As for the change from baseline in total score of 12 symptoms of COVID-19 measured at each time point, the AUC from initiation of administration (Day 1) up to 120 hours (Day 6) was divided by the evaluation period (unit: hour) when calculating the corresponding AUC, to calculate the time-weighted average change.

As the primary analysis for this primary endpoint, pairwise comparison will be performed between each S-217622 intervention group and the placebo group, analysis of covariance will be applied with time-weighted average change as response, and by time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours), SARS-CoV-2 vaccination history, and the total score of the 12 symptoms of COVID-19 at baseline as covariates in participants with mild/moderate SARS-CoV-2 infection whose total score of 12 symptoms of COVID-19 is one or higher at the initiation of administration (Day 1) in the ITT1 population. In addition, as the primary analysis for change from baseline on Day 4 in SARS-CoV-2 viral titer, pairwise comparison will be performed between each S-217622 intervention group and placebo group, analysis of covariance will be applied with change from baseline in SARS-CoV-2 viral titer as response, and by time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours), SARS-CoV-2 vaccination history, and SARS-CoV-2 viral titer at baseline as covariates in participants with mild/moderate SARS-CoV-2 infection in the ITT1 population.

9.4.2.1.3 Primary Efficacy Endpoint in Phase 3 Part: Participants with Mild/Moderate SARS-CoV-2 Infection

The primary efficacy endpoint in participants with mild/moderate SARS-CoV-2 infection in Phase 3 Part is time to resolution of COVID-19 symptoms.

The time to resolution of COVID-19 symptoms is defined as the time from the start of the study intervention to resolution of all 5 symptoms of COVID-19 (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness). The symptoms of COVID-19 will be evaluated on 4-point scale (0, None; 1, Mild; 2, Moderate; 3, Severe) using participant diary and resolution of symptoms will be assessed according to the following rules:

- For the pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination), the severity should be improved or remain the same.
  - Severe at baseline: Moderate, Mild, or None
  - Moderate at baseline: Mild, or None
  - Mild at baseline: Mild, or None

  Note: The participants will be asked only for the pre-existing symptoms (in the past 30 days) and presence or absence of symptom exacerbation due to COVID-19 and evaluate the severity at baseline (pre-treatment examination). To avoid recall bias, the severity of the pre-existing symptoms prior to the onset of COVID-19 is not evaluated.

- For the pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination), the severity should remain the same or be improved.
  - Severe at baseline: Severe, Moderate, Mild, or None
  - Moderate at baseline: Moderate, Mild, or None
  - Mild at baseline: Mild, or None
- Symptoms other than the above (symptoms that have not occurred before COVID-19 onset, and occurred at or after baseline [pre-treatment examination]), the severity should become none.
  - Severe, Moderate, or Mild at baseline: None

Resolution of COVID-19 symptoms is defined as the time when all 5 COVID-19 symptoms disappear, improve, or maintain as shown above after first administration of study intervention. If the condition persists for at least 24 hours, the participants are considered to achieve this endpoint. Participants whose COVID-19 symptoms have not been confirmed to have resolved will be handled as censored cases according to the time of the last evaluation of COVID-19 symptoms or the time of the last evaluation of COVID-19 symptoms by the day before the first administration of the prohibited concomitant drugs listed below, whichever is earlier.

- Approved drugs for the treatment of SARS-CoV-2 infection
- Unapproved drugs for the treatment of SARS-CoV-2 infection (eg, interferon, convalescent plasma, monoclonal antibodies, immunoglobulins, antirheumatic drugs, corticosteroids [oral, injection, inhaled], ivermectin, favipiravir)

In addition, participants whose COVID-19 symptoms have not been confirmed to have resolved will be included in a supportive analysis as censored at the time of the last evaluation of COVID-19 symptoms.

As the primary analysis for this primary endpoint, comparison of the time to resolution of the 5 COVID-19 symptoms will be performed between the S-217622 125 mg group and the placebo group using a Peto-Prentice's stratified generalized Wilcoxon test stratified by SARS-CoV-2 vaccination history at a one-sided significance level of 0.025 in participants with mild/moderate SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization in the ITT population. As key secondary analysis of the primary endpoint, the same analysis as the primary analysis will be performed in participants with mild/moderate SARS-CoV-2 infection of the ITT population. In this analysis, stratification by the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) will be included as well as SARS-CoV-2 vaccination history. The multiplicity described in Section 9.4.1 will be applied to the primary analysis and key secondary analyses of the primary endpoint and the two key secondary endpoints.

As other analyses for this endpoint, the following analyses will be performed in participants with mild/moderate SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization out of the ITT population. Furthermore, the same analyses will be performed in the ITT population. In that case, stratification by the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) will be included as well as SARS-CoV-2 vaccination history. The multiplicity adjustment planned for the primary analysis will not be performed for between-group comparisons using statistical tests that will be performed in the following analyses.

- Comparison using the log-rank test stratified by SARS-CoV-2 vaccination history between the S-217622 125 mg group and the placebo group will be performed.
- Kaplan-Meier curves will be plotted for each treatment group and the median time to resolution of the 5 COVID-19 symptoms and its 95% confidence interval (CI) will be calculated. Moreover, the difference in median between treatment groups and its 95% CI will be calculated.
- The hazard ratio of the S-217622 125 mg group to the placebo group will be estimated using a Cox proportional hazard model stratified by SARS-CoV-2 vaccination history.
- Restricted mean survival time (RMST) with a 21-day investigation period will be estimated for each group and comparison between the S-217622 125 mg group and the placebo group will be performed.

9.4.2.1.4 Primary Efficacy Endpoint in Phase 2b/3 Part: Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection

The primary efficacy endpoint in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in Phase 2b/3 Part is the proportion of participants with development/worsening of COVID-19 symptoms. The proportion of participants with development/worsening of COVID-19 symptoms is defined as the proportion of participants in the asymptomatic/mild symptoms only SARS-CoV-2 infection population in the ITT population with development/worsening of any 12 symptoms of COVID-19, taste disorder, or smell disorder by 14 days from the first administration of the study intervention.

Taste disorder or smell disorder will be evaluated on 3-point scale (0, The same as usual; 1, Less than usual; 2, No sense of smell/taste) and the 12 symptoms of COVID-19 will be evaluated on 4-point scale (0, None; 1, Mild; 2, Moderate; 3, Severe) using participant diary, and the development/worsening of symptoms will be determined according to the following rules:

- Taste disorder and smell disorder
  - The scores for taste disorder and smell disorder worsen from 0 (The same as usual) to 1 (Less than usual) or 2 (No sense of smell/taste), or from 1 (Less than usual) to 2 (No sense of smell/taste).

    (the baseline score of 2 [No sense of smell/taste] will be excluded from the onset/worsening judgement of COVID-19 symptoms)
- Feeling hot or feverish, cough, shortness of breath (difficulty breathing)
  - The score for either symptom worsen 1 degree or more from baseline:
    - Severity of none at baseline: Worsening to Mild, Moderate, or Severe
    - Mild at baseline: Worsening to Moderate or Severe
    - Moderate at baseline: Worsening to Severe

    (severe symptoms at baseline will be excluded from the onset/worsening judgement of COVID-19 symptoms)
- Low energy or tiredness, muscle or body aches, headache, chills or shivering, stuffy or runny nose, sore throat, nausea, vomiting, and diarrhea
  - The score of 2 or more symptom worsen 1 degree or more from baseline and remain for at least 24 hours at the same time point:
    - Severity of none at baseline: Worsening to Mild, Moderate, or Severe
    - Mild at baseline: Worsening to Moderate or Severe
    - Moderate at baseline: Worsening to Severe

    (severe symptoms at baseline will be excluded from the onset/worsening judgement of COVID-19 symptoms)

  Note: The participants will be asked only for the pre-existing symptoms (in the past 30 days) and presence or absence of symptom exacerbation due to SARS-CoV-2 infection and evaluate the severity at baseline (pre-treatment

examination). To avoid recall bias, the severity of the pre-existing symptoms before the onset of SARS-CoV-2 infection is not evaluated.

As the primary analysis for this primary endpoint, comparison of the proportion of participants with development/worsening of COVID-19 symptoms will be performed between the S-217622 125 mg group and the placebo group using the Mantel-Haenszel test stratified by SARS-CoV-2 vaccination history at a one-sided significance level of 0.025 in the asymptomatic/mild symptoms only SARS-CoV-2 infection population in the ITT population. The multiplicity adjustment described in Section 9.4.1 will be applied to the primary analysis.

As an additional analysis for this primary endpoint, the risk ratio of each S-217622 treatment group to the placebo group will be estimated.

9.4.2.2 Secondary Efficacy Endpoints

There is no key secondary endpoint in Phase 2a Part and Phase 2b Part.

9.4.2.2.1 Key Secondary Efficacy Endpoints in Phase 3 Part and Phase 2b/3 Part

The key secondary endpoints in Phase 3 Part and Phase 2b/3 Part are the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA (key secondary endpoint 1), and the time to the first negative SARS-CoV-2 viral titer (key secondary endpoint 2).

Key secondary endpoint 1:

The primary analysis for the key secondary endpoint 1 is planned for participants with mild/moderate SARS-CoV-2 infection and participants with asymptomatic/mild symptoms only SARS-CoV-2 infection separately. In participants with mild/moderate SARS-CoV-2 infection, the population with < 72 hours from the COVID-19 symptom onset to randomization out of the ITT population of Phase 3 Part will be used for the primary analysis. As the primary analysis for change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA, a comparison will be performed between the S-217622 125 mg group and the placebo group. Analysis of covariance will be applied with change from baseline in amount of SARS-CoV-2 viral RNA as response, and by SARS-CoV-2 vaccination history, and amount of SARS-CoV-2 viral RNA at baseline as covariates. As key secondary analyses, the same analyses will be performed in the ITT population. In these, the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) as well as SARS-CoV-2 vaccination history and amount of SARS-CoV-2 viral RNA at baseline will be included in the covariates. As the primary analysis for change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA, comparison will be performed between the S-217622 125 mg group and the placebo group, analysis of covariance will be applied with change from baseline in amount of SARS-CoV-2 viral RNA as response, and by SARS-CoV-2 vaccination history, and amount of SARS-CoV-2 viral RNA at baseline as covariates in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in the ITT population of Phase 2b/3 Part. The multiplicity

adjustment described in Section 9.4.1 will be applied to these primary analyses and key secondary analyses.

The following analyses will be performed as other analyses of the key secondary endpoint 1. The multiplicity adjustment planned for the primary analysis will not be performed for between-group comparisons using statistical tests that will be performed in the following analyses.

- In the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population and the ITT population in Phase 3 Part for participants with mild/moderate SARS-CoV-2 infection, and in the ITT population in Phase 2b/3 Part for participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, the van Elteren test will be applied to perform a pairwise comparison of the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA between each S-217622 treatment group and the placebo group at a two-sided significance level of 0.05. As stratification factors for van Elteren test, the corresponding covariates to the primary analysis, excluding the amount of SARS-CoV-2 viral RNA at baseline, will be used.

Key secondary endpoint 2:

The time to the first negative SARS-CoV-2 viral titer is defined as the time from the start of the study intervention until the first confirmation that SARS-CoV-2 viral titer drops below the detection limit. Participants whose SARS-CoV-2 viral titer was not confirmed to be negative will be handled as censored cases according to the time of the last evaluation of virus titter of SARS-CoV-2 or the time of the last evaluation of virus titter of SARS-CoV-2 by the day before the first administration of the prohibited concomitant drugs listed below, whichever is earlier.

- Approved drugs for the treatment of SARS-CoV-2 infection
- Unapproved drugs for the treatment of SARS-CoV-2 infection (eg, interferon, convalescent plasma, monoclonal antibodies, immunoglobulins, antirheumatic drugs, corticosteroids [oral, injection, inhaled], ivermectin, favipiravir)

In addition, participants whose SARS-CoV-2 viral titer was not confirmed to be negative will be included in a supportive analysis as censored at the time of the last evaluation of SARS-CoV-2 viral titer.

The primary analysis for the key secondary endpoint 2 is planned for participants with mild/moderate SARS-CoV-2 infection and participants with asymptomatic/mild symptoms only SARS-CoV-2 infection separately. A comparison of the time to the first negative SARS-CoV-2 viral titer will be performed between the S-217622 125 mg group and the placebo group using a log-rank test stratified by SARS-CoV-2 vaccination history at a one-sided significance level of 0.025 in participants with mild/moderate

SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization out of the mITT population of Phase 3 Part. As key secondary analyses, the same analyses will be performed in the mITT population. In this population, the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) as well as SARS-CoV-2 vaccination history will be included in the stratification. A comparison of the time to the first negative SARS-CoV-2 viral titer will be compared between the S-217622 125 mg group and the placebo group using a log-rank test stratified by the SARS-CoV-2 vaccination history at a one-sided significance level of 0.025 in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in mITT population of Phase 2b/3 Part. The multiplicity adjustment described in Section 9.4.1 will be applied to the primary analysis and key secondary analyses.

The following analyses will be performed as additional analyses for the key secondary endpoint 2. The multiplicity adjustment planned for the primary analysis will not be performed for between-group comparisons using statistical tests that will be performed in the following analyses.

- Comparison using the generalized Wilcoxon test stratified by SARS-CoV-2 vaccination history between the S-217622 125 mg group and the placebo group will be performed in the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population. In addition, the same analyses will be performed in the mITT population in Phase 3 Part. In this population, the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) as well as SARS-CoV-2 vaccination history will be included in the stratification. Comparison using the generalized Wilcoxon test stratified by the SARS-CoV-2 vaccination history between the S-217622 125 mg group and the placebo group will be performed in the mITT population in Phase 2b/3 Part.
- For each of the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population and the mITT population in Phase 3 Part, and the mITT population in Phase 2b/3 Part, Kaplan-Meier curves of each group will be plotted, and the median time to the first negative SARS-CoV-2 viral titer and its 95% CI will be calculated. Moreover, the difference in median between treatment groups and its 95% CI will be calculated.
- The hazard ratio of the S-217622 125 mg group to the placebo group will be estimated using a Cox proportional hazard model stratified by SARS-CoV-2 vaccination history in the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population in Phase 3 Part. In addition, the same analyses will be performed in the mITT population in Phase 3 Part. In this population, the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) as well as SARS-CoV-2 vaccination history will be included in the stratification. The hazard ratio of the S-217622 125 mg group to the placebo group will be estimated using a Cox proportional hazard model stratified by SARS-CoV-2 vaccination history in the mITT population in Phase 2b/3 Part.

- For each of the populations with < 72 hours from the onset of COVID-19 to randomization out of the mITT population and the mITT population in Phase 3 Part, and the mITT population in Phase 2b/3 Part, RMST with a 21-day investigation period will be estimated for each group, and a comparison between the S-217622 125 mg group and the placebo group will be performed.

9.4.2.2.2 Secondary Efficacy Endpoints in Phase 2a Part and Phase 2b Part, Other Secondary Efficacy Endpoints in Phase 3 Part and Phase 2b/3 Part

Secondary efficacy endpoints in Phase 2a Part and Phase 2b Part, and other secondary efficacy endpoints in Phase 3 Part and Phase 2b/3 Part are shown below.

[Common Endpoints for Participants with Mild/Moderate and Asymptomatic SARS-CoV-2 Infection (Phase 2a Part)]

[Endpoints for Participants with Mild/Moderate SARS-CoV-2 Infection (Phase 2b Part and Phase 3 Part)]

[Endpoints for Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection (Phase 2b/3 Part)]

- Time to the first negative SARS-CoV-2 viral titer (Phase 2a Part and Phase 2b Part only)

  This is defined as the time from the start of the study intervention until the first confirmation that SARS-CoV-2 viral titer drops below the detection limit. The same analyses as the key secondary efficacy endpoint 2 in Section 9.4.2.2.1 (except for multiplicity adjustment) will be performed in the mITT population of Phase 2a Part and ITT1 population of Phase 2b Part.
- Time to negative SARS-CoV-2 viral titer at 2 consecutive time points (Phase 2a Part and Phase 2b Part only)

  This is defined as the time from the start of the study intervention until SARS-CoV-2 viral titer drops below the detection limit at 2 consecutive time points. Two consecutive time points are the time points when the viral titers of SARS-CoV-2 are measured. The same analyses as the key secondary efficacy endpoint 2 in Section 9.4.2.2.1 (except for multiplicity adjustment) will be performed in the mITT population of Phase 2a Part, and the ITT1 population of Phase 2b Part.

- Time to sustained negative SARS-CoV-2 viral titer

  This is defined as the time from the start of the study intervention until SARS-CoV-2 viral titer drops below the detection limit and remains below the detection limit to the last measurement time point. The last measurement time point is the last time point when SARS-CoV-2 viral titer is measured. The same analysis as the key secondary efficacy endpoint 2 in Section 9.4.2.2.1 (except for

multiplicity adjustment) will be performed in the mITT population of each of Phase 2a Part, Phase 3 Part and Phase 2b/3 Part, the ITT1 population of Phase 2b Part, and the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population of Phase 3 Part.

- Proportion of participants with positive SARS-CoV-2 viral titer at each time point

  This is defined as the proportion of participants with a detectable SARS-CoV-2 viral titer (participants with positive viral titer) at each time point. The proportion of participants with positive SARS-CoV-2 viral titer at each time point will be calculated using the mITT population of each of Phase 2a Part, Phase 3 Part and Phase 2b/3 Part, the ITT1 population of Phase 2b Part, and the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population of Phase 3 Part, for the mild/moderate SARS-CoV-2 infection population and the asymptomatic/mild symptoms only SARS-CoV-2 infection population separately. In addition, the Mantel-Haenszel test will be applied in the mild/moderate SARS-CoV-2 infection population and the asymptomatic/mild symptoms only SARS-CoV-2 infection population separately to perform a pairwise comparison of the proportion of participants with positive SARS-CoV-2 viral titer at each time point between each S-217622 treatment group and the placebo group at a two-sided significance level of 0.05. The strata used in the Mantel-Haenszel test will be time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history for the mild/moderate SARS-CoV-2 infection population, and SARS-CoV-2 vaccination history for the asymptomatic/mild symptoms onlySARS-CoV-2 infection population. However, in the analyses for the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population of Phase 3 Part, the stratification factor will be SARS-CoV-2 vaccination history only.

- SARS-CoV-2 viral titer at each time point

  This is defined as the measured value of SARS-CoV-2 viral titer at each time point. Summary statistics for the SARS-CoV-2 viral titer at each time point will be calculated using the mITT population of each of Phase 2a Part, Phase 3 Part and Phase 2b/3 Part, the ITT1 population of Phase 2b Part, and the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population of Phase 3 Part, for the mild/moderate SARS-CoV-2 infection population and the asymptomatic/mild symptoms only SARS-CoV-2 infection population separately.

  In addition, in Phase 2a Part, the van Elteren test will be applied in the mild/moderate SARS-CoV-2 infection population and the asymptomatic SARS-CoV-2 infection population separately to perform a pairwise comparison of the SARS-CoV-2 viral titer at each time point between each S-217622 treatment group and the placebo group at a two-sided significance level of 0.05. The strata used in the van Elteren test will be time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history for the mild/moderate SARS-CoV-2 infection population, and SARS-CoV-2

vaccination history for the asymptomatic/mild symptoms only SARS-CoV-2 infection population.

In Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part, in addition to the van Elteren test, analysis of covariance will be applied in the mild/moderate SARS-CoV-2 infection population and the asymptomatic/mild symptoms only SARS-CoV-2 infection population separately to perform a pairwise comparison of the SARS-CoV-2 viral titer at each time point between each S-217622 treatment group and the placebo group at a two-sided significance level of 0.05. The covariate is the strata used in the van Elteren test with baseline SARS-CoV-2 viral titer added. In the analyses for the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population of Phase 3 Part, the time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) will be excluded from the stratification used for the van Elteren test and the covariates for analysis of covariance.

- Change from baseline in SARS-CoV-2 viral titer at each time point (Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part)

  This is defined as the absolute change from baseline in SARS-CoV-2 viral titer at each time point. The same analysis as the SARS-CoV-2 viral titer will be performed at each time point in the ITT1 population of Phase 2b Part, the mITT population of each of Phase 3 Part and Phase 2b/3 Part, and the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population of Phase 3 Part.

- Relative change rate from baseline in SARS-CoV-2 viral titer at each time point

  This is defined as the relative change rate from baseline in SARS-CoV-2 viral titer at each time point. Relative change rate is defined as the absolute change from baseline divided by the baseline value. The same analysis as the SARS-CoV-2 viral titer will be performed at each time point in the mITT population of each of Phase 2a Part, Phase 3 Part and Phase 2b/3 Part, the ITT1 population of Phase 2b Part, and the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population of Phase 3 Part.

- AUC of change in SARS-CoV-2 viral titer

  This is defined as the AUC of the change from baseline in SARS-CoV-2 viral titer. The AUC will be evaluated from Day 1 to Day 6 and from Day 1 to Day 9. The AUC will be calculated by the trapezoidal method. The same analysis as the SARS-CoV-2 viral titer will be performed at each time point in the mITT population of each of Phase 2a Part, Phase 3 Part and Phase 2b/3 Part, the ITT1 population of Phase 2b Part, and the population with < 72 hours from the onset of COVID-19 to randomization out of the mITT population of Phase 3 Part.

- Time to the first negative RT-PCR result (Phase 2a Part and Phase 2b Part only)

This is defined as the time from the start of the study intervention to the first confirmation of a negative RT-PCR result. The same analysis as the key secondary efficacy endpoint 2 in Section 9.4.2.2.1 (except for multiplicity adjustment) will be performed in each of the ITT population (Phase 2a Part), the ITT1 population (Phase 2b Part).

- Time to negative RT-PCR results at 2 consecutive time points (Phase 2a Part and Phase 2b Part only)

  This is defined as the time from the start of the study intervention to confirmation of negative RT-PCR results at 2 consecutive time points. Two consecutive time points are the time points when RT-PCR results are observed. The same analysis as the key secondary efficacy endpoint 2 in Section 9.4.2.2.1 (except for multiplicity adjustment) will be performed in each of the ITT population (Phase 2a Part), the ITT1 population (Phase 2b Part).

- Time to sustained negative RT-PCR results (Phase 2a Part and Phase 2b Part only)

  This is defined as the time from the start of the study intervention until negative RT-PCR results which continues negative to the last observation time point. The last observation time point is the time point where the last RT-PCR result is observed. The same analysis as the key secondary efficacy endpoint 2 in Section 9.4.2.2.1 (except for multiplicity adjustment) will be performed in each of the ITT population (Phase 2a Part), the ITT1 population (Phase 2b Part).

- Proportion of participants with positive RT-PCR result at each time point

  This is defined as the proportion of participants who tested positive on RT-PCR at each time point. The same analysis as the proportion of participants with positive SARS-CoV-2 viral titer will be performed at each time point in each of the ITT population (Phase 2a Part, Phase 3 Part and Phase 2b/3 Part), the ITT1 population (Phase 2b Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part).

- Amount of SARS-CoV-2 viral RNA at each time point

  This is defined as the measured value of amount of SARS-CoV-2 viral RNA at each time point. The same analysis as the SARS-CoV-2 viral titer will be performed at each time point in each of the ITT population (Phase 2a Part, Phase 3 Part and Phase 2b/3 Part), the ITT1 population (Phase 2b Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part).

- Change from baseline in amount of SARS-CoV-2 viral RNA at each time point

  This is defined as the absolute change from baseline in amount of SARS-CoV-2 viral RNA at each time point. The same analysis as the SARS-CoV-2 viral titer will be performed at each time point in each of the ITT population (Phase 2a Part, Phase 3 Part and Phase 2b/3 Part), the ITT1 population (Phase 2b Part), and the

population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part).

- Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point

  This is defined as the relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point. The same analysis as the SARS-CoV-2 viral titer will be performed at each time point in each of the ITT population (Phase 2a Part, Phase 3 Part and Phase 2b/3 Part), the ITT1 population (Phase 2b Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part).

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

  This is defined as the AUC of the change from baseline in amount of SARS-CoV-2 viral RNA. The AUC will be evaluated from Day 1 to Day 6 and from Day 1 to Day 9. The AUC will be calculated by the trapezoidal method. The same analysis as the SARS-CoV-2 viral titer will be performed at each time point in each of the ITT population (Phase 2a Part, Phase 3 Part and Phase 2b/3 Part), the ITT1 population (Phase 2b Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part).

- Proportion of participants with a score of ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6, and 7 on the 8-Point Ordinal Scale at each time point and during the investigation period

  This is defined as the proportion of participants with a score of ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6, and 7 on the 8-Point Ordinal Scale during the investigation period (the treatment period and the follow-up period). The proportion of participants with each event at each time point and during the investigation period will be calculated for each of the mild/moderate SARS-CoV-2 infection population and the asymptomatic/mild symptoms only SARS-CoV-2 infection population in each of the ITT population (Phase 2a Part, Phase 3 Part and Phase 2b/3 Part), the ITT1 population (Phase 2b Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part). In addition, the Mantel-Haenszel test will be applied separately in the mild/moderate SARS-CoV-2 infection population and the asymptomatic/mild symptoms only SARS-CoV-2 infection population to perform a pairwise comparison of each proportion between each S-217622 treatment group and the placebo group at a two-sided significance level of 0.05. The strata used in the Mantel-Haenszel test will be time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history for the mild/moderate SARS-CoV-2 infection population, and SARS-CoV-2 vaccination history for the asymptomatic/mild symptoms only SARS-CoV-2 infection population. However, in the analyses for the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population of Phase 3 Part, the stratification factor will be SARS-CoV-2 vaccination history only. The risk ratio of each S-217622 treatment group to the placebo group will also be estimated.

- Time to score of ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6, and 7 on the 8-Point Ordinal Scale

  This is defined as the time (days) from the start of the study intervention to observation of the score of ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6, and 7 on the 8-Point Ordinal Scale. The same analysis as the key secondary efficacy endpoint 2 in Phase 3 Part and Phase 2b/3 Part (except for multiplicity adjustment) will be performed in the ITT population (Phase 2a Part, Phase 3 Part and Phase 2b/3 Part), the ITT1 population (Phase 2b Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part) (see Section 9.4.2.2.1). However, in the analyses for the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population of Phase 3 Part, the stratification factor will be SARS-CoV-2 vaccination history only.

- SpO_2 at each time point

  This is defined as the observed value of SpO_2 at each time point. The same analysis as the SARS-CoV-2 viral titer will be performed at each time point in each of the ITT population (Phase 2a Part, Phase 3 Part and Phase 2b/3 Part), the ITT1 population (Phase 2b Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part). However, in the analyses for the population with < 72 hours from COVID-19 symptom onset to randomization out of the ITT population of Phase 3 Part, the stratification factor will be SARS-CoV-2 vaccination history only.

