2. SYNOPSIS

Sponsor: Shionogi & Co., Ltd. Shionogi B.V.	**Individual Study Table** **Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	:
Name of Active Ingredient: S-217622	**Page:**	

Study Title:
A Phase 2/3 Study of S-217622 in Participants Infected with SARS-CoV-2

Investigators and Study Centers: This was a multicenter global study conducted at 94 sites in Japan (65 sites), South Korea (26 sites), Vietnam (2 sites), and Singapore (1 site) in Phase 3 Part. There was no participant enrolled from the site in Singapore.

Publication (reference): Not applicable

Studied Period: From 10 Feb 2022 (Enrollment date of the first participant in Phase 3 Part) to 8 Aug 2022 (Last observation date of the last participant in Phase 3 Part)

Phase of Development: Phase 2/3

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 severe acute respiratory syndrome coronavirus 2 (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	• The following endpoints concerning SARS-CoV-2 viral titer – Time to the first negative SARS-CoV-2 viral titer

participants with SARS-CoV-2 infection.	– Time to negative SARS-CoV-2 viral titers 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 – Area under the curve (AUC) of change in SARS-CoV-2 viral titer • The following endpoints concerning reverse transcription polymerase chain reaction (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 the amount of SARS-CoV-2 viral RNA at each time point – Relative change rate from baseline in the amount of SARS-CoV-2 viral RNA at each time point – AUC of change in the amount of SARS-CoV-2 viral RNA
• To investigate the effect in preventing aggravation following 5-day administration of S-217622 in	• Proportion of participants with the following or higher scores on the 8-Point Ordinal Scale and the time

participants with SARS-CoV-2 infection.	from the first dose of study intervention to reach the scores – 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) • Saturation of percutaneous oxygen (SpO_2) at each time point
• To investigate quality of life (QOL) following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Change from baseline in EuroQol 5 dimensions 5-level (EQ-5D-5L)
• To confirm the pharmacokinetics (PK) 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 (AEs), laboratory tests, and vital signs (systolic/diastolic blood pressure, pulse rate, respiratory rate), electrocardiography (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 first improvement of coronavirus disease 2019 (COVID-19) symptoms[b, c] • Time to first improvement of COVID-19 symptoms (duration of recovery, 72 hours [3 days] or longer)[b, c, d] • Time to first improvement of COVID-19 symptoms (duration of recovery, 120 hours [5 days] or longer)[b, c, d]

	• Time to first improvement of each COVID-19 symptom[b, c] • Change from baseline in the 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 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. • 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

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 first improvement of COVID-19 symptoms[b, c] • Time to first improvement of COVID-19 symptoms (duration of recovery, 72 hours [3 days] or longer)[b, c, d] • Time to first improvement of COVID-19 symptoms (duration of recovery, 120 hours [5 days] or longer)[b, c, d] • Time to first 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

• 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 resolution of fever (< 37.0°C) • The following endpoints concerning SARS-CoV-2 viral titer – Time to the first negative SARS-CoV-2 viral titer – Time to negative SARS-CoV-2 viral titers 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 endpoints 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 the amount of SARS-CoV-2 viral RNA at each time point

	– Relative change rate from baseline in the amount of SARS-CoV-2 viral RNA at each time point – AUC of change in the 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 the 8-Point Ordinal Scale and the time from the first dose of study intervention to reach the scores – 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 PK 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.	• AEs, 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 study intervention administration
• To evaluate the antiviral activity of S-217622 against SARS-CoV-2 in participants' specimen.	• Half maximal effective concentration (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

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	• Change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA

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 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 endpoints 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 endpoints 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 the amount of SARS-CoV-2 viral RNA at each time point – Relative change rate from baseline in the amount of SARS-CoV-2 viral RNA at each time point – AUC of change in the 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 the 8-Point Ordinal Scale and time from the first dose of study intervention to reach the scores – 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	• Change from baseline in EQ-5D-5L

of placebo in participants with SARS-CoV-2 infection.	
• To confirm the PK 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.	• AEs, 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 study intervention 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 < lower limit of quantitation (LLOQ) and the negative RT-PCR result • Time to the first viral RNA < lowest amount of virus that could be detected with a positivity rate greater than 95% by probit analysis ($LLOD_{95}$)

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.	• 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 endpoints 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 endpoints 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 the amount of SARS-CoV-2 viral RNA at each time point – Relative change rate from baseline in the amount of SARS-CoV-2 viral RNA at each time point – AUC of change in the 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 the 8-Point Ordinal Scale and time from the first dose of study intervention to reach the scores – 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 PK 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.	• AEs, 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	• Gene sequence of 3CL protease (nsp5) and its cleavage site

administration of S-217622 in participants with SARS-CoV-2 infection.	following study intervention 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 <$LLOD_{95}$

a Participants with mild/moderate SARS-CoV-2 infection were defined as participants who met inclusion criterion #2 to #4 in Section 9.3.1.1 but did not meet exclusion criterion #1 to #5 in Section 9.3.2.1; participants with asymptomatic/mild symptoms only SARS-CoV-2 infection were defined as participants who met inclusion criterion #2 and #3 in Section 9.3.1.2 but did not meet exclusion criterion #1 to #5 in Section 9.3.2.2.

b The following 12 symptoms were 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 were 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 was defined as the time from the start of study intervention to when all of the symptoms met 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 remained improved to moderate or better, or moderate symptoms at baseline 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 remained severe or better, or moderate symptoms at baseline remained moderate or improved for 24 hours.
- Symptoms other than the above (Symptoms that had not occurred before the onset of COVID-19, occurred after baseline [pre-treatment examination]): Mild or better condition remained for 24 hours.

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

e A total of 14 symptoms were evaluated: taste disorder and smell disorder were added to the 12 symptoms, ie, 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.

f Of the 14 symptoms in COVID-19, taste disorder and smell disorder were 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 were 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 were defined as participants who had symptoms meeting any of the following criteria.

- The scores for taste disorder or smell disorder worsened from 0 (The same as usual) to 1 (Less than usual) or 2 (No sense of smell/taste).
- Feeling hot or feverish, cough, or shortness of breath (difficulty breathing): Severity of none at baseline worsened to mild or worse, mild symptoms at baseline worsened to moderate or worse, or moderate symptoms at baseline worsened to severe on any of the symptoms (severe symptoms at baseline were 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, or diarrhea: Severity of none at baseline worsened to mild or worse, mild symptoms at baseline worsened to moderate or worse, or moderate symptoms at baseline worsened to severe on 2 or more symptoms at the same point (severe symptoms at baseline were excluded from the onset judgement of COVID-19 symptoms).

g Aggravation markers included platelet count, hemoglobin, white blood cell count, lymphocyte count, ALT, LDH, albumin, CRP, CK, PT-INR, IL-6, IFN-λ3, TARC (CCL17), D-dimer, procalcitonin, and KL-6.

h The 12 symptoms of COVID-19 were 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 was defined as the time from the start of study intervention to when all of the symptoms met 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 remained improved to moderate or better, moderate symptoms at baseline remained improved to mild or better, and mild symptoms at baseline 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 remained severe or improved, moderate symptoms at baseline remained moderate or improved, and mild symptoms at baseline remained mild or improved for 24 hours.
- Symptoms other than the above (symptoms that had not occurred before the onset of COVID-19, and occurred after baseline [pre-treatment examination]): The condition with no symptoms remained for 24 hours.

i The 12 symptoms of COVID-19 were 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 was defined as the proportion of participants with one or more 12 COVID-19 symptoms which had 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. Resolution of COVID-19 symptoms at the final evaluation point was 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 improved to moderate or better, moderate symptoms at baseline improved to mild or better, and mild symptoms at baseline 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 remained severe or improved, moderate symptoms at baseline remained moderate or improved, and mild symptoms at baseline remained mild or improved at the final evaluation point.