- Change from baseline in EQ-5D-5L

  For each of the ITT population (Phase 2a Part, Phase 3 Part and Phase 2b/3 Part), the ITT1 population (Phase 2b Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part), the change from baseline in the utility value calculated from EQ-5D-5L at each time point will be summarized by treatment group.

[Endpoints for Participants with Mild/Moderate SARS-CoV-2 Infection]

- Time to resolution of the 5 COVID-19 symptoms without recurrence (duration of resolution: 48 hours [2 days] or longer) (Phase 3 Part only)

  For the time to achieve continued resolution of the 5 symptoms for 48 hours or longer without any recurrence of the 5 symptoms for 2 days (48 hours) or longer after the resolution of the 5 COVID-19 symptoms, the same analyses as for the time to resolution of the 5 COVID-19 symptoms which is the primary endpoint in Phase 3 Part will be performed in the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population and the ITT population (Phase 3 Part) (except for multiplicity adjustment) (see Section 9.4.2.1.3). The definition of recurrence is described below.

  Recurrence will be judged if any score of the 5 COVID-19 symptoms becomes ≥ moderate (moderate or severe) at the time point from the resolution of the 5

COVID-19 symptoms till the last observation of participant diary and the condition persists for 48 hours or longer. However, if the severity of pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline is severe at baseline, or if the severity of pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline is moderate at baseline, recurrence will be judged if the score becomes severe and the condition persists for 48 hours or longer. In case that the severity is severe at baseline for pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline, recurrence assessment will not be performed.

- Time to resolution of the 12 COVID-19 symptoms/time to resolution of COVID-19 symptom groups (Phase 3 Part only)

  For the time to resolution of the 12 COVID-19 symptoms/time to resolution of COVID-19 symptom groups out of the 12 symptoms, the same analyses as for the time to resolution of the 5 COVID-19 symptoms which is the primary endpoint in Phase 3 Part will be performed in the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population and the ITT population (Phase 3 Part) (except for multiplicity adjustment) (see Section 9.4.2.1.3).

  Time to resolution of the 12 COVID-19 symptoms and time to resolution of COVID-19 symptom groups are defined as the time from the start of the study intervention to resolution of all 12 COVID-19 symptoms (low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath [difficulty breathing], nausea, vomiting, and diarrhea) or all symptoms in the symptom groups, respectively. The symptoms of COVID-19 will be evaluated on 4-point scale (0, None; 1, Mild; 2, Moderate; 3, Severe) using participant diary and resolution of symptoms will be assessed according to the definition of resolution described in Section 9.4.2.1.3.

  Resolution of COVID-19 symptoms is defined as the time when all 12 COVID-19 symptoms or all symptoms in the symptom groups disappear, improve, or maintain as shown in Section 9.4.2.1.3. If the condition persists for at least 24 hours, the participants are considered to achieve this endpoint. Participants whose COVID-19 symptoms have not been confirmed to have resolved will be handled as censored cases according to the time of the last evaluation of COVID-19 symptoms or the time of the last evaluation of COVID-19 symptoms by the day before the first administration of the prohibited concomitant drugs listed below, whichever is earlier.

  - Approved drugs for the treatment of SARS-CoV-2 infection
  - Unapproved drugs for the treatment of SARS-CoV-2 infection (eg, interferon, convalescent plasma, monoclonal antibodies,

immunoglobulins, antirheumatic drugs, corticosteroids [oral, injection, inhaled], ivermectin, favipiravir)

Definitions of each of the symptom groups are as described below.

- Respiratory symptoms: stuffy or runny nose, sore throat, cough, shortness of breath (difficulty breathing)
- General symptoms: low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish
- Gastrointestinal symptoms: nausea, vomiting, and diarrhea

- Time to improvement of the 12 COVID-19 symptoms (Phase 2a Part and Phase 2b Part only)

  For the time to improvement of the 12 COVID-19 symptoms, the same analyses as for the time to resolution of the 5 COVID-19 symptoms which is the primary endpoint in Phase 3 Part will be performed for participants with mild/moderate SARS-CoV-2 infection in the ITT population (Phase 2a Part) and the ITT1 population (Phase 2b Part) (except for multiplicity adjustment) (see 9.4.2.1.3). The time to improvement of the 12 COVID-19 symptoms is defined as the time from the start of the study intervention to improvement of all 12 symptoms of COVID-19 (low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath [difficulty breathing], nausea, vomiting, and diarrhea). The symptoms of COVID-19 will be evaluated on 4-point scale (0, None; 1, Mild; 2, Moderate; 3, Severe) using participant diary and improvement of symptoms will be assessed according to the following rules:

  - For the pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination), the severity should be improved.
    - Severe at baseline: Moderate, Mild, or None
    - Moderate at baseline: Mild, or None
  - For the pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination), the severity should remain the same or be improved.
    - Severe at baseline: Sever, Moderate, Mild, or None
    - Moderate at baseline: Moderate, Mild, or None
  - Symptoms other than the above (symptoms that have not occurred before COVID-19 onset, and occurred at or after baseline [pre-treatment examination]), the severity should become Mild or None.
    - Severe or Moderate at baseline: Mild, or None

Improvement of 12 COVID-19 symptoms is defined as the time when all 12 COVID-19 symptoms disappear, maintain, or improve as shown above after first administration of study intervention. If the condition persists for at least 24 hours, the participants are considered to achieve this endpoint. Participants whose COVID-19 symptoms have not been confirmed to have improved will be handled as censored cases according to the time of the last evaluation of COVID-19 symptoms or the time of the last evaluation of COVID-19 symptoms by the day before the first administration of the prohibited concomitant drugs listed in Section 9.4.2.1.3, whichever is earlier.

- Time to improvement of the 12 COVID-19 symptoms (duration of recovery) (Phase 2a Part and Phase 2b Part only)

  Analysis of the time to improvement of the 12 COVID-19 symptoms will be performed by changing the definition of the duration of recovery of COVID-19 symptoms from 24 hours to 72 hours and 120 hours. The same analysis as the primary endpoint in Phase 3 Part (time to resolution of the 5 COVID-19 symptoms) (except for multiplicity adjustment) will be performed in participants with mild/moderate SARS-CoV-2 infection of each of the ITT population (Phase 2a Part) and ITT1 population (Phase 2b Part) (see Section 9.4.2.1.3).

- Time to improvement of each COVID-19 symptom (Phase 2a Part and Phase 2b Part only)

  This is defined as the time from the start of the study intervention to improvement of each COVID-19 symptom described above. As for the definition and assessment of improvement of COVID-19 symptoms, the description above in the paragraph of “Time to improvement of COVID-19 symptoms” shall be followed. The same analysis as the primary endpoint in Phase 3 Part (time to resolution of the 5 COVID-19 symptoms) (except for multiplicity adjustment) will be performed in the mild/moderate SARS-CoV-2 infection population in each of the ITT population (Phase 2a Part) and ITT1 population (Phase 2b Part) (see Section 9.4.2.1.3).

- Time to resolution of the 14 COVID-19 symptoms including taste disorder and smell disorder (Phase 3 Part only)
  As for the time to resolution of the 14 COVID-19 symptoms including taste disorder and smell disorder, the same analysis as the primary endpoint in Phase 3 Part (time to resolution of the 5 COVID-19 symptoms) (except for multiplicity adjustment) will be performed in the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population, and the ITT population (Phase 3 Part) (see Section 9.4.2.1.3). Definition and assessment of resolution of COVID-19 symptoms including taste disorder and smell disorder is defined as the time when all 14 COVID-19 symptoms (low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath (difficulty breathing), nausea, vomiting, diarrhea, taste disorder, and smell disorder) resolve after first administration of study intervention. The assessment rules for resolution of the 12 COVID-19

symptoms except for taste disorder and smell disorder are described in Section 9.4.2.1.3. In addition, taste disorder and smell disorder will be evaluated on 3-point scale (0, The same as usual; 1, Less than usual; 2, No sense of smell/taste) using participant diary recorded by participants, and the resolution will be assessed according to the following rules:

- For the pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination), the symptom score should be improved or remain the same.
  - "No sense of smell/taste" at baseline: "Less than usual", or "The same as usual"
  - "Less than usual" at baseline: "Less than usual", or "The same as usual"
- For the pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination), the severity at baseline should remain the same or be improved.
  - "No sense of smell/taste" at baseline: "No sense of smell/taste", "Less than usual", or "The same as usual"
  - "Less than usual" at baseline: "Less than usual", or "The same as usual"
- Symptoms other than the above (symptoms that have not occurred before COVID-19 onset, and occurred at or after baseline [pre-treatment examination]), the symptom score should become "The same as usual".
  - "No sense of smell/taste", "Less than usual", or "The same as usual" at baseline: "The same as usual"

Resolution of COVID-19 symptoms including taste disorder and smell disorder is defined as the time when all 14 COVID-19 symptoms disappear, improve, or maintain as shown above after first administration of study intervention. If the condition persists for at least 24 hours, the participants are considered to achieve this endpoint. Participants whose COVID-19 symptoms have not been confirmed to have resolved will be handled as censored cases according to the time of the last evaluation of COVID-19 symptoms or the time of the last evaluation of COVID-19 symptoms by the day before the first administration of the prohibited concomitant drugs listed in Section 9.4.2.1.3, whichever is earlier.

- Time to resolution of each of the 5 COVID-19 symptoms (Phase 3 Part only)
  The time to resolution of each of the 5 COVID-19 symptoms is defined as the time from the start of the study intervention to resolution of each symptom of COVID-19 (stuffy or runny nose, sore throat, cough, feeling hot or feverish, low energy or tiredness). As for the definition and assessment of resolution of COVID-19 symptoms, those for the time to resolution of each COVID-19 symptom including taste disorder and smell disorder shall be followed. The same analysis as the primary endpoint in Phase 3 Part (time to resolution of 5 COVID-19 symptoms) (except for multiplicity adjustment) will be performed in the

population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population, and the ITT population (Phase 3 Part) (see Section 9.4.2.1.3).

- Change from baseline in total score of 12 COVID-19 symptoms and each symptom score at each time point (Phase 2a Part and Phase 2b Part only)

  This is defined as the absolute change from baseline in total score of 12 COVID-19 symptoms and the absolute change from baseline in each symptom score at each time point. The same analysis as the SARS-CoV-2 viral titer will be performed at each time point in the mild/moderate SARS-CoV-2 infection population in the ITT population (Phase 2a Part), the ITT1 population (Phase 2b Part). However, the analysis will be performed only in the mild/moderate SARS-CoV-2 infection population.

- Proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point (Phase 2a Part and Phase 2b Part only)

  This is defined as the proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point. Improvement of symptoms is defined in the "Time to improvement of COVID-19 symptoms" description above. The same analysis as the proportion of participants with positive SARS-CoV-2 viral titer will be performed for COVID-19 symptoms and each symptom at each time point in the mild/moderate SARS-CoV-2 infection population in each of the ITT population (Phase 2a Part) and ITT1 population (Phase 2b Part). However, the analysis will be performed only in the mild/moderate SARS-CoV-2 infection population, and the strata used in the Mantel-Haenszel test will be time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) and the SARS-CoV-2 vaccination history.

- Proportion of participants with taste disorder or smell disorder at each time point

  This is defined as the proportion of participants with taste disorder or smell disorder at each time point. The same analysis as the proportion of participants with positive SARS-CoV-2 viral titer will be performed at each time point in the mild/moderate SARS-CoV-2 infection population in each of the ITT population (Phase 2a Part and Phase 3 Part), the ITT1 population (Phase 2b Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part). However, the analysis will be performed only in the mild/moderate SARS-CoV-2 infection population, and the strata used in the Mantel-Haenszel test will be time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) and the SARS-CoV-2 vaccination history for the ITT population of Phase 2a Part and the ITT1 population of Phase 2b Part, and SARS-CoV-2 vaccination history for the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population of Phase 3 Part. For the ITT population of Phase 3 Part, SARS-CoV-2 vaccination history, and time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) will be used as the strata. The same analysis will be performed for the proportion of participants

with taste disorder and smell disorder and with each of taste disorder and smell disorder confirmed in Phase 3 Part.

- Time to resolution of fever

  This is defined as the time from the start of the study intervention to time to resolution of fever. Fever is considered to be resolved when the axillary temperature measured by participants returns to normal (< 37.0℃) and is sustained for at least 24 hours. The same analysis as the time to resolution of the 5 COVID-19 symptoms (except for multiplicity adjustment) will be performed in the mild/moderate SARS-CoV-2 infection population in each of the ITT population (Phase 2a Part and Phase 3 Part), the ITT1 population (Phase 2b Part), and the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population (Phase 3 Part) (see Section 9.4.2.1.3).

- Proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration (Phase 3 Part only)

  The proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration is defined as the proportion of participants with one or more 12 COVID-19 symptoms (low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath [difficulty breathing], nausea, vomiting, and diarrhea) which has not been resolved at the final evaluation point after 3 weeks of administration, that is, on or after Day 18 (after 432 hours [18 days] from initiation of administration) taking into account the time allowance of Day 21 (Table 1-9). The symptoms of COVID-19 will be evaluated on a 4-point scale (0, None; 1, Mild; 2, Moderate; 3, Severe) using participant diary and the resolution of symptoms will be assessed according to the following rules:

  - For the pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant to have worsened at baseline (pre-treatment examination), the severity should be improved or remain the same at the final evaluation point.
    - Severe at baseline: Moderate, Mild, or None
    - Moderate at baseline: Mild, or None
    - Mild at baseline: Mild, or None

    Note: The participants will be asked only for the pre-existing symptoms (in the past 30 days) and presence or absence of symptom exacerbation due to COVID-19 and evaluate the severity at baseline (pre-treatment examination). To avoid recall bias, the severity of the pre-existing symptoms prior to the onset of COVID-19 is not evaluated.

  - For the pre-existing symptoms that were present prior to the onset of COVID-19 and considered by the participant not to have worsened at baseline (pre-treatment examination), the severity should remain the same or be improved at the final evaluation point.

- Severe at baseline: Severe, Moderate, Mild, or None
- Moderate at baseline: Moderate, Mild, or None
- Mild at baseline: Mild, or None

- Symptoms other than the above (symptoms that have not occurred before COVID-19 onset, and occurred at or after baseline [pre-treatment examination]), the severity should become none at the final evaluation point.
  - Severe, Moderate, or Mild at baseline: None

Day 18 was set taking into account the time allowance of Day 21 (Table 1-9), which is the last day of the evaluation of COVID-19 symptoms. Participants whose final evaluation point was earlier than 432 hours (18 days) from the initiation of administration will be handled as those who did not have resolution of COVID-19 symptoms.

For participants with mild/moderate SARS-CoV-2 infection with < 72 hours from the onset of COVID-19 to randomization out of the ITT population of Phase 3 Part, comparison between the S-217622 125 mg group and the placebo group will be performed in the proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration using the Mantel-Haenszel test stratified by SARS-CoV-2 vaccination history with one-sided significant level of 0.025. The same analysis will be performed using the Mantel-Haenszel test stratified by SARS-CoV-2 vaccination history, and time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) for the ITT population of Phase 3 Part.

[Endpoints for Participants with Asymptomatic SARS-CoV-2 Infection]

- Proportion of participants with development of COVID-19 symptoms

  This is defined as the proportion of participants with asymptomatic SARS-CoV-2 infection with development of any of the 12 symptoms of COVID-19, taste disorder, or smell disorder during the evaluation period of patient diary. The same analysis as the primary endpoint in Phase 2b/3 Part (proportion of participants with development/worsening of COVID-19 symptoms) (except for multiplicity adjustment) will be performed in the asymptomatic SARS-CoV-2 infection population in each of the ITT population (Phase 2a Part and Phase 2b/3 Part). The development will be evaluated during the evaluation period of patient diary in Phase 2a Part and until 14 days from the first administration of the study intervention in Phase 2b/3 Part.

  The 12 symptoms of COVID-19, taste disorder, or smell disorder is defined below.

  - Taste disorder and smell disorder:
    - The scores for taste disorder and smell disorder worsen from 0 (The same as usual) to 1 (Less than usual) or 2 (No sense of smell/taste)

- Feeling hot or feverish, cough, shortness of breath (difficulty breathing):
  - The score for either symptom worsen 1 degree or more from baseline:
    - Severity of none at baseline: Worsening to Mild, Moderate, or Severe
    - Mild at baseline: Worsening to Moderate or Severe
    - Moderate at baseline: Worsening to Severe

(severe symptoms at baseline will be excluded from the onset judgement of COVID-19 symptoms)

- Low energy or tiredness, muscle or body aches, headache, chills or shivering, stuffy or runny nose, sore throat, nausea, vomiting, and diarrhea:
  - The score of 2 or more symptom worsen 1 degree or more from baseline at the same time point:
    - Severity of none at baseline: Worsening to Mild, Moderate, or Severe
    - Mild at baseline: Worsening to Moderate or Severe
    - Moderate at baseline: Worsening to Severe

(severe symptoms at baseline will be excluded from the onset judgement of COVID-19 symptoms)

Note: The participants will be asked only for the pre-existing symptoms (in the past 30 days) and presence or absence of symptom exacerbation due to SARS-CoV-2 infection and evaluate the severity at baseline (pre-treatment examination). To avoid recall bias, the severity of the pre-existing symptoms before the onset of SARS-CoV-2 infection is not evaluated.

- Proportion of participants with development of COVID-19 symptoms with fever (Phase 2a Part)

  This is defined as the proportion of participants in the asymptomatic SARS-CoV-2 infection population in the ITT population of Phase 2a Part with development of the following #1 and #2 at the same time during the evaluation period of participant diary.

  #1 Participants with development of any 12 symptoms of COVID-19, taste disorder, or smell disorder (See "Proportion of participants with development of COVID-19 symptoms (Phase 2a Part)" of this section for definition of development)

  #2 Fever (the axillary temperature is ≥ 37.0℃)

  The same analysis as the primary endpoint in Phase 2b/3 Part (proportion of participants with development/worsening of COVID-19 symptoms) (except for multiplicity adjustment) will be performed in the asymptomatic SARS-CoV-2 infection population in the ITT population (see Section 9.4.2.1.4).

- Proportion of participants with development of COVID-19 symptoms with fever (Phase 2b/3 Part)

  This is defined as the proportion of participants in the asymptomatic SARS-CoV-2 infection population in the ITT population of Phase 2b/3 Part with

development of the following #1 and #2 at the same time by 14 days from the first administration of the study intervention.

#1 Participants with development of any of the 12 symptoms of COVID-19, taste disorder, or smell disorder (See "Proportion of participants with development of COVID-19 symptoms (Phase 2b/3 Part)" of this Section for definition of development)

#2 Fever (the axillary temperature is ≥ 37.0°C)

The same analysis as the primary endpoint in Phase 2b/3 Part (proportion of participants with development/worsening of COVID-19 symptoms) (except for multiplicity adjustment) will be performed in the asymptomatic SARS-CoV-2 infection population in the ITT population (see Section 9.4.2.1.4).

9.4.3 Pharmacokinetic Analyses

For the PK concentration population, plasma concentrations of S-217622 will be listed by treatment group and Day along with the time elapsed from the last dosing of study intervention prior to blood sampling each for Phase 2a Part, Phase 2b Part, Phase 3 Part and Phase 2b/3 Part. Plasma S-217622 concentrations (C_{24}) will be summarized at 24 hours post-dose (allowable range, 20 to 28 hours) on Day 2 with N, mean, SD, coefficient of variation (CV%, calculated as SD/mean × 100), geometric mean and its coefficient of variation (CV% geometric mean, calculated as $\{\exp[sd^2] - 1\}^{1/2} \times 100$), sd is the standard deviation of natural log-transformed values), median, minimum, and maximum, each for Phase 2a Part, Phase 2b Part, Phase 3 Part and Phase 2b/3 Part. If possible, also summarize by the age group. The time elapsed from the last dosing of study intervention prior to blood sampling and the plasma concentrations of S-217622 will be graphically presented appropriately.

After measurement of plasma concentration, data for which inappropriateness for analysis can be clearly explained by the person in charge of PK analysis at the sponsor will be excluded. If excluded, the reason for exclusion will be documented in the clinical study report.

The relationship between C_{24} and efficacy endpoints will be evaluated across S-217622 treatment groups, as appropriate. PK/PD analyses of each efficacy endpoint will include participants with C_{24} values and each evaluable efficacy result. If analyses are performed, a separate PK/PD analysis plan and report will be prepared. If possible, population PK analyses will be performed using nonlinear mixed effects modeling with NONMEM version 7.4 (or higher). If population PK analyses are performed, a separate population PK analysis plan and report will be prepared.

9.4.4 Safety Analyses

All safety analyses will be performed in the safety population for Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part, and these parts combined. As for each combined population, analyses will be performed in the mild/moderate SARS-CoV-2 infection

population, the asymptomatic/mild symptoms only SARS-CoV-2 infection population, and the combined population of these populations.

9.4.4.1 Adverse Events

AEs 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). AEs reported on the eCRF that occur after the first dose of study intervention (ie, treatment-emergent adverse events [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 dose. 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 (ADRs) 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.

9.4.4.2 Laboratory Tests

Summary statistics for observed values and changes from baseline at each scheduled time point 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 time points.

9.4.4.3 Vital Signs

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

9.4.4.4 ECG

Only in Phase 2a Part, summary statistics for ECG findings (normal, abnormal but not clinically significant, or abnormal and clinically significant) at each scheduled time point after randomization (including baseline) will be calculated by treatment group.

9.4.5 Other Analyses

In principle, other analyses will be performed in each of ITT population (Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part) and ITT1 population (Phase 2b Part) separately for each of Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part unless otherwise specified. For Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part, analyses other than those specified in Section 9.4.5.6 (pooled analysis of the efficacy endpoints in the combined mild/moderate and asymptomatic/mild symptoms only SARS-CoV-2 infection populations) will be performed separately in the mild/moderate SARS-CoV-2 infection population, the asymptomatic/mild symptoms only SARS-CoV-2 infection population,

and the combined population. Detailed analyses will be specified in the statistics analysis plan (SAP).

9.4.5.1 Spike Gene Sequence Analysis

Spike gene sequence analysis will be performed only for Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part. Analysis population and methods will be described in the SAP.

9.4.5.2 Polymorphism and Drug-Induced 3CL Protease (nsp5) and its Cleavage Site Gene Sequence Analysis

A listing of the location of amino acid substitution in participants with amino acid substitution due to polymorphisms in the 3CL protease domain compared to reference strains will be provided. For participants with amino acid substitution in the 3 CL protease and its cleavage site domain due to administration of the study intervention, the location of amino acid substitution will be presented. The analysis for polymorphism and 3CL protease gene sequence will be performed for Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part, and the analysis for 3CL protease cleavage site gene sequence will be performed for all Parts.

9.4.5.3 S-217622 Antiviral Activity (Drug Antiviral Activity)

Summary statistics for the 50% effective concentration (EC_{50}) of S-217622 in the virus isolated from baseline samples and the ratio of baseline EC_{50} to EC_{50} of reference strains will be calculated. A list of EC_{50} of S-217622 for the virus isolated from baseline samples and EC_{50} of reference strains will also be provided. These will be performed for Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part.

9.4.5.4 SARS-CoV-2 Neutralizing Antibody Titer (Immunity Analysis)

For the log-transformed SARS-CoV-2 neutralizing antibody titers at baseline and scheduled time points after randomization, the mean value and its 95% CI for each treatment group will be calculated, and their geometric mean antibody titer and its 95% CI will be estimated by converting them back to the original scale.

9.4.5.5 Change from Baseline in Aggravation Markers

The change from baseline in each aggravation marker will be summarized by treatment group at each time point. The type of aggravation marker is provided in Section 8.8.1.

9.4.5.6 Pooled Analysis of Efficacy Endpoints

For some of the efficacy endpoints described in Section 9.4.2, a pooled analysis combining the mild/moderate and asymptomatic/mild symptoms only SARS-CoV-2 infection populations will be performed for Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part. In addition, a pooled analyses of the mild/moderate SARS-CoV-2 infection population of Phase 2a Part, Phase 2b Part, and Phase 3 Part combined and of the asymptomatic/mild symptoms only SARS-CoV-2 infection population of Phase 2a Part and Phase 2b/3 Part combined will be performed separately. The details of the efficacy endpoints to be analyzed and the analysis methods will be specified in the SAP.

9.4.5.7 Proportion of Participants with Post-acute COVID-19 Syndrome at Each Time Point

The proportion of participants with at least one post-acute COVID-19 syndrome (shown in Attachment 3) at each time point and the risk ratio to the placebo group will be calculated. In addition, the proportion of participants for each post-acute COVID-19 syndrome at each time point and the risk ratio will be calculated. Other detailed analyses will be specified in the SAP.

9.4.5.8 Time to Less Than LLOQ of SARS-CoV-2 Viral RNA and the Negative RT-PCR Result (Phase 3 Part and Phase 2b/3 Part Only)

This is defined as the time from the start of the study intervention to the first confirmation of the SARS-CoV-2 viral RNA of < LLOQ (2.08 $\log_{10}$ copies/mL) without viral rebound and of the negative RT-PCR result at the same time. Viral rebound is defined as that the viral RNA of ≥ LLOQ is confirmed after the confirmation of the viral RNA of < LLOQ and the negative RT-PCR result. The same analyses as the key secondary efficacy endpoint 2 in Section 9.4.2.2.1 (except for multiplicity adjustment) will be performed in the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population of Phase 3 Part and the ITT population of Phase 2b/3 Part.

9.4.5.9 Time to Less Than $LLOD_{95}$ of SARS-CoV-2 Viral RNA

This is defined as the time from the start of the study intervention to when less than $LLOD_{95}$ viral RNA (less than 2.27 $\log_{10}$ copies/mL) is confirmed after first administration of study intervention. The same analyses as the key secondary efficacy endpoint 2 in Section 9.4.2.2.1 (except for multiplicity adjustment) will be performed in the ITT population with < 72 hours from the onset of COVID-19 to randomization in Phase 3 Part and the ITT population in Phase 2b/3 Part.

9.4.5.10 [redacted]

9.4.6 Disposition of Participant Population

Analyses will be performed in the randomized population separately for Phase 2a Part, Phase 2b Part, Phase 3 Part, Phase 2b/3 Part, and these parts combined. As for each combined population, analyses will be performed separately for the mild/moderate SARS-CoV-2 infection population and the asymptomatic/mild symptoms only SARS-CoV-2 infection population.

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.

9.4.7 Demographic and Baseline Characteristics

Analyses will be performed in the ITT population or ITT1 population (Phase 2b Part only) and safety population for Phase 2a Part, Phase 2b Part, Phase 3 Part, Phase 2b/3 Part, and the combined one of these parts. In Phase 3 Part, analyses will also be performed in the population with < 72 hours from the onset of COVID-19 to randomization out of the ITT population. As for each combined population, analyses will be performed separately for the mild/moderate SARS-CoV-2 infection population, the asymptomatic/mild symptoms only SARS-CoV-2 infection population, and the combined population.

Demographic and baseline characteristics will be summarized by treatment group using descriptive statistics.

9.4.8 Medical Histories and Complications

Participants with medical histories and complications will be listed separately for Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part.

9.4.9 Prior and Concomitant Therapies

Analyses will be performed separately for Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part. Prior medications will be coded using the WHO Drug Dictionary, and the number of participants who received each medication will be tabulated by treatment group in the ITT population or ITT1 population (Phase 2b Part only) and the safety population. The same tabulation will be performed for prior therapies. Participants who received prior therapies will be listed for the safety population. The same analyses as the prior medications and therapies will be performed for concomitant medications and therapies. Analyses will be performed separately for the mild/moderate SARS-CoV-2 infection population and the asymptomatic/mild symptoms only SARS-CoV-2 infection population.

9.4.10 Treatment Compliance

Analyses will be performed separately for Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part. Whether or not study intervention was administered will be tabulated in

the randomized population. Summary statistics of the number of days of administration of study intervention and the compliance rate will be calculated by treatment group for the ITT population or ITT1 population (Phase 2b Part only) and the safety population. Analyses will be performed separately for the mild/moderate SARS-CoV-2 infection population and the asymptomatic/mild symptoms only SARS-CoV-2 infection population.

9.5 Interim Evaluation

In this study, no interim analysis will be performed in Phase 2a Part for the purpose of discontinuing the study or changing the study design, but analysis including viral titer and viral amount of viral RNA will be performed as needed in all participants with mild/moderate or asymptomatic SARS-CoV-2 infection in Phase 2a Part for the purpose of early confirmation of the antiviral effect of S-217622. At this time, given that the measurement of viral titers and amount of viral RNA would reveal blindedness of the study, they will be measured by anonymizing the participants. The analysis of Phase 2a Part will be performed during the enrollment of Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part, and the dose selection of Phase 3 Part and Phase 2b/3 Part may be considered. In addition, measurement and analysis of the drug concentration may be performed as needed for S-217622 125 mg group and S-217622 250 mg group only in Phase 2a Part. At this time, information of the drug concentration will be treated under blind. The procedures for measurements and analysis are specified in a separate procedure manual. In addition, a document that specifies who can access the results of the analysis will be fixed before performing the analysis.

Unblind interim evaluations may be performed several times under unblinded fashion in Phase 2a Part to confirm efficacy and safety of S-217622 at an early stage. It will be performed based on the results collected by when all participants have been observed on Day 9, by approximately 4 weeks after the initiation of Phase 2a Part. Since interim evaluations will be performed along with unblinding, the manual of interim evaluations will be prepared and finalized before the first one is performed. The manual will define folders that store allocation information and results of interim evaluations, and people who can access them.

9.6 Interim Analysis for the Purpose of Stopping for Efficacy (Phase 2b/3 Part)

For the participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in Phase 2b/3 Part, an interim analysis for the purpose of stopping for efficacy is planned depending on the enrollment rate. The interim analysis plan is summarized below:

- The interim analysis will be made on the primary analysis of the primary endpoint, the key secondary endpoint 1, and the key secondary endpoint 2 of Phase 2b/3 Part.
- The number of analyses shall be 2 in total including the final analysis (1 interim analysis), and the interim analysis will be performed for the purpose of stopping for efficacy when the follow-up has been completed in 50% of the target sample

size.

- As the criteria for stopping for efficacy based on the α-spending function, the O'Brien–Fleming boundary will be adopted for the primary analysis of the primary endpoint and the Pocock boundary will be adopted for the primary analysis of the key secondary endpoint 1 and the key secondary endpoint 2. The nominal significance level which corresponds to the rejection region in the interim analysis and the final analysis will be calculated based on the information fraction for each endpoint at the time of interim analysis.
- If the dose selection is to be made, the interim analysis will be performed after the dose selection.

9.7 Data and Safety Monitoring Board

In this study, the Data and Safety Monitoring Board will be established for the purpose of third-party evaluation of safety throughout the study period. The details of the organization, roles, responsibilities, processes, and safety evaluation methods will be specified separately in the procedure manual of the Data and Safety Monitoring Board.

9.8 Independent Data Monitoring Committee (IDMC)

The IDMC will be established for the interim analyses which are described in Section 9.1.3. It will control such unblinded information as the results of key code break and analysis which may have an impact on the conduct or evaluation of Phase 2b/3 Part. The governance, role, and detailed operations of the IDMC, timing to determine whether the interim analysis is to be performed or not, judgement criteria of the interim analysis including enrollment rates, and stopping criteria for efficacy will be stipulated in the standard operation procedures of IDMC in advance and will be finalized before performing the interim analysis. In addition, the standard operation procedures of interim analysis which defines the procedures and methods to perform interim analyses under the strictly controlled information status in the unblinded fashion, including stopping for efficacy or the scope of information disclosure when recommending continuation of the study, will also be prepared and will be finalized before performing the interim analysis.

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 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
- The protocol, protocol amendments, ICF/assent, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated. Competent authority notification, review and approval may be required as appropriate according to requirements.
- Any amendments to the protocol will require competent authority and/or IRB approval (as appropriate) before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to ICH guidelines, the IRB, and all other applicable regulations
  - Reporting cases of suspected child abuse and/or neglect according to local regulations for minor participants

10.1.2 Financial Disclosure

- Investigators/subinvestigator 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/subinvestigator is 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, subinvestigator, or his/her representative must explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign an ICF that meets regulatory, ICH guidelines, and IRB or site requirements.
- The medical record must include a statement that written informed consent was obtained before the 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.
- 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 must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.
- This study is for participants with SARS-CoV-2 infection. As of September 2021, COVID-19 is classified as Pandemic Influenza (Novel Influenza or Re-emerging Influenza) in Infectious Disease Law, and needed specific measures. Therefore, the nature of the study may be explained remotely and informed consent may be obtained via an online examining system. In that case, after the investigator/subinvestigator records a statement that written informed consent was obtained and the time on the source document, the participant can be enrolled. After that, investigator/subinvestigator will sign on the ICF as soon as possible. If the date is different between obtaining and signature, investigator/subinvestigator records that situation on the ICF.

10.1.3.1 For Minor Participants

- Participants must be informed that their participation is voluntary. Participants or their legally acceptable representative will be required to provide a statement of informed consent/assent that meets the requirements of local regulations, ICH guidelines, where applicable, and the IRB or study center.
- The medical record must include a statement that legally acceptable representative consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained before the 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 participant's legally acceptable representative. The acceptable person obtaining the informed consent must also sign the ICF.
- Participants and their legally acceptable representative must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.
- Minor 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 participant or the participant's legally acceptable representative.

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 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 members, and by inspectors from regulatory authorities.

10.1.5 Study Administrative Structure

Sponsor	Shionogi & Co., Ltd. (head office) 1-8, Doshomachi 3 chome, Chuo-ku, Osaka 541-0045, Japan
Sponsor contact information	[redacted]
Emergency contact	[redacted]
Sponsor's Chief Medical Officer	[redacted]
Medical Monitor	[redacted]
Medical Expert	[redacted]
Coordinating Investigator	[redacted]
Data and Safety Monitoring Board	[redacted]

Independent Data Monitoring Committee	[redacted]
Study Sites and Investigators	Described in the attachment
Clinical Research Associate	Described in the attachment
Contract organization for monitoring, data management, and statistical analysis	[redacted]
Monitoring	[redacted]
Laboratory for measurement of virological test (nasopharyngeal swab)	[redacted]
Laboratory test measurement facility	[redacted]
Drug concentration measurement laboratory	[redacted]
Laboratory for measurement of neutralizing antibody titer Laboratory for cedar/cypress allergy test	[redacted]

10.1.6 Dissemination of Clinical Study Data

The information and results of this study will be disclosed at the clinical study registration site and other sites.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on an eCRF 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 physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

- 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, Contract Research Organizations [CROs]).
- Study monitors will perform ongoing source data verification to confirm that data entered into 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.
- Records and documents, including signed ICFs/assents, pertaining to the conduct of this study must be retained by the investigators and study sites for the longest period of the following, unless regulations or institutional policies require a longer retention period.
  - Until the date of approval of manufacture and sale of the study intervention or for 3 years after the decision of discontinuation of further development
  - For 3 years after discontinuation or completion of the study
- If the retention period needs to be extended beyond the above period, the retention period may be extended upon agreement with the sponsor. If the investigator withdraws from the responsibility of retaining the study records, custody must be transferred to an appropriate person willing to accept the responsibility. 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 trial).

10.1.9 Study and Site Start and Closure

The start date of the study is defined as the date of informed consent obtained from the first participant. The end of study is defined as the date of the last visit of the last participant in the exploratory period.

The sponsor/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.

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:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator/subinvestigator 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/subinvestigator 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 by the laboratory test measurement facility listed in Section 10.1.5.
- Local laboratory results are only required in the event that the laboratory test measurement facility results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for the laboratory test measurement facility is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- 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/subinvestigator or required by regulations.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator/subinvestigator or required by regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- The investigator/subinvestigator must review each laboratory report and document it in the eCRF.

Table 10-1 Protocol-required Safety Laboratory Assessments

Laboratory assessments	Parameters
Hematology	Platelet count, red blood cell count, hemoglobin, hematocrit Red blood cell index (MCV, MCH, reticulocyte count), white blood cell count, differential white blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Blood chemistry[a]	AST, ALT, total bilirubin and direct bilirubin, γ-GTP, LDH, ALP, uric acid, cholinesterase, total protein, albumin, BUN, serum creatinine, sodium, potassium, chloride (Cl), calcium, phosphorus, total cholesterol, blood glucose (fasting), HDL-C, LDL-C, TG, CRP, CK, iron, ferritin, UIBC
Coagulation test	PT-INR, APTT, fibrinogen
Serology	IgG, IgM, haptoglobin
Urinalysis	pH, glucose, protein (qualitative), occult blood, ketones, bilirubin, urobilinogen
Other	[redacted]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CCL = C-C motif ligand; CK = creatine kinase; CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; [redacted]; IgG = immunoglobulin G; IgM = immunoglobulin M; [redacted] INR = international normalized ratio; [redacted] LDH = lactate dehydrogenase; LDL-C = low-density lipoprotein cholesterol; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; [redacted]; TG = triglycerides; UIBC = unsaturated iron binding capacity; ULN = upper limit of normal; γ-GTP = γ-glutamyltransferase

a Details of liver chemistry stopping criteria and suggested actions and follow-up assessments after liver stopping are given in Section 7.1.1 and 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 patient or clinical study participant, temporally associated with the use of study intervention, 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) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (eg, hematology, blood chemistry, or urinalysis) or other safety assessments (eg, 12-lead ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator/subinvestigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- 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 which are associated with the underlying disease, unless judged by the investigator/subinvestigator 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.
- Hospitalization for preplanned and elective procedures to treat a pre-existing condition that did not worsen after start of study will not be considered an AE, and therefore will not be considered an SAE despite requiring hospitalization. The exception is when the patient experiences another event which is fatal, is life-threatening, results in disability, leads to prolonged hospitalization or is considered to be medically significant 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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. Note that hospitalization for signs/symptoms of the primary disease (SARS-CoV-2 infection) is not considered an SAE.

An SAE is defined as any untoward medical occurrence that, at any dose:

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 detained (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 pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent 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), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other medically important condition:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, 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/subinvestigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator/subinvestigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator/subinvestigator to send photocopies of the participant's medical records to the sponsor 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. 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.
- The investigator/subinvestigator 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 Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator/subinvestigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The relationship of an event to the study intervention will be determined by the investigator/subinvestigator 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.
- The investigator/subinvestigator will use clinical judgment to determine the relationship.

- 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/subinvestigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- The investigator/subinvestigator should provide rationale for the causality assessment in the Medical Comment field in EDC or if reporting via paper, the rationale for causality should be provided in the narrative section of paper SAE form.
- There may be situations in which an SAE has occurred and the investigator/subinvestigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator/subinvestigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator/subinvestigator 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/subinvestigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor 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 health care professionals.
- If a participant dies during the study or the follow-up period, the investigator/subinvestigator will provide the sponsor with a copy of autopsy findings including histopathology findings.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator/subinvestigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

All SAEs must be reported to the sponsor in detail on the SAE form within 24 hours from the time point when the investigator/subinvestigator first becomes aware of the SAE.

SAE Reporting to the sponsor via the SAE form

- For SAE information, prepare an SAE form and send it by fax, e-mail, or other ways to the sponsor.
- In rare circumstances (eg, in the absence of facsimile nor mailing equipment), notification by telephone is acceptable with a copy of the SAE form sent by overnight mail or courier service.
- Even if the initial notification via telephone is completed, the investigator/subinvestigator must prepare and sign an SAE form within the designated reporting time frames.
- Contact for SAE is presented in "Sponsor contact information" (Section 10.1.5).

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:
Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

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 hormonal 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 one of the nonestrogen hormonal highly 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.

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]
● 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.)*
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 Male condoms must be used in addition to hormonal contraception. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

Collection of Pregnancy Information

Male participants with partners who become pregnant

- If a female partner of a male participant becomes pregnant while the male participant is in this study, the investigator/subinvestigator should discontinue the study intervention for the participant and make efforts to collect the partner's pregnancy information. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator/subinvestigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination

of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator/subinvestigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial pregnancy information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- 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.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any pregnancy after follow-up period related SAE considered reasonably related to the study intervention by the investigator/subinvestigator will be reported to the sponsor as described in Section 8.3.4. While the investigator/subinvestigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 Appendix 5: Liver Safety: Suggested Actions and 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>ALT</td><td>ALT ≥ 5 × ULN</td></tr>
<tr><td>Duration of ALT elevation</td><td>ALT ≥ 3 × ULN persists for ≥ 4 weeks</td></tr>
<tr><td>Bilirubin[1,2]</td><td>ALT ≥ 3 × ULN AND bilirubin ≥ 2 × ULN (> 35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3 × ULN AND INR > 1.5, if INR obtained</td></tr>
<tr><td>Monitoring not possible</td><td>ALT ≥ 3 × ULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptoms[3]</td><td>ALT ≥ 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 “SAE” page if the event also meets the criteria for an SAE[2].
● 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 ≥ 3 × ULN AND bilirubin ≥ 2 × ULN or INR > 1.5:
● Repeat liver function tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform</td><td>● Viral hepatitis serology[4]
● Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend.
● If the study is discontinued during the treatment period, collect blood for measurement of plasma concentrations to measure the plasma concentrations of S-217622[5].
● 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 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>

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 ≥ 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 ≥ 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) [14]) ● Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete the Liver Event Form.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥ 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.
2. **All** events of ALT ≥ 3 × ULN **AND** bilirubin ≥ 2 × ULN (>35% direct bilirubin) or ALT ≥ 3 × ULN **AND** INR > 1.5 may indicate severe liver injury (possible 'Hy's Law') and **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. 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).
4. 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 IgA antibody.
5. 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 × ULN ≤ ALT ≤ 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 10.5 will be followed. ● If, after 4 weeks of monitoring, ALT < 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 Symptom Score

COVID-19 symptoms score will be evaluated using a partially modified index with reference to the FDA guidance [13].

Example of an Assessment of 14 Common COVID-19-Related Symptoms: Items and Response Options

Example items *For items 1–10, sample item wording could be: "What was the severity of your [insert symptom] at its worst over the last 24 hours?"*	**Example response options and scoring***
1. Stuffy or runny nose	None = 0 Mild = 1 Moderate = 2 Severe = 3
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	
11. Vomiting (throw up)	
12. Diarrhea (loose or watery stools)	
13. Rate your sense of **smell** in the last **24 hours**	My sense of smell is THE SAME AS usual = 0 My sense of smell is LESS THAN usual = 1 I have NO sense of smell = 2
14. Rate your sense of **taste** in the last **24 hours**	My sense of taste is THE SAME AS usual = 0 My sense of taste is LESS THAN usual = 1 I have NO sense of taste = 2

* Note: Score values are included in the table for ease of reference. FDA cautions against including the score values within the response options presented to trial subjects to avoid confusing subjects.

10.7 Appendix 7: 8-Point Ordinal Scale

Each score of 8-Point Ordinal Scale is based on the following conditions.

Descriptor	Score
Asymptomatic	0
Symptomatic, no limitation of activities	1
Symptomatic, limitation of activities	2
Hospitalized, no oxygen therapy	3
Hospitalized, with oxygen therapy (< 5 L/min)	4
Hospitalized, with oxygen therapy (≥ 5 L/min)	5
Hospitalized, with ventilation	6
Death	7

10.8 Appendix 8: 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

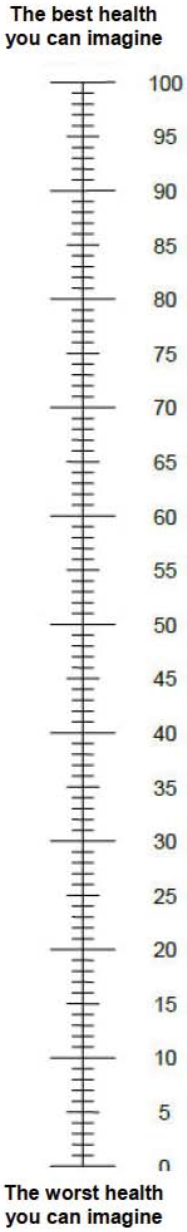
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- **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

10.9 Appendix 9: Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}24hr}$	area under the plasma concentration-time curve from time 0 to 24 hour
$AUC_{0\text{-}\tau}$	area under the plasma concentration-time curve over the dosing interval τ
BCRP	breast cancer resistance protein
C_{24}	plasma concentration at 24 hours after the administration
CI	confidence interval
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiograph(y)
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5 dimensions 5-level
FSH	follicle stimulating hormone
GCP	good clinical practice
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intention-to-treat
LAMP	loop-mediated isothermal amplification

LDH	lactate dehydrogenase
MATE	multidrug and toxin extrusion
mITT	modified intention-to-treat
MRT	mean residence time
N	number
OATP	organic anion transporter polypeptide
OCT	organic cation transporter
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
RMST	restricted mean survival time
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAP	statistics analysis plan
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SpO_2	saturation of percutaneous oxygen
TEAE	treatment-emergent adverse event
TMA	transcription mediated amplification
ULN	upper limit of normal

10.10 Appendix 10: Investigator's Signature

Study Title	: A Phase 2/3 Study of S-217622 in Participants Infected with SARS-CoV-2
Study Number	: 2108T1221
Date of Original	: [redacted]
Date of Latest Amendment	: 20 Sep 2022

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:_____

Name of Medical Institution	:
Name of Investigator	:

11. REFERENCES

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Statistical Analysis Plan

Study Title:	A Phase 2/3 study of S-217622 in participants infected with SARS-CoV-2
Study Number:	2108T1221
Product Name:	S-217622
Version Number:	7.0

SIGNATURE PAGE

Company Name	Approver	Date
Shionogi & Co., Ltd. Biostatistics Center	[redacted] (Refer to the flag page)	Refer to the flag page
EPS Corporation Data Science Center	[redacted] (Refer to the flag page)	Refer to the flag page

RECORDS ON REVISIONS

Document History

Version	Date	Author	Memo
1.0	[redacted]	[redacted]	
2.0	[redacted]	[redacted]	Dealing with protocol version 5 change Description adjustment
3.0	[redacted]	[redacted]	Change test for primary endpoint in Phase 2a Part Description adjustment
4.0	[redacted]	[redacted]	Description adjustment
5.0	[redacted]	[redacted]	Description adjustment Dealing with protocol version 7 change
6.0	[redacted]	[redacted]	Description adjustment Dealing with protocol version 8 change
7.0	[redacted]	[redacted]	Description adjustment Dealing with protocol version 10 change

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence Interval
CK	Creatine kinase
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRP	C-reactive protein
ECG	Electrocardiogram
GGT	Gamma glutamyl transpeptidase
GMT	Geometric mean antibody titer
HDL-C	High Density Lipoprotein cholesterol
ICF	Informed consent form
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
ITT	Intention-to-treat
KL	Krebs von den Lungen
LDH	Lactate dehydrogenase
LDL-C	Low Density Lipoprotein cholesterol
$LLOD_{95}$	Lowest amount of virus that could be detected with a positivity rate greater than 95% by probit analysis
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified intention-to-treat
N	Number of non-missing observations
PCR	Polymerase Chain Reaction
PT INR	Prothrombin time international normalized ratio
QOL	Quality of life
RMST	Restricted mean survival time
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SpO_2	Oxygen saturation
TARC	Thymus and activation-regulated chemokine
TEAE	Treatment-emergent adverse event
UIBC	Unsaturated iron binding capacity

WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data handlings to be employed for the analysis of the study Protocol 2108T1221, Version 9 dated 8 July 2022. Table, listing and figure mock-ups are provided in the TLF shells prepared separately. This document is provided for Phase 2a Part, Phase 3 Part and Phase 2b/3 Part in this study, and the SAP for Phase 2b Part is prepared as a separated document.

All the analyses described in the SAP will be performed in the EPS Corporation. Any deviations from the SAP will be documented in the clinical study report.

2. OVERVIEW

This study consists of 4 parts that are Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part. Phase 2a Part consists of the 2 populations in participants with mild/moderate and asymptomatic SARS-CoV-2 infection. Phase 2b Part and Phase 3 Part are for participants with mild/moderate SARS-CoV-2 infection (cohort to evaluate time to improvement: Cohort A), and Phase 2b/3 Part is for participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort to evaluate development/worsening: Cohort B), respectively. This study is a multi-center, randomized, double-blind, placebo-controlled study. This study consists of 3 group of S-217622 125 mg group, S-217622 250 mg group and placebo group.

After completion of participants enrollment in Phase 2a Part, participants enrollment in Phase 2b Part and Phase 2b/3 Part will be started. After enrollment of Phase 2b Part is completed, enrollment of Phase 3 Part will be initiated. During the enrollment in Phase 3 Part and Phase 2b/3 Part, the dose selection for Phase 3 Part and/or Phase 2b/3 Part may be done based on the results of the Phase 2a Part and/or Phase 2b Part. After selection of dosage, only selected dosage group and placebo group will be continued enrollment of participants.

The study will consist of the following 3 periods.

- Treatment period (Day 1 to 5)
- Follow-up period (Day 6 to 28)
- Exploratory period (Day 29 to 337)

The study design is shown in Figure 2-1.

Figure 2-1 Study Design

Screening	Treatment					Follow-up					Exploratory**		
	V1	V2	Op V1	V3	Op V2	V4	V5	V6	V7	V8	V9	V10	V11
	Day 1	Day 2	Day 3*	Day 4	Day 5*	Day 6	Day 9	Day 14	Day 21	Day 28	Day 85	Day 169	Day 337
	Randomization (Day 1)												
		Multiple Administration (Day 1 to Day 5)											

*Day 3 and Day 5 are optional visit (excluding administration of study intervention and participant-reported outcomes).
**Only participants who consent/assent to participate in the Exploratory period will be conducted.

3. STUDY OBJECTIVES

3.1 Primary Objective(s)

The primary objectives of this study are as follows.

3.1.1 Phase 2a Part

3.1.1.1 Participants with Mild/Moderate and Asymptomatic SARS-CoV-2 infection

- To investigate the antiviral effect of multiple doses of S-217622 for 5 days in SARS-CoV-2-infected participants.

3.1.2 Phase 3 Part

3.1.2.1 Participants with Mild/Moderate SARS-CoV-2 infection

- To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with mild/moderate SARS-CoV-2 infection who were randomized within 72 hours from COVID-19 onset, based on the time to resolution of the 5 COVID-19 symptoms.

3.1.3 Phase 2b/3 Part

3.1.3.1 Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 infection

- To compare the effect of 5-day administration of S-217622 on preventing development or worsening of symptoms with that of placebo in participants with SARS-CoV-2 infection.

3.2 Secondary Objective(s)

3.2.1 Phase 2a Part

3.2.1.1 Participants with Mild/Moderate and Asymptomatic SARS-CoV-2 infection

- To investigate the antiviral effect of multiple-dose administration of S-217622 for 5 days other than primary endpoint in SARS-CoV-2-infected participants.

- To investigate the effect to prevent aggravation following multiple-doses of S-217622 for 5 days in SARS-CoV-2-infected participants.

- To investigate the QOL of multiple-dose administration of S-217622 for 5 days to SARS-CoV-2-infected participants.

- To confirm the pharmacokinetics of multiple-dose administration of S-217622 for 5 days to SARS-CoV-2-infected participants.

- To investigate the safety and tolerability of multiple-dose administration of S-217622 for 5 days to participants infected with SARS-CoV-2.

3.2.1.2 Participants with Mild/Moderate SARS-CoV-2 infection

- To investigate the effect on the symptomatic improvement of multiple-dose administration of S-217622 for 5 days to SARS-CoV-2-infected participants.

3.2.1.3 Participants with Asymptomatic SARS-CoV-2 infection

- To investigate the effect on preventing onset of multiple-dose administration of S-217622 for 5 days to SARS-CoV-2-infected participants.

3.2.2 Phase 3 Part (Participants with Mild/Moderate SARS-CoV-2 infection)

3.2.2.1 Key Secondary Objective(s)

The key secondary objectives of this study are as follows.

- To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection who were randomized within 72 hours from COVID-19 onset, based on the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA.
- To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection who were randomized within 72 hours from COVID-19 onset, based on time to the first negative SARS-CoV-2 viral titer.
- To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in all randomized participants with mild/moderate SARS-CoV-2 infection, based on the time to resolution of the 5 COVID-19 symptoms.
- To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in all randomized participants with SARS-CoV-2 infection, based on the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA.
- To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in all randomized participants with SARS-CoV-2 infection, based on time to the first negative SARS-CoV-2 viral titer.

3.2.2.2 Other Secondary Objective(s)

The other secondary objectives of this study are as follows.

- To compare the effect in improving clinical symptoms following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.

- To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.

- To compare the effect to prevent aggravation following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.

- To compare QOL following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.

- To confirm the pharmacokinetics following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.

- To compare the safety and tolerability following 5-day administration of S-217622 with those of placebo in participants with SARS-CoV-2 infection.

3.2.3 Phase 2b/3 Part (Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection)

3.2.3.1 Key Secondary Objective(s)

The key secondary objectives of this study are as follows.

- To compare the antiviral effect following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection, based on the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA.
- To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection, based on time to the first negative SARS-CoV-2 viral titer.

3.2.3.2 Other Secondary Objective(s)

The other secondary objectives of this study are as follows.