– Symptoms other than the above (symptoms that had not occurred before the onset of COVID-19, and occurred after baseline [pre-treatment examination]): No symptoms were observed at the final evaluation point.

k Of the 14 symptoms in COVID-19, taste disorder and smell disorder were 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 were 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 was defined as the time from the start of study intervention to when all of the symptoms met 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) remained improved to 1 (Less than usual) or better, or 1 (Less than usual) remained 1 (Less than usual) or better for 24 hours; and as for the other 12 symptoms, severe symptoms at baseline remained improved to moderate or better, moderate symptoms at baseline remained improved to mild or better, or mild symptoms at baseline 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) remained 2 (No sense of smell/taste) or improved, or 1 (Less than usual) remained 1 (Less than usual) or improved for 24 hours; and as for the other 12 symptoms, severe symptoms at baseline remained severe or improved, moderate symptoms at baseline have remained moderate or improved, or mild symptoms at baseline remained mild or improved for 24 hours.

– Symptoms other than the above (symptoms that had 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 remained for 24 hours.

m Of the 14 symptoms in COVID-19, taste disorder and smell disorder were 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 were 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 were defined as participants who had symptoms meeting the following criteria.

– The scores for taste disorder and smell disorder 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] was 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 worsened to mild or worse, mild symptoms at baseline worsened to moderate or worse, or moderate symptoms at baseline worsened to severe on either symptom (severe symptoms at baseline were 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 worsened to mild or worse, mild symptoms at baseline worsened to moderate or worse, or moderate symptoms at baseline worsened to severe which were maintained for 24 hours on 2 or more symptoms at the same point (severe symptoms at baseline were excluded from the onset/worsening judgement of COVID-19 symptoms).

n While the primary analysis population was defined as a population with < 72 hours of time from the onset of COVID-19 to randomization out of the intention-to-treat (ITT) population or modified

intention-to-treat (mITT) population, the evaluation was performed in the ITT population or mITT population as well.

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

p Recurrence was judged if any symptom met 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 became severe, moderate or mild symptoms at baseline became moderate or worse, and 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 became severe, and mild symptoms at baseline became moderate or worse, and remained so for 48 hours (symptoms with the severity of severe at baseline were not evaluated as recurrence).
- Symptoms other than above (symptoms that had not occurred before the onset of COVID-19, and occurred after baseline [pre-treatment examination]): The symptoms became moderate or worse and remained so for 48 hours.

q COVID-19 symptom groups to be evaluated included 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

Methodology:

This study consisted of four parts: Phase 2a Part enrolling participants with mild/moderate or asymptomatic SARS-CoV-2 infection, Phase 2b Part and Phase 3 Part enrolling participants with mild/moderate SARS-CoV-2 infection (cohort A to evaluate time to improvement), and Phase 2b/3 Part enrolling participants with asymptomatic/mild symptoms only SARS-CoV-2 infection (cohort B to evaluate development/worsening). This study was a multicenter, randomized, double-blind, placebo-controlled study. The participants were at home, at accommodation facilities, or in a hospital.

In each part, eligible participants were randomly assigned to S-217622 125 mg group, S-217622 250 mg group, or placebo group.

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

Each Part consisted of the intervention period (Days 1 to 5), the follow-up period (Days 6 to 28), and the exploratory period (Days 29 to 337), which was common for all Parts. Participants were considered to have completed the study if he/she had

completed the follow-up period. Only participants who agreed to participate in the exploratory period were evaluated in the period.

In this study, the Data and Safety Monitoring Board was established for the purpose of third-party evaluation of safety throughout the study period. The Independent Data Monitoring Committee (IDMC) was established for the interim analyses of the primary endpoint and the key secondary endpoint of Phase 2b/3 Part for the purpose of decision on stopping the study for efficacy reasons. It was to control such unblinded information as the key codes and the results of analysis which could have an impact on the conduct or evaluation of Phase 2b/3 Part.