- To investigate the preventive effect of 5-day administration of S-217622 in participants with asymptomatic SARS-CoV-2 infection.

- To compare the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.

- To compare the effect to prevent aggravation following 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.

- To compare QOL following 5-day administration of S-217622 with that of placebo

in participants with SARS-CoV-2 infection.

- To confirm the pharmacokinetics following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.

- To compare the safety and tolerability following 5-day administration of S-217622 with those of placebo in participants with SARS-CoV-2 infection.

3.3 Exploratory Objective(s)

The exploratory objectives of this study are as follows.

3.3.1 Phase 2a Part

3.3.1.1 Participants with Mild/Moderate and Asymptomatic SARS-CoV-2 infection

- To evaluate the amino acid substitutions in 3CL protease (nsp5) cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.

- To evaluate the immunocompetence of participants infected with SARS-CoV-2.

- To evaluate the effects on severity markers of multiple-dose administration of S-217622 for 5 days to participants infected with SARS-CoV-2.

- To investigate the effects on post-acute COVID-19 syndrome of multiple-dose administration of S-217622 for 5 days to participants infected with SARS-CoV-2.

3.3.2 Phase 3 Part (Participants with Mild/Moderate SARS-CoV-2 infection)

- To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infection.

- To perform polymorphism analysis of 3CL protease (nsp5) for participants with SARS-CoV-2 infection.

- To evaluate the amino acid substitutions in 3CL protease (nsp5) and its cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.

- To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participant's specimen.

- To evaluate immunity in participants with SARS-CoV-2 infection.

- To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection.

- To investigate the effect on post-acute COVID-19 syndrome following 5-day

administration of S-217622 in participants with SARS-CoV-2 infection.

- To explore the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.

3.3.3 Phase 2b/3 Part (Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection)

- To analyse SARS-CoV-2 lineage for participants with SARS-CoV-2 infection.
- To perform polymorphism analysis of 3CL protease (nsp5) for participants with SARS-CoV-2 infection.
- To evaluate the amino acid substitutions in 3CL protease (nsp5) and its cleavage site following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.
- To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participant's specimen.
- To evaluate immunity in participants with SARS-CoV-2 infection.
- To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection.
- To investigate the effect on post-acute COVID-19 syndrome following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.
- To explore the antiviral effect of 5-day administration of S-217622 with that of placebo in participants with SARS-CoV-2 infection.

4. STUDY DESIGN

4.1 Study Schedule

This study consists of Treatment Period (Day 1 ~ 5), Follow-up Period (Day 6 ~ 28) and Exploratory Period (Day 29 ~ 337). Day 3 and Day 5 are optional visit. The study schedule is shown in Appendix 1.

4.2 Study Blinding and Randomization

This study will be conducted as a double-blind study using a placebo that is indistinguishable from S-217622 in appearance, labeling and packaging. Participants who are qualified will be randomized to either S-217622 125 mg, S-217622 250 mg, or placebo in a ratio of 1 : 1 : 1 using the interactive response technology (IRT) system.

Randomization for participants with mild/moderate SARS-CoV-2 infection will be stratified using the time to randomization from onset of COVID-19 (< 72 hours or ≥ 72

hours) and the presence or absence of COVID-19 vaccination. Randomization for participants with asymptomatic SARS-CoV-2 infection will be stratified using the presence or absence of COVID-19 vaccination.

The stratification using presence or absence of COVID-19 vaccination will be conducted by whether first vaccination finished. For the time to randomization from onset of COVID-19 and the presence or absence of COVID-19 vaccination as stratification factors, the data entered in IRT will be used.

At interim assessment of Phase 2a Part, after Phase 2a Part completion and after study completion, the study drug allocation list will be obtained from the IRT after all the eCRF data are fixed.

In Phase 3 Part and Phase 2b/3 Part in which enrollment and follow-up has completed first, unblinding will be permitted for the Part. If an interim analysis is performed, the study intervention allocation table will be submitted to the IDMC.

4.3 Sample Size

4.3.1 Phase 2a Part

The sample size of participants with mild/moderate and asymptomatic SARS-CoV-2 infection whose virus titer of SARS-CoV-2 before administration is positive in Phase 2a Part is 11 participants / group.

In the phase 2a study of Molnupiravir, the virus titer was detected in 44% (74/170) of participants who assessed the baseline virus titer [1]. Assuming that the proportion of the participants with positive result of RT-PCR test and detectable virus titer at baseline is about 50%, the sample size of participants with mild/moderate and asymptomatic SARS-CoV-2 infection in Phase 2a Part was calculated to be 69 participants (23 participants / group).

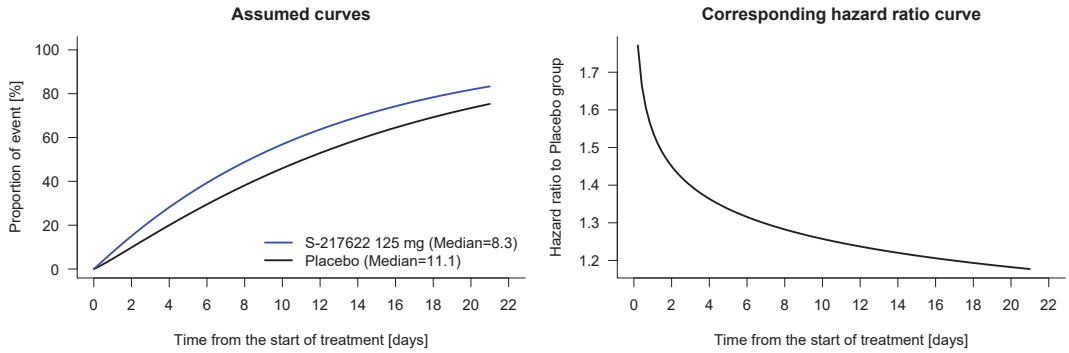
4.3.2 Phase 3 Part (Participants with Mild/Moderate SARS-CoV-2 infection)

For mild/moderate SARS-CoV-2 infected participants in Phase 3 Part, the population of SARS-CoV-2 infected participants with less than 72 hours from COVID-19 onset to randomization is the primary analysis population. Therefore, the required number of subjects was considered in this population. The primary analysis for the primary endpoint in Phase 3 Part in mild/moderate SARS-CoV-2 infected participants is to compare the time of resolution of the 5 COVID-19 symptoms of in a population with <72 hours from COVID-19 onset to randomization between the S-217622 125 mg group and the placebo group.

First, a comparison between the S-217622 125 mg group and the placebo group in the time to resolution of the 5 COVID-19 symptoms will be performed. In the population of SARS-CoV-2 infected participants with less than 72 hours from COVID-19 onset to randomization in Phase 2b Part, referring to the Kaplan-Meier curve of the time to resolution of the 5 COVID-19 symptoms and considering the possibility of observing the

conservative treatment effect in the active drug group, the Weibull distribution for the time to resolution of the 5 COVID-19 symptoms was assumed as shown in Figure. X. The assumed median times correspond to 8.3 days in the S-217622 125 mg group and 11.1 days in the placebo group.

Figure X. Plots of Weibull distribution and hazard ratio assumed in calculation of sample size for Phase 3 Part for the time to resolution of the 5 COVID-19 symptoms.



The number of participants required to detect this difference with a power of 80% using the Peto-Prentice's generalized Wilcoxon test with a one-sided significance level of 0.025 was calculated to be 230 per group as participants with than 72 hours from onset to randomization. Based on this, assuming about 10% of dropouts due to negative RT-PCR in the test immediately before enrollment, the number of participants with less than 72 hours from COVID-19 onset to randomization to be enrolled was 260 per group and a total of 780 participants in the 3 groups.

4.3.3 Phase 2b/3 Part (Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection)

Proportion of participants who were positive of RT-PCR test and completed the follow-up period without symptoms of SARS-CoV-2 was reported approximately 70% [3]. In this study, the proportion of participants with development/worsening of COVID-19 symptoms in the placebo group in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in Phase 2b/3 Part was conservatively estimated to be 20%. The proportion of participants with development/worsening of COVID-19 symptoms in each S-217622 treatment groups was assumed to be 8% (risk ratio of 0.4 to placebo).

4.3.3.1 In case of performing an interim analysis

In case of performing an interim analysis for the purpose of stopping for efficacy, the number of participants required at the time of final analysis was calculated to be a total of 438 (146 per group) participants with asymptomatic/mild symptoms only SARS-CoV-2 infection for the 3 groups assuming the information fraction for the primary endpoint is 50% at the time of interim analysis and that the criteria for stopping for efficacy are adopted using the O'Brien–Fleming boundary based on α-spending function. The

nominal significance level calculated from the significance level (one-sided 0.025) allocated to a comparison between S-217622 125 mg group and the placebo group was used in order to detect these differences with the power of 80% in Wald test for the risk ratio. In addition, assuming that the drop-out rate due to a negative RT-PCR result in the test immediately before enrollment would be approximately 10%, the required number of enrolled participants with asymptomatic/mild symptoms only SARS-CoV-2 infection was calculated to be 495 (165 per group).

4.3.3.2 In case of not performing an interim analysis

Since multiplicity adjustment by the Bonferroni method is planned, the sample size required to detect these differences with 80% power using a Fisher's exact test at a one-sided significance level of 0.025 was calculated to be 429 participants (143 participants/group) in all 3 groups of participants with asymptomatic/mild symptoms only SARS-CoV-2 infection. Assuming that the dropout rate due to a negative RT-PCR result immediately before enrollment would be approximately 10%, the sample size of participants with asymptomatic/mild symptoms only SARS-CoV-2 infection to be enrolled was calculated to be 480 participants (160 participants/group).

4.4 Study Intervention

The following groups will be performed.

Table 4.1 Participant Breakdown (Part 2a Part)

Group	Dosage		Target participants	Number of participants	Total
	loading dose	maintenance dose			
S-217622 125 mg	375 mg	125mg	Mild/Moderate SARS-CoV-2 or Asymptomatic SARS-CoV-2	23	69
S-217622 250 mg	750 mg	250 mg	Mild/Moderate SARS-CoV-2 or Asymptomatic SARS-CoV-2	23	
Placebo	---	---	Mild/Moderate SARS-CoV-2 or Asymptomatic SARS-CoV-2	23	

Table 4.2 Participant Breakdown (Part 3 Part)

Group	Dosage		Target participants*	Number of participants	Total
	loading dose	maintenance dose			
S-217622 125 mg	375 mg	125 mg	Mild/Moderate SARS-CoV-2	260	780
S-217622 250 mg	750 mg	250 mg	Mild/Moderate SARS-CoV-2	260	
Placebo	---	---	Mild/Moderate SARS-CoV-2	260	

* Time from COVID-19 onset to randomization: less than 72 hours

Table 4.2 Participant Breakdown (Part 2b/3 Part)

Group	Dosage		Target participants	Number of participants*	Total*
	loading dose	maintenance dose			
S-217622 125 mg	375 mg	125 mg	Asymptomatic/mild symptoms only SARS-CoV-2	165 [160]	495 [480]
S-217622 250 mg	750 mg	250 mg	Asymptomatic/mild symptoms only SARS-CoV-2	165 [160]	
Placebo	---	---	Asymptomatic/mild symptoms only SARS-CoV-2	165 [160]	

* : [ ] indicates the number of participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in case no interim analysis is to be performed (the same applies to the brackets below).

5. ANALYSIS POPULATIONS

The analysis population in this study is defined as follows.

5.1 Enrolled Participants

All participants who signed on the informed consent form (ICF).

5.2 All Randomized Participants

All participants randomly assigned to the study intervention.

5.3 Intention-to-Treat Population

Intention-to-Treat (ITT) Population is defined as all participants who were randomized to the study intervention and were confirmed of infection with SARS-CoV-2. The infection with SARS-CoV-2 will be confirmed by RT-PCR result at Visit 1 (pre-intervention) based on nasopharyngeal swab sample. Participants will be analyzed according to the assigned study intervention.

5.4 Intention-to-Treat 1 Population

Intention-to-Treat 1 (ITT1) Population is defined as all participants who were randomized to the study intervention and whose SARS-CoV-2 virus titer were detected at the baseline. SARS-CoV-2 virus titer at baseline will be confirmed based on nasopharyngeal swab sample. Participants will be analyzed according to the assigned study intervention.

5.5 Modified Intention-to-Treat Population

Modified Intention-to-Treat (mITT) Population includes all participants who met following criteria.

- Randomly assigned to study intervention
- Confirmed of SARS-CoV-2 infection by RT-PCR
- Detected virus titer of SARS-CoV-2 at the baseline

The infection with SARS-CoV-2 and detection of virus titer of SARS-CoV-2 will be confirmed by RT-PCR result at baseline and virus titer assessment based on nasopharyngeal swab sample. Participants will be analyzed according to the assigned study intervention.

The infection with SARS-CoV-2 and detection of virus titer of SARS-CoV-2 will be confirmed by RT-PCR result and viral titer assessment based on nasopharyngeal swab sample. Participants will be analyzed according to the assigned study intervention.

5.6 Per Protocol Set

Per Protocol Set (PPS) includes all participants in the ITT or ITT1 Populations and without any important protocol deviations.

5.7 Safety Analysis Population

All participants randomly assigned to study intervention and who received at least 1 dose of study intervention. Participants will be analyzed according to the initial intervention they actually received.

5.8 PK Concentration Population

PK Concentration Population includes all participants who received at least one dose of S-217622 with at least one evaluable plasma concentration value.

6. STATISTICAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLINGS

6.1 Statistical Reporting

In general, continuous variables will be summarized by the number of non-missing observations, arithmetic mean, standard deviation (SD), median, minimum, and maximum values as summary statistics; categorical variables will be summarized by the frequency count and the percentage of participants in each category.

All analyses will be performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA).

6.2 Statistical Testing

All statistical tests will be performed using a two-sided significance level of 0.05 unless otherwise stated.

In Phase 3 Part for participants with mild/moderate SARS-CoV-2 infection and in Phase 2b/3 Part for participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, in the primary analyses of the primary endpoints and the key secondary endpoints, the type I error rate control will be applied. The type I error rate control will not be applied for the analyses in all endpoints in Phase 2a Part, or other secondary endpoints and exploratory endpoints in Phase 3 Part and Phase 2b/3 Part.

6.2.1 Phase 2b/3 Part (in case of performing an interim analysis for the purpose of stopping for efficacy)

When performing an interim analysis for the purpose of stopping for efficacy, with respect to the primary analyses of the primary endpoint, the key secondary endpoint (1) and the key secondary endpoint (2) in participants with asymptomatic/mild symptoms

only SARS-CoV-2 infection for the interim analysis and the final analysis, the same procedures are used for type I error rate control as when not performing the interim analysis for stopping for efficacy as described below. In comparison between S-217622 125 mg group and placebo group, this will be done following the fixed sequence procedure between endpoints. For the nominal significance level utilized in each comparison, the O'Brien–Fleming boundary will be adopted for the primary analysis of the primary endpoint and the Pocock boundary will be adopted for each primary analysis of the key secondary endpoint (1) and the key secondary endpoint (2) for the criteria for stopping for efficacy based on α-spending function. The significance level (one-sided 0.025) allocated to a comparison between S-217622 125 mg and placebo calculated based on the information fraction for each endpoint at the time of interim analysis will be used.

6.2.2 Phase 3 Part

For each primary analysis and key secondary analysis of the primary endpoint, the key secondary endpoint (1), and the key secondary endpoint (2) of participants with mild/moderate SARS-CoV-2 infection with less than 72 hours from COVID-19 onset to randomization and participants in the ITT Population or mITT Population, the type I error control using the fixed sequence procedure will be applied for each analysis in each endpoint in comparison of S-217622 125 mg group and placebo group. The pre-specified sequence of hypotheses for the fixed sequence procedure as follows.

1. Primary analysis of the primary endpoint: In the ITT Population with less than 72 hours from COVID-19 onset to randomization, time to resolution of the 5 COVID-19 symptoms will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

2. Primary analysis of the key secondary endpoint (1): In the ITT Population with less than 72 hours from COVID-19 onset to randomization, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #1, the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

3. Primary analysis of the key secondary endpoint (2): In the mITT Population with less than 72 hours from COVID-19 onset to randomization, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #2, the time to the first negative SARS-CoV-2 viral titer will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

4. Key secondary analysis of the primary endpoint: In the ITT Population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #3, time to resolution of the 5 COVID-19 symptoms will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

5. Key secondary analysis of the key secondary endpoint (1): In the ITT Population,

only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #4, the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

6. Key secondary analysis of the key secondary endpoint (2): In the mITT Population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #5, the time to the first negative SARS-CoV-2 viral titer will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

6.2.3 Phase 2b/3 Part (in case of not performing an interim analysis for the purpose of stopping for efficacy)

For each primary analysis of the primary endpoint, the key secondary endpoint (1) and the key secondary endpoint (2) of participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, the type I error control using the fixed sequence procedure will be applied between outcomes in comparison of S-217622 125mg group and placebo group. The pre-specified sequence of hypotheses for the fixed sequence procedure as follows:

1. Primary analysis of the primary endpoint: In the ITT Population, the proportion of participants with development/worsening of COVID-19 symptoms will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.
2. Primary analysis of the key secondary endpoint (1): In the ITT Population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #1, the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.
3. Primary analysis of the key secondary endpoint (2): In the mITT Population, only when a significant difference is detected in the comparison of the S-217622 125 mg group and the placebo group in #2, the time to the first negative SARS-CoV-2 viral titer will be compared between the S-217622 125 mg group and the placebo group with a one-sided significance level of 0.025.

In Phase 2b/3 Part and Phase 3 Part, comparisons between S-217622 250 mg group and placebo group will be performed in the same manner as those between S-217622 125 mg group and placebo group for all efficacy endpoints including primary and key secondary endpoints and adjustment of multiplicity will not be applied to comparisons between S-217622 250 mg group and placebo group.

6.3 Confidence Interval

The Clopper-Pearson method will be used to calculate the confidence interval (CI) of the proportion unless otherwise stated.

The 95% CI of difference of median time will be obtained by the bootstrap percentile method. The 10,000 bootstrap samples will be generated. A random seed of 217622 and 226712 will be used for comparison between the S-217622 125mg and the Placebo or the S-217622 250 mg and the Placebo, respectively. Then, the treatment group difference in median time will be calculated by each bootstrapped sample and its 95% CI will be constructed using percentiles of the bootstrap distribution.

6.4 Analysis Visit Windows

The acceptable time windows shown in Table 6-1 and 6-2. The acceptable time windows shown in Table 6-1 will be used to collect data from the patient diary.

Table 6-1 Acceptable Time Windows for Parameters of the Patient Diary

Time Point	Specified Assessment Time Point	Acceptable Time Window
Pre-dose	-	Pre-dose from -24 hours before first dosing to first dosing
12 hours post-dose	Time of first dosing + 12 hours	Between ≥ 6 and < 18 hours after first dosing
24 hours post-dose	Time of first dosing + 24 hours	Between ≥ 18 and < 30 hours after first dosing
36 hours post-dose	Time of first dosing + 36 hours	Between ≥ 30 and < 42 hours after first dosing
48 hours post-dose	Time of first dosing + 48 hours	Between ≥ 42 and < 54 hours after first dosing
60 hours post-dose	Time of first dosing + 60 hours	Between ≥ 54 and < 66 hours after first dosing
72 hours post-dose	Time of first dosing + 72 hours	Between ≥ 66 and < 78 hours after first dosing
84 hours post-dose	Time of first dosing + 84 hours	Between ≥ 78 and < 90 hours after first dosing
96 hours post-dose	Time of first dosing + 96 hours	Between ≥ 90 and < 102 hours after first dosing
108 hours post-dose	Time of first dosing + 108 hours	Between ≥ 102 and < 114 hours after first dosing
120 hours post-dose	Time of first dosing + 120 hours	Between ≥ 114 and < 126 hours after first dosing
132 hours post-dose	Time of first dosing + 132 hours	Between ≥ 126 and < 138 hours after first dosing
144 hours post-dose	Time of first dosing + 144 hours	Between ≥ 138 and < 150 hours after first dosing
156 hours post-dose	Time of first dosing + 156 hours	Between ≥ 150 and < 162 hours after first dosing
168 hours post-dose	Time of first dosing + 168 hours	Between ≥ 162 and < 174 hours after first dosing
180 hours post-dose	Time of first dosing + 180 hours	Between ≥ 174 and < 186 hours after first dosing
192 hours post-dose	Time of first dosing + 192 hours	Between ≥ 186 and < 198 hours after first dosing
204 hours post-dose	Time of first dosing + 204 hours	Between ≥ 198 and < 210 hours after first dosing
228 hours post-dose	Time of first dosing + 228 hours	Between ≥ 216 and < 240 hours after first dosing
252 hours post-dose	Time of first dosing + 252 hours	Between ≥ 240 and < 264 hours after first dosing
276 hours post-dose	Time of first dosing + 276 hours	Between ≥ 264 and < 288 hours after first dosing
300 hours post-dose	Time of first dosing + 300 hours	Between ≥ 288 and < 312 hours after first dosing
324 hours post-dose	Time of first dosing + 324 hours	Between ≥ 312 and < 336 hours after first dosing
348 hours post-dose	Time of first dosing + 348 hours	Between ≥ 336 and < 360 hours after first dosing
372 hours post-dose	Time of first dosing + 372 hours	Between ≥ 360 and < 384 hours after first dosing
396 hours post-dose	Time of first dosing + 396 hours	Between ≥ 384 and < 408 hours after first dosing
420 hours post-dose	Time of first dosing + 420 hours	Between ≥ 408 and < 432 hours after first dosing
444 hours post-dose	Time of first dosing + 444 hours	Between ≥ 432 and < 456 hours after first dosing
468 hours post-dose	Time of first dosing + 468 hours	Between ≥ 456 and < 480 hours after first dosing
492 hours post-dose	Time of first dosing + 492 hours	Between ≥ 480 and < 504 hours after first dosing
Day 85 [a]	Date of first dosing + 85 days	Between ≥ 71 and ≤ 99 days after first dosing
Day 169 [a]	Date of first dosing + 169 days	Between ≥ 155 and ≤ 183 days after first dosing
Day 337 [a]	Date of first dosing + 337 days	Between ≥ 323 and ≤ 351 days after first dosing

a : Time point for analyses of Post-acute COVID-19 Syndrome in the exploratory period.

The acceptable time windows shown in Table 6-2 will be used for the assessment of items other than data from the patient diary.

Table 6-2 Acceptable Time Windows for Parameters Other than Data from the Patient Diary

Time Point	Acceptable Time Window
Pre-dose at Visit 1 (Day 1: Day -1 to Day1)	Pre-dose from Day -1 to Day 1
Post-dose at Visit 1 (Day 1)	Post-dose at Day 1 for Electrocardiograms
Visit 2 (Day 2) [a]	Between Day 2 and Day 3
Optional Visit 1 (Day 3)	Day 3
Visit 3 (Day 4) [b]	Between Day 4 and Day 5
Optional-Visit 2 (Day 5)	Day 5
Visit 4 (Day 6)	Between Day 6 and Day 7
Visit 5 (Day 9)	Between Day 8 and Day 10
Visit 6 (Day 14)	Between Day 12 and Day 16
Visit 7 (Day 21)	Between Day 18 and Day 24
Visit 8 (Day 28)	Between Day 25 and Day 31
Early termination	Date of early termination + 3 days

a : If it is not observed on Day 2 but is implemented on Day 3, Day 3 will be set as Visit 2.
b : If it is not observed on Day 4 but is implemented on Day 5, Day 5 will be set as Visit 3.

Measurements collected within the acceptable time window for each scheduled assessment time point, including data obtained at the time of withdrawal, will be used for the analyses of all endpoints at each assessment time point. For all participants with multiple measurements within a visit window, the measurement obtained closest to the target time point will be used. If there exist two measurements collected with the same time deviation before and after the target time point, the measurement obtained before the target time point will be adopted for analysis. The assessment time point having no measurements within the corresponding acceptable time window will be considered as missing.

In the patient diary, if there are multiple measurements which may be adopted for a scheduled assessment, even though the above rules have been strictly followed, the measurements of the earlier assessment date or the earlier assessment time of day will be adopted (with the priority given to morning, followed by evening, in this order). If multiple measurements are collected with the same time (date and hour) for body temperature, the highest measurement will be adopted.

In the assessment of items from other than the patient diary, if there are multiple measurements which may be adopted for a scheduled assessment time point (even though the above rules have been strictly followed), the measurements at the time point entered in the CRF will be adopted.

Analyses for time-to-event endpoints (e.g. Time to resolution of the 5 COVID-19 symptoms) will be performed based on the time (hour). The time (hour) will be calculated from collected start/end datetime.

6.5 Missing Data

Missing values will not be imputed. All statistical analyses will be based on observed cases unless otherwise stated.

When the assessment time of participant diary after initial administration of the study intervention is missing, the time will be imputed. The missing time of morning will be imputed as 11:59:59, and the missing time of evening will be imputed as 23:59:59 in Day 2 to 9. The missing time will be imputed as 23:59:59 in Day 10 to 21.

When the symptom score is missing but the date and time of assessment are recorded, then the following rules will be applied to each endpoint.

- The following rule will be applied to the assessment of time-to-event endpoints for resolution or improvement of COVID-19 symptoms (e.g. Time to resolution of the 5 COVID-19 symptoms).If the symptom score is missing but the date and time of assessment are recorded, the missing assessment will conservatively be treated as not resolved/improved (as failures) at the corresponding date and time of assessment.

- If the symptom score is missing but the date and time of assessment are recorded at baseline, the resolution/improvement of COVID-19 symptoms consisting of the missing symptoms will not be assessed.

- After the resolution of the 5 COVID-19 symptoms, if the symptom score is missing but the date and time of assessment are recorded, the missing assessment will conservatively be treated as recurrence (condition that persists for 48 hours or longer need to be considered separately) at the corresponding date and time of assessment.

- The following rule will be applied to the assessment of “time to first occurrence of taste disorder or smell disorder and each symptom”.

  - If the symptom score is missing but the date and time of assessment are recorded, the missing assessment will conservatively be treated as occurrence (as failures) at the corresponding date and time of assessment.

- The following rule will be applied to the assessment of proportion of participants

without resolution.

  - If the symptom score is missing but the date and time of assessment are recorded, the missing assessment will conservatively be treated as not resolution (as failures) at the corresponding date and time of assessment (last time point of COVID-19 symptoms observed after Day 18 (after 432 hours of first administration)).

- The following rule will be applied to the assessment of proportion of participants with development/worsening or occurrence of COVID-19 symptoms.

  - If the symptom score is missing but the date and time of assessment are recorded, the missing assessment will conservatively be treated as development, worsening, and occurrence (as failures) at the corresponding date and time of assessment.

6.6 Definition

6.6.1 Study Day

Study Day 1 refers to the date of initial administration of the study intervention (S-217622 or placebo). Other study days are defined relative to Study Day 1, and previous day to Study Day 1 is expressed as Day -1 (there is no Study Day 0).

6.6.2 Baseline

The baseline is defined as the last value obtained before the study intervention administration (S-217622 or placebo) unless otherwise stated. For the baseline for efficacy, measurements collected within the acceptable time windows (shown in Pre-dose of Table 6-1 and Pre-dose at Visit1 of Table 6-2) will be used. If there are multiple measurements within a visit window, the measurement obtained closest to the time of first study intervention administration.

6.6.3 Viral Data

In Phase 2a Part only, viral data sample for efficacy analyses will be excluded from analyses based on the time from sample collection to cryopreservation. When the time is 48 hours or more, sample excluded from analyses. This exclusion will not be applied in Phase 3 and 2b/3 Parts.

If the result is below the detection limit, the detection limit value will be used for summary statistics and reported value will be used for lists. Similarly, if the result is below or above the limit of quantification, the limit of quantification value will be used for summary statistics and reported value will be used for lists. For example, when the result is “<=0.03”, “0.03” will be used for summary statistics, and “<=0.03” will be used for lists.

6.6.4 External Vendors for Virus Titer

For SARS-CoV-2 virus titer used in statistical analyses in each Part, the virus titer reported by following vendors will be used.

[redacted]

6.6.5 Analysis Populations for Merged parts

In general, all merged analyses will be performed for the ITT Population (Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part), the ITT1 Population (Phase 2b Part), or Safety Analysis Population (shown in section 5). Furthermore, merged analyses will be also performed for participants with less than 72 hours from COVID-19 onset to randomization of mild/moderate SARS-CoV-2 infection in Phase 2a Part (the ITT Population), Phase 2b Part (the ITT1 Population) and Phase 3 Part (the ITT Population).

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Participant Disposition

In general, the following analyses in this section will be performed for the All Randomized Participants in Phase 2a Part, Phase 3 Part, Phase 2b/3 Part and merged all parts including Phase 2b Part. For Phase 2a Part, Phase 3 Part, Phase 2b/3 Part and merged all parts including Phase 2b Part, these analyses will be performed in each population with participants with mild/moderate and asymptomatic/mild symptoms only SARS-CoV-2-infection.

The number and proportion of participants who completed/discontinued the study will be counted by treatment group. In addition, the reason for discontinuation from the study will be summarized by treatment group.

The number and proportion of participants in each analysis population will be summarized as well as the reasons for exclusion from each analysis population.

The number and proportion of participants who met to important protocol deviation categories will be summarized and listed with the reason for deviation.

7.2 Demographic and Baseline Characteristics

Demographic data and baseline characteristics shown in Table 7-1 will be summarized descriptively by treatment group for the ITT Population and the Safety Analysis Population in three populations which are participants with mild/moderate, asymptomatic/mild symptoms only SARS-CoV-2 infection, and merged the two populations. For merged all part, demographic data and baseline characteristics will be

summarized by treatment group for the ITT Population (Phase 2a Part, Phase 3 Part and Phase 2b/3 Part) and ITT1 Population (Phase 2b Part). For Phase 3 Part, the same summarization will be performed in the ITT population with less than 72 hours from COVID-19 onset to randomization.

Table 7-1. Demographic and Baseline Characteristics

Continuous variables	• Age (years old at informed consent obtained) • Height (cm) • Weight (kg) • BMI
Categorical variables	• Sex (Male, Female) • Ethnicity (Not Hispanic or Latino, Hispanic or Latino, Not reported, Unknown) • Race (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other) • Drinking habits (Yes, No) • Smoking habits (Yes, No) • Condition of subject (Hospitalization, Outpatient, Recuperation at home, Recuperation at accommodation (hotel), Other) • Pathogen Test Method • COVID-19 Symptom (Mild/Moderate SARS-CoV-2-infected participants, Asymptomatic SARS-CoV-2-infected participants) • Time from onset to randomization [a] (< 72 hours, ≥ 72 hours) • Time from onset to randomization [a] (< 24 hours, between ≥ 24 and < 48 hours, between ≥ 48 and < 72 hours, between ≥ 72 and < 96 hours, between ≥ 96 and ≤ 120 hours, > 120 hours) • Days from day of close contact with SARS-CoV-2 patients to enrollment [b] (0 days, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, > 7days, Unknown) • Vaccination of SARS-CoV-2 (Yes, No) • Pollen allergy conditions (Yes, No) • Past medical conditions (Yes, No) • Current medical conditions (Yes, No) • Prior drugs (Yes, No) • Concomitant drugs (Yes, No) • Prior therapies (Yes, No) • Concomitant therapies (Yes, No)

BMI = Body mass index
Note: Use the last value before the initial administration if multiple results are obtained for participants who have taken study intervention. Use the last value for participants who have not taken study intervention.
a : Only participants with mild/moderate SARS-CoV-2 infection
b : Only participants with asymptomatic SARS-CoV-2-infection

Past medical conditions and current medical conditions will be listed by treatment group.

8. STUDY CONDUCT

8.1 Prior and Concomitant Drugs/Therapies

The analyses will be performed for the ITT Population and the Safety Analysis Population in each of three Parts. Prior drugs/therapies are defined as drugs/therapies which have been taken prior to initial administration of study intervention. Concomitant drugs/therapies are defined as drugs/therapies taken at or after administration of study intervention. Prior and concomitant drugs will be coded using the WHO Drug Dictionary Version March 2021.

The number and proportion of participants who took prior and concomitant medications will be summarized by WHO Drug Dictionary Preferred Term (PT) by treatment group. If a participant has more than one drug that codes to the same PT, the participant will be counted only once for that PT.

The number and proportion of participants who took prior and concomitant therapies will be summarized by the reported therapy name in each treatment group. Participants for whom a particular therapy was reported more than once will be counted only once for that therapy.

Moreover, prior drugs/therapies will be listed by treatment group for the Safety Analysis Population.

These analyses will be performed in each population of participants with mild/moderate and asymptomatic/mild symptoms only SARS-CoV-2-infection.

8.2 Treatment Exposure and Compliance

The analyses will be performed for the ITT Population and the Safety Analysis Population in each of three Parts. Total days of administration and cumulative amount of study intervention will be summarized descriptively by treatment group. The number and proportion of total days of administration will be summarized by treatment group

Total days of administration is defined as total number of days of administration (S-217622 or placebo). In case of discontinuation, total days of planned administration are calculated by the date of discontinuation, not the date of the final administration.

Treatment compliance rate will be summarized descriptively by treatment group.

Treatment compliance rate is defined as;

$$\frac{\text{total days of administration as planned}}{\text{total days of planned administration}} * 100\ (\%)$$

Moreover, the compliance will be listed for the All Randomized Participants.

9. EFFICACY

In general, efficacy analyses will be performed for the mITT Population or ITT Population by treatment group. For Phase 3 Part, in general, efficacy analyses will be performed for the ITT Population or mITT Population with less than 72 hours from COVID-19 onset to randomization. Furthermore, in Phase 3 Part, efficacy analyses will also be performed for the ITT Population or the mITT Population. For primary analysis of primary endpoint in Phase 2a Part, will also be performed for participants in PPS who have SARS-CoV-2 viral titer detected at baseline. For primary endpoint and key secondary endpoints in Phase 3 Part and Phase 2b/3 Part, these primary analyses and key secondary analyses (only Phase 3 Part) for the ITT Population will also be performed for the ITT1 Population and PPS, and these primary analyses and key secondary analyses (only Phase 3 Part) for the mITT population will also be performed for participants in the ITT1 Population and the PPS who have SARS-CoV-2 viral titer detected at baseline. For analyses in Phase 2b/3 Part, these analyses for asymptomatic/mild symptoms only SARS-CoV-2 infection and mild symptoms only SARS CoV-2 infection will be also performed for asymptomatic SARS-CoV-2 infection.

Table 9-1 Statistical Methods Used to Analyze Each Endpoint (Phase 2a Part)

Endpoint Analysis		Unit	Statistical Method
Primary Endpoint (Mild/Moderate and Asymptomatic)	Change from baseline in SARS-CoV-2 viral titer at each time point	log_{10} $TCID_{50}$/mL	4, 10, 12
Secondary Endpoints (Mild/Moderate and Asymptomatic	Time to the first negative SARS-CoV-2 viral titer	hours	1, 2, 5, 6, 7, 8, 9
	Time to negative SARS-CoV-2 viral titer at 2 consecutive time points	hours	1, 2, 5, 6, 7, 8, 9
	Time to sustained negative SARS-CoV-2 viral titer	hours	1, 2, 5, 6, 7, 8, 9
	Proportion of participants with positive SARS-CoV-2 viral titer at each time point	%	3
	SARS-CoV-2 viral titer at each time point	log_{10} $TCID_{50}$/mL	4,10
	Relative change rate from baseline in SARS-CoV-2 viral titer at each time point	%	4,10
	AUC of the change from baseline in SARS-CoV-2 viral titer	log_{10} $TCID_{50}$/mL×hours	4,10
	Time to the first negative RT-PCR result	Hours	1, 2, 5, 6, 7, 8, 9
	Time to negative RT-PCR results at 2 consecutive time points	hours	1, 2, 5, 6, 7, 8, 9
	Time to sustained negative RT-PCR results	hours	1, 2, 5, 6, 7, 8, 9
	Proportion of participants with positive RT-PCR	%	3

	Endpoint Analysis	Unit	Statistical Method
	result at each time point		
	Amount of SARS-CoV-2 viral RNA at each time point	log_{10} copies/mL	4,10
	Change from baseline in amount of SARS-CoV-2 viral RNA at each time point	log_{10} copies/mL	4,10
	Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point	%	4,10
	AUC of the change from baseline in amount of SARS-CoV-2 viral RNA	log_{10} copies/mL×hours	4,10
	Proportion of participants with a score ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6, ≥ 7 on 8-Point Ordinal Scale at each time point and during the investigation period	%	3
	Time to score of ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6 and ≥ 7 on 8-Point Ordinal Scale	days	1, 2, 5, 6, 7, 8, 9
	SpO_2 at each time point	%	4,10
	Change from baseline in EQ-5D-5L Index Value	-	10
	EQ-5D-5L Index Value at each time point	-	10
Secondary Endpoints (Mild/Moderate)	Time to first improvement of COVID-19 symptoms*	hours	1, 2, 5, 6, 7, 8, 9
	Time to first improvement of COVID-19 symptoms (duration of recovery, 72 hours or more)*	hours	1, 2, 5, 6, 7, 8, 9
	Time to first improvement of COVID-19 symptoms (duration of recovery, 120 hours or more)*	hours	1, 2, 5, 6, 7, 8, 9
	Time to first improvement of each COVID-19 symptom*	hours	1, 2, 5, 6, 7, 8, 9
	Change from baseline in total score of COVID-19 symptoms at each time point	-	4,10
	Total score of COVID-19 symptoms at each time point	-	4,10
	Proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point	%	3
	Proportion of participants with taste disorder or smell disorder at each time point	%	3
	Time to resolution of fever **	hours	1, 2, 5, 6, 7, 8, 9
Secondary Endpoints (Asymptomatic)	Proportion of participants with occurrence of COVID-19 symptoms	%	3
	Proportion of participants with occurrence of COVID-19 symptoms and fever	%	3

*: Analyses will be conducted on participants with at least one moderate or more COVID-19 symptoms at baseline.

**: Analyses will be conducted on participants with body temperature of 37 ℃ or higher at baseline.

[Statistical test methods]

1. Stratified log rank test
2. Stratified Peto-Prentice's generalized Wilcoxon test
3. Mantel-Haenszel test
4. van Elteren test
5. Stratified Cox proportional hazard model
6. Restricted mean survival time

[Summarization methods]

7. Kaplan-Meier curve
8. Median time and its 95% CI
9. Treatment group difference in median time and its 95% CI (Bootstrap method)
10. Summary statistics (continuous variables)
11. Summary statistics (categorical variables)
12. Wilcoxon rank sum test

Table 9-2 Statistical Methods Used to Analyze Each Endpoint (Phase 3 Part)

Endpoint Analysis		Unit	Statistical Method
Primary Endpoint	Time to resolution of the 5 COVID-19 symptoms	hours	1, 2, 5, 6, 8, 9, 10
Key secondary Endpoints	Change from baseline on Day 4 in amount of SARS-CoV-2 viral RNA	$\log_{10}$ copies/mL	4, 7, 11
	Time to the first negative SARS-CoV-2 viral titer	hours	1, 2, 5, 6, 8, 9,10
Secondary Endpoints	Time to resolution of the 12 COVID-19 symptoms	hours	1, 2, 5, 6, 8, 9, 10
	Time to resolution of the sub-symptoms of COVID-19 symptoms	hours	1, 2, 5, 6, 8, 9, 10
	Time to resolution of the 5 COVID-19 symptoms without recurrence (duration of resolution, 48 hours or more)	hours	1, 2, 5, 6, 8, 9, 10
	Time to resolution of the 14 COVID-19 symptoms including taste disorder and smell disorder	hours	1, 2, 5, 6, 8, 9, 10
	Time to resolution of each COVID-19 symptom*	hours	1, 2, 5, 6, 8, 9, 10

Endpoint Analysis	Unit	Statistical Method
Proportion of participants with taste disorder or smell disorder at each time point	%	3
Proportion of participants without resolution of the 12 COVID-19 symptoms after 3 weeks of administration	%	3
Proportion of participants without resolution of the 14 COVID-19 symptoms after 3 weeks of administration (including taste disorder and smell disorder)	%	3
Proportion of participants without resolution of each COVID-19 symptoms after 3 weeks of administration.	%	3
Time to resolution of fever**	hours	1, 2, 5, 6, 8, 9, 10
Time to first occurrence of taste disorder or smell disorder and each symptom	hours	1, 2, 5, 6, 8, 9, 10
Time to sustained negative SARS-CoV-2 viral titer	hours	1, 2, 5, 6, 8, 9, 10
Proportion of participants with positive SARS-CoV-2 viral titer at each time point	%	3
SARS-CoV-2 viral titer at each time point	$\log_{10}$ $TCID_{50}$/mL	4, 7, 11
Change from baseline in SARS-CoV-2 viral titer at each time point	$\log_{10}$ $TCID_{50}$/mL	4, 7, 11
Relative change rate from baseline in SARS-CoV-2 viral titer at each time point	%	4, 7, 11
AUC of the change from baseline in SARS-CoV-2 viral titer	$\log_{10}$ $TCID_{50}$/mL×hours	4, 7, 11
Proportion of participants with positive RT-PCR result at each time point	%	3
Amount of SARS-CoV-2 viral RNA at each time point	$\log_{10}$ copies/mL	4, 7, 11
Change from baseline in amount of SARS-CoV-2 viral RNA at each time point	$\log_{10}$ copies/mL	4, 7, 11
Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point	%	4, 7, 11
AUC of change in amount of SARS-CoV-2 viral RNA	$\log_{10}$ copies/mL×hours	4, 7, 11
Proportion of participants with a score ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6 and ≥ 7 on 8-Point Ordinal Scale at each time point and during the investigation period	%	3
Time to score of ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6 and ≥ 7 on 8-Point Ordinal Scale	days	1, 2, 5, 6, 8, 9, 10
SpO_2 at each time point	%	4, 7, 11
Change from baseline in EQ-5D-5L Index Value	-	11
EQ-5D-5L Index Value at each time point	-	11

	Endpoint Analysis	Unit	Statistical Method
	Change from baseline in EQ VAS Score	-	11
	EQ VAS Score at each time point	-	11
Other endpoints	Time to LLOQ of SARS-CoV-2 viral RNA and negative RT-PCR without rebound	hours	1, 2, 5, 6, 8, 9, 10
	Time to less than $LLOD_{95}$ viral RNA	hours	1, 2, 5, 6, 8, 9, 10

*: Analyses will be conducted on participants with at least one moderate or more COVID-19 symptoms at baseline.

**: Analyses will be conducted on participants with body temperature of 37 ℃ or higher at baseline.

[Statistical test methods]

1. Stratified log rank test
2. Stratified Peto-Prentice's generalized Wilcoxon test
3. Mantel-Haenszel test
4. Analysis of covariance (including least squares mean and the difference compared to placebo)
5. Stratified Cox proportional hazard model
6. Restricted mean survival time
7. van Elteren test

[Summarization methods]

8. Kaplan-Meier curve
9. Median time and its 95% CI
10. Treatment group difference in median time and its 95% CI (Bootstrap method)
11. Summary statistics (continuous variables)
12. Summary statistics (categorical variables)

Table 9-3 Statistical Methods Used to Analyze Each Endpoint (Phase 2b/3 Part)

	Endpoint Analysis	Unit	Statistical Method
Primary Endpoint	Proportion of participants with development /worsening of the 14 COVID-19 symptoms	%	3
Key secondary Endpoints	Change from baseline on Day 4 in amount of SARS-CoV-2 viral RNA	log_{10} copies/mL	4, 7, 11
	Time to the first negative SARS-CoV-2 viral titer	hours	1, 2, 5, 6, 8, 9, 10
Secondary Endpoints	Proportion of participants with occurrence of the 14 COVID-19 symptoms	%	3
	Proportion of participants with occurrence of the 14 COVID-19 symptoms and fever (≥ 37.0°C)	%	3
	Time to first occurrence of taste disorder or smell	hours	1, 2, 5, 6, 8,

	Endpoint Analysis	Unit	Statistical Method
	disorder and each symptom		9, 10
	Time to sustained negative SARS-CoV-2 viral titer	hours	1, 2, 5, 6, 8, 9, 10
	Proportion of participants with positive SARS-CoV-2 viral titer at each time point	%	3
	SARS-CoV-2 viral titer at each time point	log_{10} $TCID_{50}$/mL	4, 7, 11
	Change from baseline in SARS-CoV-2 viral titer at each time point	log_{10} $TCID_{50}$/mL	4, 7, 11
	Relative change rate from baseline in SARS-CoV-2 viral titer at each time point	%	4, 7, 11
	AUC of the change from baseline in SARS-CoV-2 viral titer	log_{10} $TCID_{50}$/mL×hours	4, 7, 11
	Proportion of participants with positive RT-PCR result at each time point	%	3
	Amount of SARS-CoV-2 viral RNA at each time point	log_{10} copies/mL	4, 7, 11
	Change from baseline in amount of SARS-CoV-2 viral RNA at each time point	log_{10} copies/mL	4, 7, 11
	Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point	%	4, 7, 11
	AUC of change in amount of SARS-CoV-2 viral RNA	log_{10} copies/mL×hours	4, 7, 11
	Proportion of participants with a score ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6 and ≥ 7 on 8-Point Ordinal Scale at each time point and during the investigation period	%	3
	Time to score of ≥ 1, ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6 and ≥ 7 on 8-Point Ordinal Scale	days	1, 2, 5, 6, 8, 9, 10
	SpO_2 at each time point	%	4, 7, 11
	Change from baseline in EQ-5D-5L Index Value	-	11
	EQ-5D-5L Index Value at each time point	-	11
	Change from baseline in EQ VAS Score	-	11
	EQ VAS Score at each time point	-	11
Secondary Endpoints (Mild Symptoms only)	Time to resolution of the 5 COVID-19 symptoms	hours	1, 2, 5, 6, 8, 9, 10
Other endpoints	Time to LLOQ of SARS-CoV-2 viral RNA and negative RT-PCR without rebound	hours	1, 2, 5, 6, 8, 9, 10
	Time to less than $LLOD_{95}$ viral RNA	hours	1, 2, 5, 6, 8, 9, 10

[Statistical test methods]

1. Stratified log rank test
2. Stratified Peto-Prentice's generalized Wilcoxon test
3. Mantel-Haenszel test
4. Analysis of covariance (including least squares mean and the difference compared to placebo)

5. Stratified Cox proportional hazard model
6. Restricted mean survival time
7. van Elteren test

[Summarization methods]

8. Kaplan-Meier curve
9. Median time and its 95% CI
10. Treatment group difference in median time and its 95% CI (Bootstrap method)
11. Summary statistics (continuous variables)
12. Summary statistics (categorical variables)

9.1 Primary Endpoint

9.1.1 Phase 2a Part: Participants with Mild/Moderate or Asymptomatic SARS-CoV-2 infection

The primary endpoint is the change from baseline in SARS-CoV-2 viral titer at each time point.

The change from baseline in SARS-CoV-2 viral titer at each time point is defined as the absolute change from baseline in SARS-CoV-2 viral titer at each time point. For the mITT Population, the change from baseline in SARS-CoV-2 viral titer at each time point will be summarized in three populations, i.e., participants with mild/moderate SARS-CoV-2 infection, participants with asymptomatic SARS-CoV-2 infection and the merged population of the participants with mild/moderate and asymptomatic SARS-CoV-2-infection. For the merged population, the van Elteren test will be applied to conduct the pairwise comparison of the SARS-CoV-2 viral titer at each time point between each S-217622 treatment group and placebo group. The strata used in van Elteren test will be population of participants with mild/moderate SARS-CoV-2-infection and population of participants with asymptomatic SARS-CoV-2-infection. As other analyses for this endpoint, the following analyses will be performed. For the population of participants with mild/moderate SARS-CoV-2 infection and population of participants with asymptomatic SARS-CoV-2 infection, the Wilcoxon rank sum test will be applied to conduct the pairwise comparison of the absolute change from baseline in SARS-CoV-2 viral titer at each time point between each S-217622 treatment group and placebo group. The multiplicity adjustment will not be applied in these pairwise comparisons.

9.1.2 Phase 3 Part: Participants with Mild/Moderate SARS-CoV-2-infected Participants

The primary endpoint is the time to resolution of the 5 COVID-19 symptoms.

The time to resolution of the 5 COVID-19 symptoms is defined as the time to resolution of all 5 symptoms of COVID-19 (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness) after first administration. The symptoms of COVID-19 will be evaluated on 4-point scale (0 : None, 1 : Mild, 2 : Moderate, 3 : Severe) using participant-reported outcomes and the resolution of symptoms will be judged following the rules below:

- For the pre-existing symptoms that exist before onset of COVID-19 and participants judge to have worsened at the baseline (before administration), the severity should be improved or persisted.
  - Severe at the baseline: Moderate, Mild, or None
  - Moderate at the baseline: Mild, or None
  - Mild at the baseline: Mild, or None

  Note: The participants will be asked only for the pre-existing symptoms (in the past 30 days) and presence or absence of symptom exacerbation due to COVID-19 and evaluate the severity (to be improved) at the baseline. To avoid recall bias, the severity of the pre-existing symptoms before the onset of COVID-19 is not evaluated.
- For the pre-existing symptoms that exist before onset of COVID-19 and participants judge not to have worsened at the baseline (before administration), the severity should be persisted or improved.
  - Severe at the baseline: Severe, Moderate, Mild, or None
  - Moderate at the baseline: Moderate, Mild, or None
  - Mild at the baseline: Mild, or None
- Symptoms other than the above, which not exist before onset of COVID-19 and occur at or after baseline, should be none.
  - Severe, Moderate or Mild at baseline: None
- For the pre-existing symptoms that exist before onset of COVID-19, if presence or absence of the symptom exacerbation due to COVID-19 is missing, should be none.

Participants who have only symptoms of None will be excluded from the analyses. The resolution of the 5 COVID-19 symptoms is defined as the time when all 5 COVID-19 symptoms disappear, maintain, or improve firstly as shown above after first administration of study intervention. If the condition persists for at least 24 hours, the participants are considered to achieve this endpoint. Participants who administered the

following prohibited concomitant medications will be censored at the last time when assessed COVID-19 symptoms up to the day before the first administration of the prohibited concomitant medications, regardless of whether or not they resolved. Participants who are not confirmed the resolution of the 5 COVID-19 symptoms and not administered the prohibited concomitant medications will be censored at the last time when assessed COVID-19 symptoms. Participants who received the following prohibited concomitant medications and did not have COVID-19 symptoms assessed before administration of the prohibited concomitant medications will be excluded from the analyses.

- Approved drugs for the treatment of SARS-CoV-2 infection

- Unapproved drugs for the treatment of SARS-CoV-2 infection (eg, Interferon, Convalescent plasma, Monoclonal antibody, Immunoglobulins, Antirheumatic drugs, Corticosteroids [Oral, Injection, Inhaled], Ivermectin, Favipiravir)

For participants who are not confirmed the resolution of COVID-19 symptoms, the supplemental analysis will be performed in which the last assessment time of COVID-19 symptoms is defined as the censored time.

As the primary analysis for this primary endpoint, a comparison of the time to resolution of the 5 COVID-19 symptoms will be performed between S-217622 125 mg group and placebo group using a Peto-Prentice's generalized Wilcoxon test stratified by SARS-CoV-2 vaccination history (Yes or No) at a one-sided significance level of 0.025 in the ITT Population with less than 72 hours from COVID-19 onset to randomization. As the key secondary analysis for this primary endpoint, the same analysis as the primary analysis will be performed for the ITT Population. When performing the key secondary analysis, time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) will be included as the strata in Peto-Prentice's generalized Wilcoxon test in addition to two strata described above. For each primary analysis and key secondary analysis of the primary endpoint and two key secondary endpoints, the multiplicity adjustment shown in 6.2 will be performed.

As other analyses for this endpoint, the following analyses will be performed for the ITT Population with less than 72 hours from COVID-19 onset to randomization. The same analyses will be performed for the ITT Population with time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) added as the strata. For these analyses, the multiplicity adjustment will not be performed.

- Pairwise comparison between S-217622 125 mg group and placebo using the stratified log-rank test with SARS-CoV-2 vaccination history (Yes or No) as stratification factors.
- Kaplan-Meier curves will be plotted for each treatment group and the median and 95% CI of the time to resolution of the 5 COVID-19 symptoms will be calculated.

Moreover, differences between treatment groups and 95% CI of them will be calculated.

- The hazard ratio in S-217622 125 mg group versus placebo and the corresponding 95% CI will be calculated using a stratified Cox proportional hazard model with SARS-CoV-2 vaccination history (Yes or No) as stratification factors.
- Restricted mean survival time (RMST) up to 21 days and the corresponding two-sided 95% CI will be calculated for each treatment groups. Also, difference between the RMST of S-217622 125 mg group and placebo and the corresponding two-sided 95% CI will be calculated.
- A comparison using the Peto-Prentice's generalized Wilcoxon test stratified by sex (Male or Female) as a stratification factor between S-217622 125 mg group and placebo.

The same analyses (excluding of the stratified analysis by sex) will be performed for All Randomized Participants with less than 72 hours from COVID-19 onset to randomization and All Randomized Participants. When performing the analyses for All Randomized Participants, the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) will be added as the strata.