Number of Participants (Planned and Analyzed):

Planned:

For Phase 2a Part, 69 eligible participants with mild/moderate or asymptomatic SARS-CoV-2 infection were to be enrolled in 3 groups (23 participants/group). The number of participants by condition (mild/moderate or asymptomatic) in each group was not pre-defined.

For Phase 2b Part, 435 eligible participants with mild/moderate SARS-CoV-2 infection who had at least 1 moderate symptom were to be enrolled in 3 groups (145 participants/group).

For Phase 3 Part, 1590 eligible participants with mild/moderate SARS-CoV-2 infection were to be enrolled in 3 groups (530 participants/group). Of these, 780 eligible participants with < 72 hours from the onset of COVID-19 to randomization were to be enrolled in 3 groups (260 participants/group).

For Phase 2b/3 Part, 495 eligible participants with asymptomatic/mild symptoms only SARS-CoV-2 infection were to be enrolled in 3 groups (200 participants/group). In case it was judged that no interim analysis was to be performed for the purpose of decision on stopping for efficacy reasons, 480 eligible participants were to be randomly assigned to each of these intervention groups (160 participants/group).

Randomized (Phase 3 Part):

A total of 1821 participants were randomized in Phase 3 Part (607 in the S-217622 125 mg group, 606 in the S-217622 250 mg group, and 608 in the placebo group).

Analyzed for efficacy (Phase 3 Part):

Participants with mild/moderate SARS-CoV-2 infection

- Intention-to-treat (ITT) population with < 72 hours from the onset of COVID-19 to randomization:
  1030 participants (347 in the S-217622 125 mg group, 340 in the S-217622 250 mg group, and 343 in the placebo group)
- ITT population:
  1798 participants (603 in the S-217622 125 mg group, 595 in the S-217622 250 mg group, and 600 in the placebo group)
- Modified intention-to-treat (mITT) population with < 72 hours from the onset of COVID-19 to randomization:

602 participants (203 in the S-217622 125 mg group, 185 in the S-217622 250 mg group, and 214 in the placebo group)

- mITT population:
  956 participants (318 in the S-217622 125 mg group, 304 in the S-217622 250 mg group, and 334 in the placebo group)

Analyzed for safety (Phase 3 Part):

- Safety analysis population:
  1808 participants (604 in the S-217622 125 mg group, 599 in the S-217622 250 mg group, and 605 in the placebo group)

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

Common to participants with mild/moderate, with asymptomatic, and with asymptomatic/mild symptoms only SARS-CoV-2 infection:

- Male and female participants who were 12 to < 70 years of age, at the time of signing the informed consent/assent.
- Participants who were diagnosed as SARS-CoV-2 positive within 120 hours before randomization.
- Participants under 18 years of age at the time of assent had to weigh ≥ 40 kg.

Participants with mild/moderate SARS-CoV-2 infection only (Phase 2a Part, Phase 2b Part, and Phase 3 Part):

- Participants with a time from COVID-19 onset (when at least one of 14 symptoms of COVID-19 occurred) to randomization of ≤ 120 hours.
- Participants who had at least one moderate (COVID-19 score: 2) or severe symptom among the 12 COVID-19 symptoms at randomization (excluding symptoms present prior to COVID-19 onset)

  Or participants who had at least one moderate (COVID-19 score: 2) or severe pre-existing symptom (symptoms present prior to COVID-19 onset) which the participants considered to have worsened at baseline:

Participants with asymptomatic SARS-CoV-2 infection only (Phase 2a Part only):

- Participants who had none of the COVID-19 symptoms (except symptoms present before SARS-CoV-2 infection) within 2 weeks before randomization.