9.1.3 Phase 2b/3 Part: Participants with Asymptomatic/Mild Symptom Only SARS-CoV-2-infection

The primary endpoint for the efficacy is the proportion of participants with development/worsening of the 14 COVID-19 symptoms. The proportion of participants with development/worsening of the 14 COVID-19 symptoms is defined as the proportion of participants in the asymptomatic/mild symptoms only SARS-CoV-2 infection population in the ITT Population with development/worsening of any 12 symptoms of COVID-19, taste disorder, or smell disorder by 14 days from the first administration of the study intervention.

Taste disorder or smell disorder will be evaluated on 3-point scale (0 : As usual, 1 : Less than usual, 2 : Not at all) and the 12 symptoms of COVID-19 will be evaluated on 4-point scale (0 : None, 1 : Mild, 2 : Moderate, 3 : Severe) using participant-reported outcomes and the onset of symptoms will be judged following the rules below.

- Taste disorder or smell disorder
  The scores of taste disorder or smell disorder become worse from "0 : As usual" to "1 : Less than usual" or "2 : Not at all", or from "1: Less than usual" to "2: Not at all".

(the baseline score of "2: Not at all". will be excluded from the onset/worsening judgement of COVID-19 symptoms)

- 3 symptoms (feeling hot or feverish, cough or shortness of breath [difficulty breathing])
    - The symptom score in at least one symptom have worsened one or more from baseline:
        - None at the baseline: Worsening to Mild or Moderate or Severe
        - Mild at the baseline: Worsening to Moderate or Severe
        - Moderate at the baseline: Worsening to Severe

        (Symptoms with Severe at the baseline are excluded from the judgment of onset)
- 9 symptoms (low energy or tiredness, muscle or body aches, headache, chills or shivering, stuffy or runny nose, sore throat, nausea, vomiting, or diarrhea)
    - The symptom score in at least two symptoms have worsened one or more from baseline and remain for at least 24 hours at the same time point:
        - None at the baseline: Worsening to Mild or Moderate or Severe
        - Mild at the baseline: Worsening to Moderate or Severe
        - Moderate at the baseline: Worsening to Severe

        (Symptoms with Severe at the baseline are excluded from the judgment of onset/worsening)

As the primary analysis for the primary endpoint, a comparison between S-217622 125 mg group and placebo group will be performed using the one-sided Mantel–Haenszel test with SARS-CoV-2 vaccination history (Yes or No) as a stratification factor between each S-217622 treatment group and placebo for participants with asymptomatic SARS-CoV-2-infection in the ITT Population. The same analysis will be performed for All Randomized Participants.

As the other analysis for this endpoint, the risk ratio and the risk difference in each S-217622 treatment group versus placebo and the corresponding 95% CI will be calculated.

9.2 Secondary Endpoints

9.2.1 Key Secondary Endpoints

There is no key secondary endpoint in Phase 2a Part.

9.2.1.1 Phase 3 Part and Phase 2b/3 Part

The key secondary endpoints are the change from baseline on Day4 in the amount of SARS-CoV-2 viral RNA(key secondary endpoint (1)) and the time to the first negative SARS-CoV-2 viral titer (key secondary endpoint (2)).

9.2.1.1.1 Key Secondary Endpoint (1)

The key secondary endpoint (1) is defined as the absolute change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA. In the ITT Population with less than 72 hours from COVID-19 onset to randomization of Phase 3 Part, analysis of covariance (ANCOVA) will be performed as primary analysis to conduct the comparison of the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA between S-217622 125 mg group and placebo group. In the Phase 3 Part, SARS-CoV-2 vaccination history (Yes or No) and the amount of SARS-CoV-2 viral RNA at baseline will be used as the covariates in the ANCOVA model for the primary analysis. A similar analysis will be performed in the ITT Population as key secondary analysis for the key secondary endpoint (1) in Phase 3 Part. As the key secondary analysis for this key secondary endpoint (1), the same analysis as the primary analysis will be performed for the ITT Population. When performing the key secondary analysis, time from COVID-19 onset to randomization (< 72 hours or ≥ 72 hours) will be included as the covariates in the ANCOVA model in addition to two covariates described above. In the ITT Population of Phase 2b/3 Part, ANCOVA will be applied in the participants with asymptomatic/mild symptoms only SARS-CoV-2 infection as primary analysis to conduct the comparison of the change form baseline on Day 4 in the amount of SARS-CoV-2 viral RNA between S-217622 125 mg group and placebo group. In Phase 2b/3 Part, SARS-CoV-2 vaccination history (Yes or No) and the amount of SARS-CoV-2 viral RNA at baseline will be used as the covariates in the ANCOVA model for the primary analysis. For each primary analysis and key secondary analysis of the key secondary endpoint (1), the multiplicity adjustment shown in 6.2 will be used.

As other analyses for the key secondary endpoint (1), the following analyses will be performed. For these analyses, the multiplicity adjustment will not be performed.

In the ITT Population with less than 72 hours from COVID-19 onset to randomization and the ITT Population of the participants with mild/moderate SARS-CoV-2 infection, and the ITT Population of the participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, the van Elteren test will be applied to conduct the comparison of the change from baseline in amount of SARS-CoV-2 viral RNA on Day 4 in the amount of SARS-CoV-2 viral RNA between S-217622 125 mg group and placebo group. The strata used in van Elteren test will be the same covariates of primary analysis and key secondary analysis excluded the amount of SARS-CoV-2 viral RNA at baseline.

The same analyses will be performed for All Randomized Participants with less than 72 hours from COVID-19 onset to randomization, All Randomized Participants with time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) added as the strata, and merged two parts of Phase 3 Part and Phase 2b/3 Part for the ITT Population.

9.2.1.1.2 Key Secondary Endpoint (2)

The key secondary endpoint (2) is defined as the time to the first confirmation that SARS-CoV-2 viral titer drops below the detection limit. Participants who are not confirmed that SARS-CoV-2 viral titer is negative will be treated as censored cases. The censored time will be the earlier time when the last assessment of SARS-CoV-2 viral titer or the 1 day before the first administration of following prohibited concomitant medications. Participants who received the following prohibited concomitant medications and did not have COVID-19 symptoms assessed before administration of the prohibited concomitant medications will be excluded from the analyses.

- Approved medication for SARS-CoV-2 infection

- Unapproved medication for SARS-CoV-2 infection (Interferon, Convalescent plasma, Monoclonal antibody, Immunoglobulin, Anti-rheumatic drug, Corticosteroids (oral, injection or inhalation), Ivermectin, Favipiravir)

For participants who are not confirmed that the virus titer of SARS-CoV-2 is negative, the supplemental analysis will be performed in which the last assessment time of SARS-CoV-2 viral titer is defined as the censored time.

The primary analysis for the key secondary endpoint (2) is planned in each participant with mild/moderate and asymptomatic/mild symptoms only SARS-CoV-2 infection. In participants with mild/moderate SARS-CoV-2 infection, a comparison between S-217622 125 mg group and placebo of the time to the first confirmation that SARS-CoV-2 viral titer is negative will be performed using the one-sided stratified log-rank test with SARS-CoV-2 vaccination history (Yes or No) as a stratification factor for the mITT Population with less than 72 hours from COVID-19 onset to randomization. A similar analysis will be performed in the mITT Population as key secondary analysis for the key secondary endpoint (2) in Phase 3 Part. As the key secondary analysis for this key secondary endpoint (2), the same analysis as the primary analysis will be performed for the mITT Population. When performing the key secondary analysis, time from COVID-19 onset to randomization (< 72 hours or ≥ 72 hours) will be included as the strata in the stratified log-rank test in addition to the strata described above. In participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, a comparison between S-217622 125 mg group and placebo for the mITT Population of the time to the first confirmation that SARS-CoV-2 viral titer is negative will be performed using one-sided stratified log-rank test with SARS-CoV-2 vaccination history (Yes or No) as a stratification factor. For each primary analysis and key secondary analysis of the key secondary endpoint (2), the multiplicity adjustment shown in 6.2 will be used.

As other analyses for the key secondary endpoint (2), the following analyses will be performed for the mITT Population with less than 72 hours from COVID-19 onset to randomization of the participants with mild/moderate SARS-CoV-2 infection. The same analyses will be performed for the mITT Population of the participants with mild/moderate SARS-CoV-2 infection with time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) added as the strata. For these analyses, the multiplicity adjustment will not be performed.

In participants with mild/moderate SARS-CoV-2 infection, the comparison between S-217622 125 mg group and placebo will be performed using the stratified Peto-Prentice's generalized Wilcoxon test with SARS-CoV-2 vaccination history (Yes or No) as a stratification factor. A similar analysis will be performed in the mITT Population of the participants with mild/moderate SARS-CoV-2 infection. In the mITT Population of the participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, the comparison between S-217622 125 mg group and placebo will be performed using the stratified Peto-Prentice's generalized Wilcoxon test with SARS-CoV-2 vaccination history (Yes or No) as a stratification factor

In the mITT Population with less than 72 hours from COVID-19 onset to randomization and the mITT Population of the participants with mild/moderate and the mITT Population of the participants with asymptomatic/mild symptoms only SARS-CoV-2-infection, Kaplan-Meier curves will be plotted for each treatment group and the median and 95% CI of the time to the first confirmation that SARS-CoV-2 viral titer is negative will be calculated. Moreover, difference in the median betweenS-217622 125 mg group and placebo and 95% CI will be calculated.

In participants with mild/moderate SARS-CoV-2 infection, the hazard ratio in S-217622 125 mg group versus placebo will be calculated using a stratified Cox proportional hazard model with SARS-CoV-2 vaccination history (Yes or No) as a stratification factor. In participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, the hazard ratio inS-217622 125 mg group versus placebo will be calculated using a stratified Cox proportional hazard model with SARS-CoV-2 vaccination history (Yes or No) as a stratification factor.

In each mITT Population with mild/moderate and asymptomatic/mild symptoms only SARS-CoV-2-infected participants, RMST up to 21 days and 95% CI will be calculated for each treatment group. Also, difference in the RMST betweenS-217622 125 mg group and placebo and its 95% CI will be calculated.

The same analyses will be performed for All Randomized Participants with less than 72 hours from COVID-19 onset to randomization, All Randomization Participants with time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) added as the strata, and merged two parts of Phase 3 Part and Phase 2b/3 Part for the mITT Population.

9.2.2 Other Secondary Endpoint

9.2.2.1 Common to Participants with Mild/Moderate and Asymptomatic/Mild Symptom Only SARS-CoV-2 infection

- Time to the first confirmation of negative SARS-CoV-2 virus titer (Only Phase 2a Part)

  This is defined as the time to the first confirmation that SARS-CoV-2 viral titer drops below the detection limit after first administration of study intervention. For the mITT Population in Phase 2a Part, the same analyses as the key secondary endpoint (2) for the efficacy (excluding of the multiplicity adjustment) will be performed. The same analyses will be also performed in the merged population of participants with mild/moderate and asymptomatic SARS-CoV-2 infection.
- Time to negative SARS-CoV-2 viral titer at 2 consecutive time points (Only Phase 2a Part)

  This is defined as the time to SARS-CoV-2 viral titer drops below the detection limit for 2 consecutive time points after first administration of study intervention. The definition of 2 consecutive time points is based on the time points when SARS-CoV-2 viral titer are measured. For the mITT Population in Phase 2a Part, the same analyses as the key secondary endpoint (2) for the efficacy (excluding of the multiplicity adjustment) will be performed.
- Time to sustained negative SARS-CoV-2 viral titer

  This is defined as the time to SARS-CoV-2 viral titer drops below the detection limit at one time point and keep it to the final time point after first administration of study intervention. The final time point is the final time point of SARS-CoV-2 viral titer. For the mITT Population in Phase 2a Part, Phase 3 Part and Phase 2b/3 Part, and the mITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analysis as the key secondary endpoint (2) for the efficacy (excluding of the multiplicity adjustment) will be performed.
- Proportion of participants with positive SARS-CoV-2 viral titer at each time point

  This is defined as the proportion of the participants with positive result of SARS-CoV-2 viral titer. The positive rate of SARS-CoV-2 viral titer will be calculated at each time point for the mITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the mITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part. Pairwise comparison using the two-sided Mantel–Haenszel test between each S-217622 treatment group and placebo will be performed. The stratification factor of Mantel-Haenszel test will be the time from onset to randomization of COVID-19 (< 72 hours or ≥ 72 hours) and SARS-CoV-2

vaccination history (Yes or No) in participants with mild/moderate SARS-CoV-2 infection, and SARS-CoV-2 vaccination history (Yes or No) in participants with asymptomatic/mild symptoms only SARS-CoV-2-infection. For the mITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the stratification factor will only be SARS-CoV-2 vaccination history (Yes or No).

- SARS-CoV-2 viral titer at each time point
  This is defined as the measurement values of SARS-CoV-2 viral titer at each time point. SARS-CoV-2 viral titer will be summarized by treatment group at each time point for the mITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the mITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part. In Phase 2a Part, pairwise comparison using the van Elteren test between each S-217622 treatment group and placebo will be performed. The stratification factor of van Elteren test will be the time from onset to randomization of COVID-19 (< 72 hours or ≥ 72 hours) and SARS-CoV-2 vaccination history (Yes or No) in population of participants with mild/moderate SARS-CoV-2 infection, and SARS-CoV-2 vaccination history (Yes or No) in population of participants with asymptomatic/mild symptoms only SARS-CoV-2-infection. For the merged population of participants with mild/moderate and asymptomatic SARS-CoV-2 infection in Phase 2a Part, the same analyses will be performed. The stratification factor of van Elteren test will be the condition of participant (Mild/Moderate or Asymptomatic) in the merged population of Phase 2a Part. In Phase 3 Part and Phase 2b/3 Part, van Elteren test and analysis of covariance (ANCOVA) will be applied in the mild/moderate SARS-CoV-2 infection population and the asymptomatic/mild symptoms only SARS-CoV-2 infection population separately to conduct the pairwise comparison of the SARS-CoV-2 viral titer at each time point between each S-217622 treatment group and placebo group. SARS-CoV-2 viral titer at baseline and the same stratification factors used in van Elteren test will be used as the covariates in the ANCOVA model. Least squares means and the difference compared to placebo group will be also calculated based on the ANCOVA model. For the mITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the time from onset to randomization of COVID-19 (< 72 hours or ≥ 72 hours) will be excluded from the stratification factors of van Elteren test and the covariates of the ANCOVA model. Summary statistics for the SARS-CoV-2 viral titer at each time point will be calculated by each group.
- Change from baseline in SARS-CoV-2 viral titer at each time point (Phase 3 Part and

Phase 2b/3 Part).

This is defined as the absolute change from baseline in SARS-CoV-2 viral titer at each time point. For the mITT Population in Phase 3 Part and Phase 2b/3 Part, and the mITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as SARS-CoV-2 viral titer at each time point will be performed.

- Relative change rate from baseline in virus titer of SARS-CoV-2 at each time point
  This is defined as the relative change rate from baseline in virus titer of SARS-CoV-2 at each time point. The relative change rate will be calculated by dividing the absolute change from baseline by the baseline value. For the mITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the mITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as SARS-CoV-2 viral titer at each time point will be performed.
- Area under the curve (AUC) of the change from baseline in SARS-CoV-2 viral titer
  This is defined as the AUC of the change from baseline in virus titer of SARS-CoV-2. The assessment ranges of AUC will be Days 1 to 6 and Days 1 to 9. The AUC will be calculated using trapezoidal rules. Participants in the mITT Population in Phase 2a Part, Phase 3 Part and Phase 2b/3 Part, and the mITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part with available sample on the last time points of the assessment ranges (Day 6 or Day 9) will be included in this analysis. For the mITT Population, the same analyses as SARS-CoV-2 viral titer at each time point will be performed.
- Time to first negative RT-PCR result (Only Phase 2a Part)
  This is defined as the time to first negative RT-PCR result is confirmed after first administration of study intervention. For the ITT Population, the same analyses as the key secondary endpoint (2) (excluding of the multiplicity adjustment) will be performed. For Phase 2a Part, the same analyses will be also performed in the merged population of participants with mild/moderate and asymptomatic SARS-CoV-2 infection.
- Time to negative RT-PCR results at 2 consecutive time points (Only Phase 2a Part)
  This is defined as the time to negative RT-PCR results are confirmed for 2 consecutive time points after first administration of study intervention. The definition of 2 consecutive time points is based on the time points when the RT-PCR results are observed. For the ITT Population, the same analyses as the key secondary endpoint (2) (excluding of the multiplicity adjustment) will be performed.
- Time to sustained negative RT-PCR results (Only Phase 2a Part)

This is defined as the time to negative RT-PCR results is confirmed at one time point and keeps it to the final time point after first administration of study intervention. The final time point is the final time point of RT-PCR. For the ITT Population, the same analysis as the key secondary endpoint (2) for the efficacy (excluding of the multiplicity adjustment) will be performed.

- Proportion of participants with positive RT-PCR result at each time point.
  This is defined as the proportion of participants with positive RT-PCR result at each time point. For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analysis as the proportion of participants with positive SARS-CoV-2 viral titer at each time point will be performed.
- Amount of SARS-CoV-2 viral RNA at each time point
  This is defined as the evaluated value of amount of SARS-CoV-2 viral RNA at each time point. For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as SARS-CoV-2 viral titer at each time point will be performed. SARS-CoV-2 viral RNA at baseline and the same stratification factors as those in van Elteren test will be used as the covariates in the ANCOVA model.
- Change from baseline in amount of SARS-CoV-2 viral RNA at each time point
  This is defined as the absolute change from baseline in amount of SARS-CoV-2 viral titer at each time point. For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as SARS-CoV-2 viral titer at each time point will be performed. SARS-CoV-2 viral RNA at baseline and the same stratification factors as those in van Elteren test will be used as the covariates in the ANCOVA model.
- Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point
  This is defined as the relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point. For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as SARS-CoV-2 viral titer at each time point will be performed. SARS-CoV-2 viral RNA at baseline and the same stratification factors as those in van Elteren test will be used as the covariates in the ANCOVA model.

- 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. The assessment ranges of AUC will be Days 1 to 6 and Days 1 to 9. The AUC will be calculated using trapezoidal rules. Participants in the ITT Population and the ITT Population with less than 72 hours from COVID-19 onset to randomization with available sample on the last time points of the assessment ranges (Day 6 or Day 9) will be included in this analysis. For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as SARS-CoV-2 viral titer at each time point will be performed. SARS-CoV-2 viral RNA at baseline and the same stratification factors as those in van Elteren test will be used as the covariates in the ANCOVA model.
- Proportion of participants reaching each score on 8-Point Ordinal Scale
  This is defined as the proportion of participants reaching the following each score on 8-Point Ordinal Scale as below in the investigation period (Treatment period and Follow-up period). Participants reaching the following each score at baseline will be excluded from the analysis.
  - Symptomatic, no limitation of activities (Score 1) or more
  - Symptomatic, limitation of activities (Score 2) or more
  - Hospitalized, no oxygen therapy (Score 3) or more
  - Hospitalized, with oxygen therapy (< 5 L/min) (Score 4) or more
  - Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) or more
  - Hospitalized, with ventilation (Score 6) or more
  - Death (Score 7)

  The proportion of participants observed each event will be calculated for the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, and pairwise comparison using the two-sided Mantel‑Haenszel test between each S-217622 treatment group and placebo will be performed. The stratification factor of Mantel-Haenszel test will be the time from onset to randomization of COVID-19 (< 72 hours or ≥ 72 hours) and SARS-CoV-2 vaccination history (Yes or No) in population of participants with mild/moderate SARS-CoV-2 infection, and SARS-CoV-2 vaccination history (Yes or No) in population of participants with asymptomatic SARS-CoV-2 infection. For the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the stratification factor will only be SARS-CoV-2 vaccination history (Yes or No). Moreover, the risk

ratio and the risk difference in each S-217622 treatment group versus placebo will be calculated.

- Time to reaching each score on 8-Point Ordinal Scale

  This is defined as the time to reaching the following each score on 8-Point Ordinal Scale after first administration of study intervention. Participants reaching the following each score at baseline will be excluded from the analysis.

  - Symptomatic, no limitation of activities (Score 1) or more
  - Symptomatic, limitation of activities (Score 2) or more
  - Hospitalized, no oxygen therapy (Score 3) or more
  - Hospitalized, with oxygen therapy (< 5 L/min) (Score 4) or more
  - Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) or more
  - Hospitalized, with ventilation (Score 6) or more
  - Death (Score 7)

  For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as the key secondary endpoint (2) (excluding of the multiplicity adjustment) will be performed. For the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the stratification factor will only be SARS-CoV-2 vaccination history (Yes or No).

- SpO_2 at each time point

  This is defined as the evaluated values of SpO_2 at each time point. For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as virus titer of SARS-CoV-2 at each time point will be performed. SpO_2 at baseline and the same stratification factors of van Elteren test will be used as the covariates in the ANCOVA model. For the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the stratification factor will only be SARS-CoV-2 vaccination history (Yes or No).

- EQ-5D-5L Index Value at each time point

  For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the index value calculated from the EQ-5D-5L questionnaire at each time point will be summarized by treatment group. The index value will be calculated by EQ-5D-5L Crosswalk Index Value Calculator (Version 24OCT2019) [4] for Japanese participants, and Korean preference weights for EQ-5D-5L [5] for Korean participants.

- Change from baseline in EQ-5D-5L Index Value at each time point
  For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, change from baseline in the index value calculated from the EQ-5D-5L questionnaire at each time point will be summarized by treatment group. The index value will be calculated by same manner of EQ-5D-5L Index Value at each time point.
- VAS score (EQ-5D-5L) at each time point
  This is defined as the evaluated values of VAS score of EQ-5D-5L at each time point. For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the VAS score of EQ-5D-5L will be summarized by treatment group.
- Change from baseline in VAS score (EQ-5D-5L) at each time point
  This is defined as the absolute change from baseline in VAS score of EQ-5D-5L at each time point. For the ITT Population in Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the VAS score of EQ-5D-5L will be summarized by treatment group.
- Time to first occurrence of taste disorder or smell disorder and each symptom (Phase 3 Part and Phase 2b/3 Part)
  This is defined as the time to occurrence of taste disorder or smell disorder and each symptom after first administration of study intervention. The occurrence of taste disorder or smell disorder and each symptom is defined as follows.
  - Taste disorder
    The occurrence of taste disorder. Participants with taste disorder at baseline will be excluded from the analysis.
  - Smell disorder
    The occurrence of smell disorder. Participants with smell disorder at baseline will be excluded from the analysis.
  - Taste disorder or smell disorder
    The occurrence of the one of these symptoms. Participants with taste disorder or smell disorder at baseline will be excluded from the analysis.

  The occurrence of taste disorder / smell disorder will be judged following the rules below.
  - Taste disorder / smell disorder

The scores of taste disorder / smell disorder become worse from “0 : As usual” to “1 : Less than usual” or “2 : Not at all”.

In the ITT Population in Phase 3 Part and Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as the time to resolution of the 5 COVID-19 symptoms (primary endpoint for the efficacy in Phase 3 Part) will be performed (excluding of the multiplicity adjustment). For the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the stratification factor will only be SARS-CoV-2 vaccination history (Yes or No). For the ITT Population in Phase 3 Part, the stratification factor will be the time from onset to randomization of COVID-19 (< 72 hours or ≥ 72 hours) and SARS-CoV-2 vaccination history (Yes or No). For Phase 2b/3 Part, the stratification factor will be SARS-CoV-2 vaccination history (Yes or No).

9.2.2.2 For Participants with Mild/Moderate SARS-CoV-2 infection

- Time to first improvement of COVID-19 symptoms (Only Phase 2a Part)
  In the ITT Population, the same analyses as the time to resolution of the 5 COVID-19 symptoms (primary endpoint for the efficacy in Phase 3 Part) will be performed (excluding the multiplicity adjustment). The symptoms of COVID-19 will be evaluated on 4-point scale (0 : None, 1 : Mild, 2 : Moderate, 3 : Sever) using participant-reported outcomes and the improvement of symptoms will be judged following the rules below:

  - For the pre-existing symptoms that exist before onset of COVID-19 and participants judge to have worsened at the baseline (before administration), the severity should be improved.
    - Severe at the baseline: Moderate, Mild, or None
    - Moderate at the baseline: Mild, or None

  - For the pre-existing symptoms that exist before onset of COVID-19 and participants judge not to have worsened at the baseline (before administration), the severity should be persisted or improved.
    - Severe at the baseline: Severe, Moderate, Mild, or None
    - Moderate at the baseline: Moderate, Mild, or None

  - Symptoms other than the above, which not exist before onset of COVID-19 and occur at or after baseline, should be none.
    - Severe or Moderate at baseline: Mild, or None

- For the pre-existing symptoms that exist before onset of COVID-19, if presence or absence of the symptom exacerbation due to COVID-19 is missing, should be mild or none.

Participants who have only symptoms of Mild or None at baseline will be excluded from the analyses. The improvement of COVID-19 symptoms is defined as the time when all 12 COVID-19 symptoms disappear, maintain, or improve firstly as shown above after first administration of study intervention. If the condition persists for at least 24 hours, the participants are considered to achieve this endpoint. Participants who administered the prohibited concomitant medications will be censored at the last time when assessed COVID-19 symptoms up to the day before the first administration of the prohibited concomitant medications, regardless of whether or not they improved. Participants who are not confirmed the improvement of COVID-19 symptoms and not administered the prohibited concomitant medications (Section 9.1.2) will be censored at the last time when assessed COVID-19 symptoms. Participants who received the prohibited concomitant medications and did not have COVID-19 symptoms assessed before administration of the prohibited concomitant medications will be excluded from the analyses.

- Time to first improvement of COVID-19 symptoms (Persistent improvement state: ≥ 72 hours, ≥ 120 hours) (Only Phase 2a Part)
  In the ITT Population, the same analyses as the time to resolution of the 5 COVID-19 symptoms (primary endpoint for the efficacy in Phase 3 Part) which the persistence time is changed from 24 hours to 72 hours and 120 hours will be performed (excluding of the multiplicity adjustment).
- Time to first improvement of each symptom of COVID-19 (Only Phase 2a Part)
  This is defined as the time to improvement of each symptom of COVID-19 (low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath [difficulty breathing], nausea, vomiting, and diarrhea) after first administration of study intervention. The definition and judgment of symptom of COVID-19 improvement are shown in 9.2.2 (Time to first improvement of COVID-19 symptoms (Only Phase 2a Part)). In the ITT Population, the same analyses as the time to resolution of the 5 COVID-19 symptoms (primary endpoint for the efficacy in Phase 3 Part) will be performed (excluding of the multiplicity adjustment).

- Time to resolution of the 5 COVID-19 symptoms without recurrence (Persistent resolution state: ≥ 48 hours [2 days]) (Only Phase 3 Part)

  This is defined as the time to achieve the resolution of the 5 COVID-19 symptoms (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness) lasting at least 48 hours without recurrence of all 5 symptoms lasting at least 2 days (48 hours) after the resolution of the 5 COVID-19 symptoms. The definition of recurrence is as follows.

  Recurrence will be judged if any score of the 5 COVID-19 symptoms becomes moderate or higher (moderate or severe) at any point in time from the resolution of the 5 COVID-19 symptoms till the last observation time point of participant diary and the condition persists for 48 hours or longer. However, if the symptom is an existing symptom which has been present before the onset of COVID-19 symptoms and is judged to have worsened at baseline (before administration) by participants and the severity at baseline is severe, or if the symptom is an existing symptom which has been present before the onset of COVID-19 symptoms and is judged to have not worsened at baseline (before administration) by participants and the severity at baseline is moderate, recurrence will be judged if the score becomes severe and the condition persists for 48 hours. If the symptom is an existing symptom which has been present before the onset of COVID-19 symptoms and is judged to have not worsened at baseline (before administration) by the participants and the severity at baseline is severe, recurrence assessment will not be performed.

  Participants who administered the prohibited concomitant medications described in 9.1.2 will be censored at the last time when assessed COVID-19 symptoms up to the day before the first administration of the prohibited concomitant medications, regardless of whether or not they resolved without recurrence.

  The way how to determine the censor cases is same as that for the time to resolution of the 5 symptoms.

  For the ITT Population with less than 72 hours from COVID-19 onset to randomization and the ITT Population, the same analyses as the time to resolution of the 5 COVID-19 symptoms (primary endpoint for the efficacy in Phase 3 Part) will be performed (excluding of the multiplicity adjustment).

- Time to resolution of the 12 COVID-19 symptoms or the sub-symptoms of COVID-19 (Only Phase 3 Part)

  The time to resolution of the 12 COVID-19 symptoms is defined as the time to

resolution of all 12 symptoms of COVID-19 (low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath [difficulty breathing], nausea, vomiting, and diarrhea) after first administration. The time to resolution of the sub-symptoms of COVID-19 is defined as the time to resolution of all sub-symptoms of COVID-19 symptoms after first administration. The symptoms of COVID-19 will be evaluated on 4-point scale (0 : None, 1 : Mild, 2 : Moderate, 3 : Severe) using participant-reported outcomes and the resolution of symptoms will be judged following the rules below:

- For the pre-existing symptoms that exist before onset of COVID-19 and participants judge to have worsened at the baseline (before administration), the severity should be improved or persisted.
  - Severe at the baseline: Moderate, Mild, or None
  - Moderate at the baseline: Mild, or None
  - Mild at the baseline: Mild, or None

  Note: The participants will be asked only for the pre-existing symptoms (in the past 30 days) and presence or absence of symptom exacerbation due to COVID-19 and evaluate the severity (to be improved) at the baseline. To avoid recall bias, the severity of the pre-existing symptoms before the onset of COVID-19 is not evaluated.

- For the pre-existing symptoms that exist before onset of COVID-19 and participants judge not to have worsened at the baseline (before administration), the severity should be persisted or improved.
  - Severe at the baseline: Severe, Moderate, Mild, or None
  - Moderate at the baseline: Moderate, Mild, or None
  - Mild at the baseline: Mild, or None

- Symptoms other than the above, which not exist before onset of COVID-19 and occur at or after baseline, should be none.
  - Severe, Moderate or Mild at baseline: None

- For the pre-existing symptoms that exist before onset of COVID-19, if presence

or absence of the symptom exacerbation due to COVID-19 is missing, should be none.

Participants who have only symptoms of None will be excluded from the analyses. The resolution of the 12 COVID-19 symptoms or sub-symptoms are defined as the time when all 12 COVID-19 symptoms or all sub-symptoms of COVID-19 disappear, maintain, or improve firstly as shown above after first administration of study intervention. If the condition persists for at least 24 hours, the participants are considered to achieve these endpoints. Participants who administered the following prohibited concomitant medications will be censored at the last time when assessed COVID-19 symptoms up to the day before the first administration of the prohibited concomitant medications, regardless of whether or not they resolved. Participants who are not confirmed the resolution of the 12 COVID-19 symptoms or sub-symptoms of COVID-19 and not administered the prohibited concomitant medications will be censored at the last time when assessed COVID-19 symptoms. Participants who received the following prohibited concomitant medications and did not have COVID-19 symptoms assessed before administration of the prohibited concomitant medications will be excluded from the analyses.

- Approved drugs for the treatment of SARS-CoV-2 infection

- Unapproved drugs for the treatment of SARS-CoV-2 infection (eg, Interferon, Convalescent plasma, Monoclonal antibody, Immunoglobulins, Antirheumatic drugs, Corticosteroids [Oral, Injection, Inhaled], Ivermectin, Favipiravir)

For participants who are not confirmed the resolution of COVID-19 symptoms, the supplemental analysis will be performed in which the last assessment time of COVID-19 symptoms is defined as the censored time.
Each sub-symptom of COVID-19 is defined as follows.

- Respiratory symptoms: Stuffy or runny nose, Sore throat, Shortness of breath, Cough
- Systemic symptoms: Low energy or tiredness, Muscle or body aches, Headache, Chills or shivering, Feeling hot or feverish
- Digestive symptoms: Nausea, Vomiting, Diarrhea

In the ITT Population with less than 72 hours from COVID-19 onset to randomization, the same analyses as the time to resolution of the 5 COVID-19 symptoms (primary endpoint for the efficacy in Phase 3 Part) will be performed (excluding of the multiplicity adjustment). For the time to resolution of the 12 COVID-19 symptoms, the same analyses will be performed in the ITT Population.

- Time to resolution of COVID-19 symptoms including taste disorder and smell disorder (Only Phase 3 Part)

  In the ITT Population with less than 72 hours from COVID-19 onset to

randomization and the ITT Population, the same analyses as the time to resolution of the 5 COVID-19 symptoms (primary endpoint for the efficacy in Phase 3 Part) will be performed (excluding of the multiplicity adjustment). The resolution of COVID-19 symptoms including taste disorder and smell disorder is defined as the resolution of all 14 symptoms of COVID-19 (low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath [difficulty breathing], nausea, vomiting, diarrhea, taste disorder and smell disorder) after first administration of study intervention. The definition and judgment of the 12 symptoms of COVID-19 resolution are shown in 9.2.2 (Time to resolution of the 12 COVID-19 symptoms or the sub-symptoms of COVID-19 (Only Phase 3 Part)). The definition and judgment of taste disorder and smell disorder resolution are below:

- For the pre-existing symptoms that exist before onset of COVID-19 and participants judge to have worsened at the baseline (before administration), the severity should be improved.
  - "Not at all" at the baseline: "Less than usual" or "As usual"
  - "Less than usual" at the baseline: "Less than usual" or "As usual"
- For the pre-existing symptoms that exist before onset of COVID-19 and participants judge not to have worsened at the baseline (before administration), the severity should be persisted or improved.
  - "Not at all" at the baseline: "Not at all", "Less than usual", or "As usual"
  - "Less than usual" at the baseline: "Less than usual" or "As usual"
- Symptoms other than the above, which not exist before onset of COVID-19 and occur at or after baseline, should be “As usual”.
  - "Not at all", "Less than usual", or "As usual" at baseline: "As usual"

The resolution of COVID-19 symptoms is defined as the time when all 14 COVID-19 symptoms disappear, maintain, or improve firstly as shown above after first administration of study intervention. If the condition persists for at least 24 hours, the participants are considered to achieve this endpoint. Participants who administered the prohibited concomitant medications will be censored at the last time when assessed COVID-19 symptoms up to the day before the first administration of the prohibited concomitant medications, regardless of whether or not they resolved. Participants who are not confirmed the resolution of COVID-19 symptoms and not administered the prohibited concomitant medications will be censored at the last time when assessed COVID-19 symptoms. Participants who received the prohibited

concomitant medications and did not have COVID-19 symptoms assessed before administration of the prohibited concomitant medications will be excluded from the analyses.

- Time to resolution of each symptom of COVID-19 (Only Phase 3 Part)
  This is defined as the time to resolution of each symptom of COVID-19 (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness) after first administration of study intervention. The definition and judgment of symptom of the 5 COVID-19 resolution are shown in 9.1.2. In the ITT Population with less than 72 hours from COVID-19 onset to randomization and the ITT Population, the same analyses as the time to resolution of the 5 COVID-19 symptoms (primary endpoint for the efficacy in Phase 3 Part) will be performed (excluding of the multiplicity adjustment).
  -
- Change from baseline in total score of COVID-19 symptoms at each time point (Only Phase 2a Part)
  This is defined as the absolute change from baseline in total score of COVID-19 symptoms and each score of COVID-19 symptoms at each time point. For the ITT Population, the same analyses as SARS-CoV-2 viral titer at each time point for participants with mild/moderate SARS-CoV-2 infection will be performed. As stratification factors for van Elteren test, the time from onset to randomization of COVID-19 (< 72 hours or ≥ 72 hours) and SARS-CoV-2 vaccination history (Yes or No) will be used. Total score of COVID-19 symptoms at baseline and the same stratification factors as those in van Elteren test will be used as the covariates in the ANCOVA model.
- Proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point (Only Phase 2a Part)
  This is defined as the proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point. The improvement of COVID-19 is defined as shown in 9.1.2. For the ITT Population, the same analyses as proportion of participants with positive SARS-CoV-2 viral titer at each time point for participants with mild/moderate SARS-CoV-2 infection will be performed for participants with improvement of COVID-19 symptoms and each symptom. As stratification factors for Mantel‑Haenszel test, the time from onset to randomization of COVID-19 (< 72 hours or ≥ 72 hours) and SARS-CoV-2 vaccination history (Yes or No) will be used.
- Proportion of participants with taste disorder or smell disorder at each time point

This is defined as the proportion of participants with taste disorder or smell disorder (the score of 3-point scale is "1 : Less than usual" or "2 : Not at all") at each time point. The same analyses as the positive rate of virus titer of SARS-CoV-2 at each time point for participants with mild/moderate SARS-CoV-2 infection will be performed in the ITT Population in Phase 2a Part and Phase 3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part. For the ITT Population of Phase 3 Part, SARS-CoV-2 vaccination history (Yes or No) and time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) will be used as the strata. In Phase 3 Part, the same analyses will be performed for the proportion of participants with both taste disorder and smell disorder and with each disorder.

- Proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration (Only Phase 3 Part)

  This is defined as the proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration. The participants without resolution of COVID-19 symptoms after 3 weeks of administration is defined as follows:

  - Last time point of 12 symptoms of COVID-19 (low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath [difficulty breathing], nausea, vomiting, and diarrhea) is observed after Day 18 (after 432 hours of first administration).
  - Proportion of participants who have one or more resolvedCOVID-19 symptoms which did not resolve at the last time point.

  The symptoms of COVID-19 will be evaluated on 4-point scale (0 : None, 1 : Mild, 2 : Moderate, 3 : Severe) using participant-reported outcomes and the resolution of symptoms at the last time point will be judged following the rules below:

  - For the pre-existing symptoms that exist before onset of COVID-19 and participants judge to have worsened at the baseline (before administration), the severity should be persisted or improved.
    - Severe at the baseline: Moderate, Mild, or None
    - Moderate at the baseline: Mild, or None
    - Mild at the baseline: Mild, or None

    Note: The participants will be asked only for the pre-existing symptoms (in the past 30 days) and presence or absence of symptom exacerbation due to COVID-19 and evaluate the severity (to be improved) at the baseline. To avoid recall bias, the severity of the pre-existing symptoms before the onset of COVID-19 is not evaluated.
  - For the pre-existing symptoms that exist before onset of COVID-19 and participants judge not to have worsened at the baseline (before administration), the severity should be persisted or improved.
    - Severe at the baseline: Severe, Moderate, Mild, or None

- Moderate at the baseline: Moderate, Mild, or None
- Mild at the baseline: Mild, or None

- Symptoms other than the above, which do not exist before onset of COVID-19 and occur at or after baseline, should be none.
  - Severe, Moderate or Mild at baseline: None
- For the pre-existing symptoms that exist before onset of COVID-19, if presence or absence of the symptom exacerbation due to COVID-19 is missing, should be none.

Participants whose last time point of COVID-19 symptoms is less than 432 hours (18 days) will be treated as those who did not have resolution of COVID-19 symptoms.

The comparison will be performed using the one-sided Mantel–Haenszel test at a one-sided significance level of 0.025 with SARS-CoV-2 vaccination history (Yes or No) as a stratification factor between S-217622 125 mg group and placebo for participants with mild/moderate SARS-CoV-2-infection in the ITT Population with less than 72 hours from COVID-19 onset to randomization. The same analyses will be performed using the Mantel-Haenszel test stratified by SARS-CoV-2 vaccination history (Yes or No) and time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) for the ITT Population.

As the other analysis for this endpoint, the risk ratio and the risk difference in S-217622 125 mg group versus placebo and the corresponding 95% CI will be calculated.

- Proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration (including taste disorder and smell disorder) (Only Phase 3 Part)

  This is defined as the proportion of participants without resolution of COVID-19 symptoms, symptoms including taste disorder and smell disorder after 3 weeks of first administration. The definition and judgment of 12 symptoms of COVID-19 not resolution are shown in the secondary endpoint “Proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration”. The definition and judgment of taste disorder and smell disorder not resolution are below:

  - For the pre-existing symptoms that exist before onset of COVID-19 and participants judge to have worsened at the baseline (before administration), the severity should be persisted or improved.
    - "Not at all" at the baseline: "Less than usual" or "As usual"
    - "Less than usual" at the baseline: "Less than usual" or "As usual"
  - For the pre-existing symptoms that exist before onset of COVID-19 and participants judge not to have worsened at the baseline (before administration), the severity should be persisted or improved.
    - "Not at all" at the baseline: "Not at all", "Less than usual", or "As usual"
    - "Less than usual" at the baseline: "Less than usual" or "As usual"
  - Symptoms other than the above, which do not exist before onset of COVID-19 and occur at or after baseline, should be none.

- "Not at all", "Less than usual", or "As usual" at baseline: "As usual"

The same analyses as the secondary endpoint “Proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration” will be performed.

- Proportion of participants without resolution of each COVID-19 symptom after 3 weeks of administration (Only Phase 3 Part)
  This is defined as the proportion of participants without resolution of each COVID-19 symptoms, symptoms including taste disorder and smell disorder after 3 weeks of first administration. The definition and judgment of 12 symptoms of COVID-19 not resolution are shown in 9.2.1.1.3. The definition and judgment of taste disorder and smell disorder not resolution are shown in 9.2.2.2 (Proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration (including taste disorder and smell disorder)).
- Time to resolution of fever (< 37.0°C)
  This is defined as the time to normal temperature after first administration of study intervention. Time to normal temperature is defined the time when axillary temperature become normal temperature (less than 37.0 °C) and this state keeps at least 24 hours. For the ITT Population in Phase 2a Part and Phase 3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as the time to resolution of the 5 COVID-19 symptoms (primary endpoint for the efficacy in Phase 3 Part) will be performed (excluding of the multiplicity adjustment). Participants with normal temperature (less than 37.0 °C) at baseline will be excluded from the analysis.

9.2.2.3 For Participants with Asymptomatic SARS-CoV-2 infection

Participants with asymptomatic SARS-CoV-2 infection is defined as below:

- Pre-existing symptoms that exist before onset of COVID-19: Participants judge not to have worsened at the baseline.

- Symptoms that do not exist before onset of COVID-19: Participants have no these symptoms at the baseline.

- Proportion of participants with occurrence of the 14 COVID-19 symptoms
  For the ITT Population, the same analyses as proportion of participants with development/worsening of COVID-19 symptoms (primary endpoint for the efficacy in Phase 2b/3 Part) will be performed (excluding of the multiplicity adjustment). The occurrence of COVID-19 symptoms will be evaluated during the evaluation period

of patient diary in Phase 2a Part and until 14 days from the first administration of the study intervention in Phase 2b/3 Part. Participants with taste disorder, smell disorder or severe symptoms of COVID-19 at baseline will be excluded from the analysis. The onset of symptoms will be judged following the rules below.

- Taste disorder or smell disorder
  The scores of taste disorder or smell disorder become worse from “0 : As usual” to “1 : Less than usual” or “2 : Not at all”.
- 3 symptoms (feeling hot or feverish, cough or shortness of breath [difficulty breathing])
  - The symptom score in at least one symptom have worsened one or more from baseline:
    - None at the baseline: Worsening to Mild or Moderate or Severe
    - Mild at the baseline: Worsening to Moderate or Severe
    - Moderate at the baseline: Worsening to Severe

    (Symptoms with Severe at the baseline are excluded from the judgment of onset)
- 9 symptoms (low energy or tiredness, muscle or body aches, headache, chills or shivering, stuffy or runny nose, sore throat, nausea, vomiting, or diarrhea)
  - The symptom score in at least two symptoms have worsened one or more from baseline:
    - None at the baseline: Worsening to Mild or Moderate or Severe
    - Mild at the baseline: Worsening to Moderate or Severe
    - Moderate at the baseline: Worsening to Severe

    (Symptoms with Severe at the baseline are excluded from the judgment of onset)

- Proportion of participants with occurrence of the 14 COVID-19 symptoms and fever (≥ 37.0°C) (only Phase 2a Part)
  This is defined as the proportion of participants with occurrence of following symptoms at same time.
  1. 12 symptoms of COVID-19 or taste disorder/smell disorder
  2. fever (axillary temperature, 37.0°C or more)

  For the ITT Population, the same analyses as proportion of participants with

development/worsening of COVID-19 symptoms (primary endpoint for the efficacy in Phase 2b/3 Part) will be performed (excluding of the multiplicity adjustment). Participants with taste disorder, smell disorder, severe symptoms of COVID-19 or fever (37.0 °C or more temperature) at baseline will be excluded from the analysis.

- Proportion of participants with occurrence of COVID-19 symptoms and fever (≥ 37.0°C) (only Phase 2b/3 Part)
  This is defined as the proportion of participants in the asymptomatic SARS-CoV-2 infection population in the ITT population of Phase 2b/3 Part with development of the following #1 and #2 at the same time by 14 days from the first administration of the study intervention.
  #1 Participants with development of any of the 12 symptoms of COVID-19, taste disorder, or smell disorder (See "Proportion of participants with occurrence of COVID-19 symptoms (Phase 2b/3 Part)" of this Section for definition of development)
  #2 Fever (the axillary temperature is ≥ 37.0°C)
  The same analysis as the primary endpoint in Phase 2b/3 Part (proportion of participants with development/worsening of COVID-19 symptoms) (except for multiplicity adjustment) will be performed in the asymptomatic SARS CoV-2 infection population in the ITT population.

9.2.2.4 For Participants with Mild Symptoms Only SARS-CoV-2 infection

Participants with mild symptoms only SARS-CoV-2 infection is defined as not asymptomatic participants. The definition of asymptomatic is refer to section 9.2.2.3.

- Time to resolution of the 5 COVID-19 symptoms
  For the ITT Population, the same analyses as the time to resolution of the 5 COVID-19 symptoms (primary endpoint for the efficacy in Phase 3 Part) will be performed (excluding of the multiplicity adjustment).

9.3 Subgroup Analysis

For analyses of primary endpoints in Phase 2a Part, Phase 3 Part and Phase 2b/3 Part, and key secondary endpoints in Phase 3 Part and Phase 2b/3 Part, these analyses will be performed in subgroups defined in Table 9-3. The subgroup analyses will be performed in the ITT Population or the mITT Population, and the ITT Population or mITT Population with less than 72 hours from COVID-19 onset to randomization.

Table 9-3 Subgroup analyses

Part		Endpoint Analysis	Subgroup
Phase 2a Part	Primary Endpoint	Change from baseline in SARS-CoV-2 viral titer at each time point	1, 2, 3, 4, 5, 6, 7
Phase 3 Part	Primary Endpoint	Time to resolution of the 5 COVID-19 symptoms	1, 2, 3, 7, 8, 9, 10
Phase 2b/3 Part	Primary Endpoint	Proportion of participants with development/worsening of the 14 COVID-19 symptoms	1, 2, 3, 7, 8
Phase 3 Part	Key Secondary Endpoint (1)	Change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA	1, 2, 3, 7, 8, 9
	Key Secondary Endpoint (2)	Time to the first negative SARS-CoV-2 viral titer	1, 2, 3, 7, 8, 9
	Secondary Endpoint	Time to resolution of the 12 COVID-19 symptoms	5
Phase 2b/3 Part	Key Secondary Endpoint (1)	Change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA	1, 2, 3, 7, 8
	Key Secondary Endpoint (2)	Time to the first negative SARS-CoV-2 viral titer	1, 2, 3, 7, 8

[Subgroup]

1. Country (Japan, Korea, Vietnam, and pooled population in Japan and Vietnam)
2. Serostatus at baseline (Positive, Negative)
3. Age (< 18, ≥ 18)
4. Age (< 18, ≥ 18) in Japanese participants
5. Number of moderate or more COVID-19 symptoms at baseline (≤ 2 symptoms, ≥ 3 symptoms)
6. Number of moderate or more COVID-19 symptoms at baseline (≤ 2 symptoms, ≥ 3 symptoms) in Japanese participants
7. Vaccination history (Yes, No)
8. SARS-CoV-2 viral strain
9. Time from onset to randomization (≥ 72 hours)
10. Pollen allergy condition (Yes, No)

Subgroup analyses for 2 and 8 will be performed as other analysis.

9.4 Sensitivity Analysis

Sensitivity analyses for time-to-event endpoints in Table 9-4 will be also performed. The sensitivity analyses are as follows:

- All censored times will be Day 28
- Change the strata in the primary and the key secondary analysis for the primary endpoint in Phase 3 Part

The sensitivity analyses will be performed in the ITT Population or the mITT Population

for Phase 3 Part and Phase 2b/3 Part, and the ITT Population or mITT Population with less than 72 hours from COVID-19 onset to randomization of Phase 3 Part.

Table 9-4 Endpoints subject to Sensitivity Analyses

Part	Endpoint		Sensitivity Analyses
Phase 3 Part	Primary Endpoint	Time to resolution of the 5 COVID-19 symptoms	1, 2, 3, 4
Phase 3 Part, Phase 2b/3 Part	Key Secondary Endpoint (2)	Time to the first negative SARS-CoV-2 viral titer	1

1. All censored times will be Day 28
2. Change the strata:
   - SARS-CoV-2 vaccination history (Yes or No) and Pollen allergy conditions (Yes or No) in the ITT Population with less than 72 hours from COVID-19 onset to randomization
   - Time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours), SARS-CoV-2 vaccination history (Yes or No), and Pollen allergy conditions (Yes or No) in the ITT Population
3. Change the strata:
   - SARS-CoV-2 vaccination history (Yes or No) and Country (Japan, Korea, Vietnam) in the ITT Population with less than 72 hours from COVID-19 onset to randomization
   - Time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours), SARS-CoV-2 vaccination history (Yes or No), and Country (Japan, Korea, Vietnam) in the ITT Population
4. Change the strata:
   - Pollen allergy conditions (Yes or No) and Country (Japan, Korea, Vietnam) in the ITT Population with less than 72 hours from COVID-19 onset to randomization
   - Time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours), Pollen allergy conditions (Yes or No), and Country (Japan, Korea, Vietnam) in the ITT Population

10. SAFETY

Analyses will be performed for the Safety Analysis Population. These analyses will be performed in Phase 2a Part, Phase 3 Part, Phase 2b/3 Part and merged all parts including Phase 2b Part. All analyses will be performed in participants with mild/moderate SARS-CoV-2 infection, in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection and in the population merged the two.

Subgroup analysis for safety will be performed for merged all parts. The subgroup will be country (Japan) and age (<18, 18 to 64, ≥65).

10.1 Adverse Events

Adverse events (AEs) will be coded and classified by system organ class (SOC) and preferred term (PT) using the MedDRA Version 24.0. Unless otherwise specified, analyses will be based on treatment-emergent adverse events (TEAEs), defined as any AEs reported after the initial administration of the study intervention (S-217622 or placebo).

The number and proportion of participants who experience at least 1 TEAE will be summarized by treatment group. If a participant experiences the same TEAE more than once in different categories, the participant will be counted once in each category. The proportions will be presented along with 95% CI calculated with Clopper-Pearson method. The reported number of events will also be calculated. TEAEs with an outcome of death, serious TEAEs other than deaths and TEAE leading to discontinuation of the study intervention will be summarized in the same manner. Also, Treatment-related TEAEs, treatment-related TEAEs with an outcome of death, serious Treatment-related TEAEs other than deaths and treatment-related TEAEs leading to discontinuation of study intervention will be summarized in the same manner as TEAEs. The definitions of these events are shown in Table 10-1.

Table 10-1. Definition of Adverse Event Terms

Term	Definition
TEAE with an outcome of death	TEAE with ‘Fatal’ in terms of outcome
Serious TEAE other than deaths	TEAE with ‘Serious’ in terms of seriousness without 'Fatal' in terms of outcome
TEAE leading to discontinuation of the study intervention	TEAE with ‘Drug withdrawn’ in terms of the action taken for study intervention
Treatment-related TEAE	TEAE with ‘Related’ in terms of the causal relationship with study intervention
Treatment-related TEAEs with an outcome of death	Treatment-related TEAE with ‘Fatal’ in terms of outcome
Serious Treatment-related TEAEs other than deaths	Treatment-related TEAE with ‘Serious’ in terms of seriousness without 'Fatal' in terms of outcome
Treatment-related TEAE leading to discontinuation of study intervention	Treatment-related TEAE with ‘Drug withdrawn’ in terms of the action taken for study intervention

The number and proportion of participants who experience TEAEs will be summarized by SOC and PT by treatment group. For these summaries, participants with multiple TEAEs will be counted only once within each SOC and each PT. Treatment-related TEAEs will be summarized in the same manner. In Phase 3 Part and Phase 2b/3 Part, serious TEAEs will be summarized in the same manner.

The number and proportion of participants who experience TEAEs in each category of severity, outcome and period of onset will be summarized by SOC and PT by treatment group. Participants who experience the same TEAE more than once in different categories will be counted only once by the highest priority shown in Table 10-2 within

each SOC and each PT. For category of period of onset, participants who experience the same TEAE more than once in different categories will be counted in each category. Treatment-related TEAEs will be summarized in the same manner.

Table 10-2. Priority of Severity, Outcome and Period of Onset Categories

Priority	Category		
	Severity	**Outcome**	**Period of onset**
1	Severe	Fatal	Day 1
2	Moderate	Recovered/resolved with sequelae	Day 2-5
3	Mild	Not recovered/not resolved	Day 6-7
4		Recovering/resolving	Day 8-14
5		Recovered/resolved	Day 15-28
6		Unknown	> Day 28 *

*: "> Day 28" will be used in analyses for Phase 3 Part, Phase 2b/3 Part and Merged All Parts.

10.2 Laboratory Evaluations

The laboratory tests in Table 10-3 will be evaluated.

Summary statistics of measurement values and each change from baseline in laboratory test data will be calculated by treatment group for each scheduled time point after randomization (including of baseline).

Scatter plot of baseline and last measurement values will be presented by treatment group.

If the result is below the detection limit, the detection limit value will be used for summary statistics and reported value will be used for lists. For example, when the result is “<=0.03”, “0.03” will be used for summary statistics, and “<=0.03” will be used for lists.

For qualitative parameters of urinalysis, shift tables using baseline and each measurement value will be created by study intervention for each scheduled time point.

The time points are shown in Appendix 1.

Table 10-3. Laboratory Tests

	Parameter
Hematology	Platelet count, Red blood cell count, Hemoglobin, Hematocrit, Red blood cell index (MCV, MCH, Reticulocyte count, White blood cell count, Differential white blood count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)
Blood chemistry	AST, ALT, Total bilirubin, Direct bilirubin, GGT, LDH, ALP, Uric acid, Cholinesterase, Total protein, Albumin, BUN, Serum creatinine, Sodium (Na), Potassium (K), Chloride (Cl), Calcium (Ca), Phosphorus, Total cholesterol, Blood glucose (fasted), HDL-C, LDL-C, Triglyceride (TG), CRP, CK, Iron, Ferritin, UIBC

	Parameter
Coagulation test	PT-INR, APTT, Fibrinogen
Serologic test	IgG, IgM, Haptoglobin
Urinalysis	pH, Glucose, Protein (qualitative), Occult blood, Ketones, Bilirubin, Urobilinogen
Other	[redacted]

Abbreviations; ALP=Alkaline phosphatase; ALT=Alanine aminotransferase; APTT = Activated partial thromboplastin time; AST=Aspartate aminotransferase; BUN=Blood urea nitrogen; CK = Creatine kinase; CRP = C-reactive protein; GGT=Gamma glutamyl transferase; HDL-C = High Density Lipoprotein cholesterol; IgG = Immunoglobulin G; IgM = Immunoglobulin M; IFN = Interferon; INR = International normalized ratio; [redacted] LDH=Lactate dehydrogenase; LDL-C = Low Density Lipoprotein cholesterol; PT INR= Prothrombin time international normalized ratio; [redacted] UIBC = Unsaturated iron binding capacity

The following steps will be applied when participants have the laboratory data observed in both central and local laboratory for each time point:

- The laboratory data observed within acceptable time window specified in Table 6-3 will be picked out.
- If any laboratory data are observed in central laboratory within the acceptable time window, laboratory data used in the safety analysis will be determined according to the pre-specified rule in the section 6.4 among the measurements in central laboratory.
- If only laboratory data are observed in local laboratory within the acceptable time window, laboratory data used in the safety analysis will be determined according to the pre-specified rule in the section 6.4 among the measurements in local laboratory.

10.3 Vital Signs

The vital signs in Table 10-4 will be evaluated.

Summary statistics of measurement values and each change from baseline in vital signs data will be calculated by treatment group for each scheduled time point after randomization (including of TFL baseline). The time points are shown in Appendix 1.

Table 10-4. Vital Signs

	Parameter
Vital signs	Systolic blood pressure, Diastolic blood pressure, Pulse rate, Respiration rate

10.4 Electrocardiograms

For Phase 2a Part, ECG findings (Normal, Abnormal-not clinically significant, Abnormal-clinically significant) will be summarized by treatment group for each time

point using shift tables.

11. PHAMACOKINETIC ANALYSIS

All pharmacokinetic analyses will be performed in the PK Concentration Population.

Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of available documentation (e.g., bioanalytical report, clinical report). Any such exclusion will be communicated to the sponsor and clearly listed in the study report along with justification for exclusion.

The number of samples, number of samples below the lower limit of quantification, number of samples on Day 2 and number of samples on Day 6 will be summarized by part and the treatment group.

Individual plasma concentration of S-217622 with the number of doses and the elapsed time from the last dose will be listed by part, the treatment group and the study day.

The plasma concentration-time (elapsed time from the last dose) plot will be graphically presented appropriately at the linear scale by part, treatment group and study day.

Plasma S-217622 concentrations within 20 to 28 hours after the first dose on Day 2 will be summarized as plasma trough concentrations (C_{24}) by dose and part with number of non-missing observations (N), arithmetic mean (Mean), SD, coefficient of variation (CV%, calculated by SD/Mean × 100), geometric mean (Geometric Mean), coefficient of variation for geometric mean (CV% Geometric Mean), median (Median), minimum (Min), and maximum (Max) values. The CV% Geometric Mean will be calculated according to a formula, CV% Geometric Mean = $[\exp(sd^2) - 1]^{1/2} \times 100$, where sd is the standard deviation for natural log (ln)-transformed data. If possible, also summarize by the age group (12 to 18 years old, 19 to 64 years old, and over 65 years old). If N is less than 3, the data will not be summarized. For summary of plasma concentration, plasma concentration below limit of quantification (BLQ) will be treated as zero (0) for calculations of Mean, SD, CV%, Median, Min, and Max and treated as missing for calculation of Geometric Mean and CV% Geometric Mean.

12. INTERIM EVALUATION

No interim analysis for considering of continuation or discontinuation in the middle of the Phase 2a Part and Phase 3 Part of this study is planned. During enrollment of Phase 2b Part, Phase 3 Part and Phase 2b/3 Part, the analyses of Phase 2a Part will be performed and there is possibility of dose selection for Phase 2b Part, Phase 3 Part and Phase 2b/3 Part. Also, during enrollment of Phase 3 Part and Phase 2b/3 Part, the analyses of Phase 2a Part and Phase 2b Part will be performed and there is possibility of dose selection for

Phase 3 Part and Phase 2b/3 Part.

In Phase 2a Part, there is possibility that the multiple interim assessment to evaluate the efficacy and safety of S-217622 will be conducted based on the collected data at the time (i.e., completion of Day 9 measurement in all participants or about 4 weeks after the start of Phase 2a Part based on data available at that time).

13. INTERIM ANALYSIS

For the participant populations with asymptomatic/mild symptoms only SARS-CoV-2 infection in Phase 2b/3 Part, an interim analysis for the purpose of stopping for efficacy is planned depending on the enrollment rate. The interim analysis plan is summarized below:

- The interim analysis will be made on the primary analyses of the primary endpoint, and each primary analysis of the key secondary endpoint (1) and the key secondary endpoint (2) of Phase 2b/3 Part.
- The number of analyses shall be 2 in total including the final analysis (1 interim analysis), and the interim analysis will be performed for the purpose of stopping for efficacy when the follow-up has been completed in 50% of the target sample size.
- As the criteria for stopping for efficacy based on the α-spending function, the O'Brien–Fleming boundary will be adopted for the primary analysis of the primary endpoint and the Pocock boundary will be adopted for each primary analysis of the key secondary endpoint (1) and the key secondary endpoint (2). The nominal significance level which corresponds to the rejection region in the interim analysis and the final analysis will be calculated based on the information fraction for each endpoint at the time of interim analysis.
- If the dose selection is to be made, the interim analysis will be performed after the dose selection.

The details of interim analysis will be described in the interim analysis plan which will be prepared as a separated document.

14. OTHER ANALYSIS

Other analysis will be performed for the ITT Population unless otherwise stated. Other analysis excluding 14.6 (Analysis of Efficacy Endpoint using data from participants with mild/asymptomatic SARS-CoV-2-infection) will be performed in three population which are participants with mild/moderate SARS-CoV-2 infection, participants with asymptomatic/mild symptoms only SARS-CoV-2 infection and the population merged the two.

14.1 Analysis of Spike Gene Sequence

For participants who confirmed the amino-acid substitution polymorphic of spike gene

compared from reference strain in the ITT Population, the substitution position of amino-acid will be listed. These analyses will be performed in Phase 3 Part and Phase 2b/3 Part. Furthermore, for the ITT Population with less than 72 hours from COVID-19 onset to randomization of Phase 3 Part, and the ITT population of Phase 3 Part and Phase 2b/3 Part, the subgroup analysis of SARS-CoV-2 viral strain will be performed for the primary endpoint and the key secondary endpoint (1) and (2).

14.2 Analysis of Gene Sequence

For participants who confirmed the amino-acid substitution by polymorphic of 3CL protease (nsp5) and its cleavage site compared from reference strain in the ITT Population, the substitution position of amino-acid will be listed. For participants who confirmed the amino-acid substitution of polymorphic of 3CL protease (nsp5) by study drug administration in the ITT Population, the substitution position of amino-acid will be listed. These analyses of cutting site will be performed in all Parts. These analysis of polymorphic of 3CL protease (nsp5) will be performed in Phase 3 Part and Phase 2b/3 Part.

14.3 S-217622 Sensitivity

The 50% effective concentration (EC_{50}) of S-217622 at baseline and the ratio of the EC_{50} at baseline to the reference strain will be summarized. The EC_{50} of S-217622 at baseline and the EC_{50} of reference strain will be listed. These analyses will be performed in Phase 3 Part and Phase 2b/3 Part.

14.4 SARS-CoV-2 Neutralizing Antibody (Immunogenicity Analysis)

All immunogenicity analyses will be performed in the ITT Population. The GMT and the corresponding two-sided 95% CI will be calculated for each intervention group at baseline and each scheduled time point after randomization by back transformation of the arithmetic mean and its CI of the log-transformed titers. Furthermore, for the ITT Population with less than 72 hours from COVID-19 onset to randomization of Phase 3 Part, and the ITT population of Phase 3 Part and Phase 2b/3 Part, the subgroup analysis of serostatus at baseline will be performed for the primary endpoint and the key secondary endpoint (1) and (2).

14.5 Aggravation marker

A report of aggravation marker will be prepared separately from the clinical study report.

14.5.1 Change from baseline in aggravation marker

For the ITT Population, change from baseline and measurement value in each aggravation marker at each time point will be summarized by treatment group.

Table 13-1. Aggravation Marker

	Parameter
Aggravation marker	[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

14.6 Merged Analysis of Efficacy Endpoint and Other Analysis Endpoint

For each participant with mild/moderate and asymptomatic/mild symptoms only SARS-CoV-2 infection, the merged analyses will be conducted for the merged population of Phase 2a Part, Phase 2b Part, Phase 3 Part and Phase 2b/3 Part. As stratification factors/covariates for merged analyses of all parts, baseline value (when ANCOVA is

applied), the condition of participant (Mild/Moderate or Asymptomatic/Mild Symptoms Only), SARS-CoV-2 vaccination history (Yes or No) will be used. The merged analyses of viral data will be conducted for the merged population of Phase 3 Part and Phase 2b/3 Part.

Table 14-1 Merged Analyses for Efficacy Endpoint and Other Analysis Endpoint

	Merged Population	Endpoint Analysis
Efficacy (ITT population for Phase 2a, Phase 3 Part and Phase 2b/3 Part and ITT1 population for Phase 2b Part)	Mild/Moderate	Time to resolution of the 5 COVID-19 symptoms [a]
		Time to resolution of fever [a]
		Proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration [a]
	Asymptomatic/Mild Symptoms Only	Proportion of participants with development /worsening of COVID-19 symptoms
	Mild/Moderate and Mild Symptoms Only	Time to resolution of the 5 COVID-19 symptoms [a]
		Proportion of participants without resolution of COVID-19 symptoms after 3 weeks of administration [a]
Efficacy of viral Data (ITT or mITT for Phase 3 Part and Phase 2b/3 Part)	All Participants in Phase 3 Part and Phase 2b/3 Part	Change from baseline on Day 4 in amount of SARS-CoV-2 viral RNA
		Time to the first negative SARS-CoV-2 viral titer
		Time to sustained negative SARS-CoV-2 viral titer
		Proportion of participants with positive SARS-CoV-2 viral titer at each time point
		SARS-CoV-2 viral titer at each time point
		Change from baseline in SARS-CoV-2 viral titer at each time point
		Relative change rate from baseline in SARS-CoV-2 viral titer at each time point
		AUC of the change from baseline in SARS-CoV-2 viral titer
		Time to less than LLOD95 viral RNA
		Proportion of participants with positive RT-PCR result at each time point
		Amount of SARS-CoV-2 viral RNA at each time point
		Change from baseline in amount of SARS-CoV-2 viral RNA at each time point
		Relative change rate from baseline in amount of SARS-CoV-2 viral RNA at each time point
		AUC of change in amount of SARS-CoV-2 viral RNA
Other (ITT	All Participants,	SARS-CoV-2 Neutralizing Antibody

	Merged Population	Endpoint Analysis
population for Phase 2a, Phase 3 Part and Phase 2b/3 Part, and ITT1 population for Phase 2b Part)	Mild/Moderate, Asymptomatic/Mild Symptoms Only	(Immunogenicity Analysis) (section 14.4)
		Change from baseline in aggravation marker (section 14.5.1)
		Proportion of participants with post-acute COVID-19 syndrome at each timepoint (section 14.7)

a : The merged analyses will also be performed in the analysis population with less than 72 hours from COVID-19 onset to randomization.

All Participants: Participants with Mild/Moderate and Asymptomatic/Mild Symptoms Only in All Parts
Mild/Moderate: Participants with Mild/Moderate SARS-CoV-2 Infection in All Parts (Phase 2a Part, Phase 2b Part and Phase 3 Part)
Asymptomatic/Mild Symptoms Only: Participants with Asymptomatic/Mild Symptoms Only SARS-CoV-2 Infection in All Parts (Phase 2a Part and Phase 2b/3 Part)
Mild/Moderate and Mild Symptoms Only: Participants with Mild/Moderate SARS-CoV-2 Infection in Phase 2a Part, Phase 2b Part and Phase 3 Part and Mild Symptoms Only SARS-CoV-2 Infection in Phase 2b/3 Part

14.7 Post-Acute COVID-19 Syndrome

Analyses of post-acute COVID-19 syndrome will be performed in three population which are participants with mild/moderate SARS-CoV-2 infection, participants with asymptomatic/mild symptoms only SARS-CoV-2 infection and the population merged the two.

14.7.1 Summary of Post-Acute COVID-19 Syndrome at Each Time Point

The number and proportion of the answer of each post-acute COVID-19 syndrome at each time point will be summarized by treatment group in the ITT Population.

For the answer of question 1 (severity of COVID-19 symptoms over the past 4 weeks), "No symptoms" will be treated as 0, and "Mild", "Moderate" and "Severe" will be treated as 1". For the answer of question 2 (general physical health over the past 4 weeks), "Excellent", "Very good", "Good" and "Fair" will be treated as 0 and "Poor" will be treated as 1. Pairwise comparison using the two-sided Mantel–Haenszel test between each S-217622 treatment group and placebo will be performed. The stratification factor of Mantel-Haenszel test will be time from onset to randomization of COVID-19 (< 72 hours or ≥ 72 hours) and SARS-CoV-2 vaccination history (Yes or No). in population of participants with mild/moderate SARS-CoV-2 infection, and SARS-CoV-2 vaccination history (Yes or No) in population of participants with asymptomatic/mild symptoms only SARS-CoV-2-infection. As the other analysis for this endpoint, the risk ratio and the risk difference in each S-217622 treatment group versus placebo and the corresponding 95% CI will be calculated.

The cumulative logit proportional odds model will be applied at each time point. The model will include treatment group as fixed effects, and time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history (Yes or No) as covariates in population of participants with mild/moderate SARS-CoV-2

infection, and SARS-CoV-2 vaccination history (Yes or No) in population of participants with asymptomatic/mild symptoms only SARS-CoV-2-infection, as covariates. The odds ratio in the answer for each question (severity of COVID-19 symptoms /over the past 4 weeks, general physical health over the past 4 weeks) at each time point of S-217622 versus placebo, its 95% confidence interval, and two-sided p-value will be calculated.

14.7.2 Proportion of Participants with Post-Acute COVID-19 Syndrome at Each Time Point

The proportion of participants with at least one post-acute COVID-19 syndrome at each time point and the risk ratio and risk difference to the placebo group will be calculated. In addition, the proportion of participants for each post-acute COVID-19 syndrome at each time point and the risk ratio and risk difference will be calculated.

Proportion of participants with at least one post-acute COVID-19 syndrome is defined as proportion of participants who have symptoms (Mild, Moderate or Severe) that "COVID-19 Related?" is not "No".

Pairwise comparison will be performed using the two-sided Mantel-Haenszel test with time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history (Yes or No) in population of participants with mild/moderate SARS-CoV-2 infection, and SARS-CoV-2 vaccination history (Yes or No) in population of participants with asymptomatic/mild symptoms only SARS-CoV-2-infection as a stratification factor between each S-217622 treatment group and placebo in the ITT Population.

14.7.3 Proportion of Participants with Medical Visit for Post-Acute COVID-19 Syndrome at Each Time Point

The number and proportion of the answer of medical visit for post-acute COVID-19 syndrome at each time point will be summarized by treatment group in the ITT Population.

14.8 Time to less than LLOQ of SARS-CoV-2 viral RNA and RT-PCR negative

This is defined as the time from the start of study intervention to the first confirmation without viral rebound of less than LLOQ (2.08 $\log_{10}$ copies/mL) in SARS-CoV-2 viral RNA and RT-PCR negative at the same time. Viral rebound is defined as the case that greater than or equal to LLOQ is observed after confirmation of less than LLOQ in SARS-CoV-2 viral RNA and RT-PCR negative at the same time. For the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part and the ITT Population in Phase 2b/3 Part, the same analyses as the key secondary endpoint (2) for the efficacy (excluding of the multiplicity adjustment) will be performed.

14.9 Time to less than LLOD95 of SARS-CoV-2 viral RNA

This is defined as the time from the start of study intervention to when less than $LLOD_{95}$ viral RNA (less than 2.27 log_{10} copies/mL) is confirmed after first administration of study intervention. For the ITT Population in Phase 2b/3 Part, and the ITT Population with less than 72 hours from COVID-19 onset to randomization in Phase 3 Part, the same analyses as the key secondary endpoint (2) (excluding of the multiplicity adjustment) will be performed.

14.10 Measurement of viral antigen (spike Nucleocapsid), anti-viral antigen antibody (IgG, IgM), and SARS-CoV-2 viral RNA in the human blood

For the ITT Population of Phase 3 Part, summary statistics for observed value and change from baseline in each parameter (viral antigen (spike Nucleocapsid), anti-viral antigen antibody (IgG, IgM), and SARS-CoV-2 viral RNA) will be calculated by each treatment group and each time point.

15. PROGRAMMING CONVENTIONS

15.1 Formatting and Programming Rule

Unless otherwise stated, following conventions should be applied in constructing the analysis tables, figures and listings:

- Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for All Randomized Participants except for all adverse events including those reported in the Screening Period.
- Rounding for all variables will occur only at the last step, immediately prior to presentation in tables, figures and listings. No intermediate rounding will be performed on derived variables. The standard practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines.
  - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
  - Means, standard deviations, and medians will be reported to one decimal place beyond the number of decimal places with which the original endpoint is presented.
  - Calculated percentages will be reported to one decimal place.
  - For analyses of time-to-event endpoints, statistic excluded the number of event/censor cases and p-value will be reported to one decimal place.
  - The calculated value of ANCOVA will be reported to two decimal place.
  - The summarized value of Time-weighted average change will be reported to two decimal place.
  - For pharmacokinetic analyses, means, geometric means, standard deviations, medians, minimums and maxima: same precision as per each concentration or PK

parameter in the listing.

- All means presented are arithmetic unless otherwise stated.

15.2 Sample SAS Code

15.2.1 RMST

Events reported after the truncation time will be censored at the truncation time. SAS code will be specified in the statistical analysis specification.

```
ods output Means=[output for RMST];
proc lifetest data=[input dataset] conftype=loglog alpha=0.05 timelim=[τ];
   time [Survival time] * [Censoring variable] (Value indicating censoring);
  strata [treatment groups];
run;
```

15.2.2 Bootstrap Percentile Method

The 95% CI of difference of median time will be obtained by the bootstrap percentile method. The 10,000 bootstrap samples will be generated by the following SAS code.

```
proc surveyselect data = [input dataset] seed = [random seed] out = [output dataset]
method = urs rate = 1.0 rep = 10000 outhits;
 strata [treatment group];
run;quit;
```

15.2.3 Cumulative Logit Proportional Odds Model

```
proc logistic data = [input dataset];
 class [treatment group] [covariates];
 model [response variable] = [treatment group] [covariates];
 oddsratio [treatment group];
run;
```

16. REFERENCE

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3. Oran DP, Topol EJ. The proportion of SARS-CoV-2 infections that are asymptomatic: a systematic review. Ann Intern Med 2021; 174(5): 655-62.
4. EuroQol. EQ-5D-5L Crosswalk Index Value Calculator. Version 24OCT2019. https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/
5. Kim, SH., Ahn, J., Ock, M. et al. The EQ-5D-5L valuation study in Korea. Qual Life Res 25, 1845–1852 (2016). https://doi.org/10.1007/s11136-015-1205-2
6. 2108T1221_External Data Specifications (Viroclinics)_V5.0_29 July 2022, Document Number: VV-TMF-694051
7. 2108T1221_VCB Laboratory Protocol_V4,0_11 May 2022, Document Number: VV-TMF-682965

Appendix 1 Time and Events Schedule

	Treatment Period						Follow-up Period					Exploratory Period			Early Termination [b]
Day	**1**		**2**	**3**	**4**	**5**	**6**	**9**	**14**	**21**	**28**	**85**	**169**	**337**	
	−1	-	+1	-	+1	-	+1	±1	±2	±3	±3	±14	±14	±14	+3
Visit [a]	**V1**		**V2**	**Op V1**	**V3**	**Op V2**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	
	pre-dose	**post-dose**													
Informed consent	X														
Inclusion and exclusion criteria [c]	X														
Randomization	X														
Study Intervention [d]		X	X	X	X	X									
Medical examination	X		X		X		X	X	X	X	X				X
Demographics	X														
Pregnancy test [e]	X										X				X
SARS-CoV-2 Nasopharynx swab sample collection [f]	X		X	X	X	X	X	X	X	X					X
Patient Diary [g]	X	Twice Daily							Once Daily						
8-Point Ordinal Scale [h]	X		X		X		X	X	X	X	X				X
Laboratory Evaluations [i]	X						X		X		X				X
Vital Signs [j]	X		X		X		X	X	X	X	X				X
Electrocardiograms [k]	X		X		X		X								
Adverse Events	X	←				X		→							X
Concomitant drugs/therapies [l]	X		X		X		X	X	X	X	X				X
Blood collection for drug concentration measurement [m]			X				X								X
Blood collection for Immunogenicity [n]	X										X				X
Post-acute COVID-19 syndrome [o]												X	X	X	

SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2

a. Day 3 (Op V1) and Day 5 (Op V2) are optional visit (study intervention and patient diary will be performed). The assessment at pre-dose on Day 1 (V1) will be allowed to perform in Day -1. Visits for Day 85 (V9), Day 169 (V10), and Day 337 (V11) will be performed only for participants who agree/assent to participate in the exploratory period. For participants of recuperation at home of recuperation at accommodation, visiting medical examination, online medical examination and visiting nurses will be performed in each visits.
b. The examination at early termination for discontinued participants will be performed as far as possible.
c. The explanation of the study description and informed consent obtained may be performed via the online medical system
d. The study intervention will be administered once daily in Day 1 to Day 5. The loading dose will be administered in Day 1, the maintenance dose will be administered in Day 2 to Day 5. There is no allowance for the study intervention. The study drug of Day 2 to Day 5 will be handed over on Day 1.
e. Pregnancy test will be performed on Day 1(pre-dose) and Day 28 for only female of child bearing potential.

f. SARS-CoV-2 nasopharynx swab sample collection will be performed on Day 2 ~ Day 6, Day 9, Day 14 and Day 21. The SARS-CoV-2 nasopharynx swab sample collection on Day 3 (Op V1) and Day 5 (Op V2) will be optional.
g. Participants will be entered the results of COVID-19 symptom, EQ-5D-5L assessment, SpO2 and body temperature twice daily (morning and evening) from pre-dose of Day 1 to Day 9, and once daily (evening) from Day 10 to Day 21, at the same time whenever possible. The first entry on Day 1 will be performed before the study intervention. If acetaminophen is taken for antipyretic or analgesic, assessment of COVID-19 symptom score and measurement of body temperature should not be performed until 4 hours after taking the drug.
h. 8-Point Ordinal Scale will be performed on Day 1 (pre-dose), Day 2, Day 4, Day 6, Day 9, Day 14, Day 21 and Day 28.If the change of the score is confirmed (excluding change between Score 0 to Score 2), The date and score will be entry in eCRF.
i. Laboratory tests will be performed on Day 1 (pre-dose), Day 6, Day 14 and Day 28.
j. Systolic / diastolic blood pressure, pulse rate and respiratory rate will be measured for vital signs. Measurement will be performed on Day 1 (pre-dose), Day 2, Day 4, Day 6, Day 9, Day 14, Day 21 and Day 28.
k. Only in Phase 2a Part, to be performed with 2-lead or more Electrocardiogram (It is possible to be performed by the participant himself/herself). The measurement will not be performed immediately after blood collection. The measurement will be performed on Day 1 (pre-dose, 1 ~ 8 hours after study intervention), Day 2, Day 4 and Day 6. If abnormal result is confirmed on Day 1 (1 ~ 8 hours after study intervention), participants will contact the principal investigator (subinvestigator).
l. Prior medications will be checked on Day 1 (pre-dose).
m. Blood collection for drug concentration measurement will be performed on Day 2 and Day 6. If participants discontinued before day 5, the blood collection will be performed as the early termination.
n. Blood collection for immunogenicity will be performed on Day 1 (pre-dose) and Day 28.
o. To be performed only for participants who agree/assent to participate in the exploratory period. The participant himself/herself will evaluate his/her post-acute COVID-19 syndrome on Days 85, 169, and 337. Then the participant will enter the results in the participant diary.

Appendix 2 8-Point Ordinal Scale

Descriptor	Score
Asymptomatic	0
Symptomatic, no limitation of activities	1
Symptomatic, limitation of activities	2
Hospitalized, no oxygen therapy	3
Hospitalized, with oxygen therapy (< 5 L/min)	4
Hospitalized, with oxygen therapy (≥ 5 L/min)	5
Hospitalized, with ventilation	6
Death	7

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