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

- Participants who did not have any moderate (COVID-19 symptom score: 2) or severe symptoms out of the 12 symptoms due to COVID-19 within 2 weeks before randomization (excluding symptoms present prior to COVID-19 onset).

2. Exclusion criteria

- Participants with a SpO_2 during wakefulness of ≤ 93% (room air)
- Participants who needed oxygen administration or a respirator

- Participants who were strongly suspected to have worsening of symptoms of SARS-CoV-2 infection within 48 hours after randomization, in the opinion of the investigator/subinvestigator
- Participants with suspected active and systemic infections requiring treatment at the time of randomization (excluding SARS-CoV-2)

Test Product, Dose and Mode of Administration, Lot Number (Phase 3 Part):

Study Intervention Name	Packaging Lot No.
S-217622 tablet 250 mg S-217622 tablet 125 mg	Japan: Day1, [redacted] Days 2 to 5, [redacted]
	South Korea/Singapore: Day1, [redacted] Days 2 to 5, [redacted]
	Vietnam: Day1, [redacted] Days 2 to 5, [redacted]

S-217622 tablet 250 mg or S-217622 tablet 125 mg was orally administered as described in the Methodology.

Duration of Treatment:

Once daily for 5 days

Reference Therapy, Dose and Mode of Administration, Lot Number (Phase 3 Part):

Study Intervention Name	Packaging Lot No.
S-217622 tablet Placebo-D S-217622 tablet Placebo-B	Japan: Day1, [redacted] Days 2 to 5, [redacted]
	South Korea/Singapore: Day1, [redacted] Days 2 to 5, [redacted]
	Vietnam: Day1, [redacted] Days 2 to 5, [redacted]

S-217622 tablet Placebo-D and/or S-217622 tablet Placebo-B was orally administered as described in the Methodology.

Criteria for Evaluation:

Efficacy Assessment:

1. Virologic Examination

   The investigator or his/her designee took nasopharyngeal swab from participants. SARS-CoV-2 virus titer and amount of viral RNA were measured, whether the sample was positive or negative was determined by RT-PCR.

2. Participant Diary

   Participants assessed their COVID-19 symptom scores and EQ-5D-5L, measured SpO_2 and temperature, and entered the results in the participant diary.

   - COVID-19 Symptom Score

     Of the 14 COVID-19 symptoms listed below, participants assessed 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) according to the protocol-specified schedule.

     – 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
- SpO_2

  Participants measured SpO_2 using a pulse oximeter according to the protocol-specified schedule.
- Body Temperature

  Participants measured axillary temperature according to the protocol-specified schedule.
- EQ-5D-5L

  Participants assessed EQ-5D-5L according to the protocol-specified schedule.

  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.

3. 8-Point Ordinal Scale

   The investigator/subinvestigator assessed the participant's condition on the 8-Point Ordinal Scale of 0 to 7 according to the protocol-specified schedule.

   The scores on the 8-Point Ordinal Scale are 0) Asymptomatic; 1) Symptomatic, no limitation of activities; 2) Symptomatic, limitation of activities; 3) Hospitalized, no oxygen therapy; 4) Hospitalized, with oxygen therapy (< 5 L/min); 5) Hospitalized, with oxygen therapy (≥ 5 L/min); 6) Hospitalized, with ventilation; and 7) Death.

Other Assessments:

Results of the following assessments will be reported separately from the clinical study report (CSR).

- Biomarkers (aggravation markers)
- SARS-CoV-2 lineage
- Polymorphisms of 3CL Protease (nsp5)
- Proportion of amino acid substitution in 3CL protease (nsp5) and its cleavage site
- Drug antiviral activity
- Immunity (SARS-CoV-2 neutralizing antibody titers)
- allergy antigen test (cedar/cypress allergy)

Safety Assessment:

Safety was assessed through physical examinations, laboratory tests, vital signs, and ECGs. All AEs/serious AEs (SAEs) were collected from the date of signing of the informed consent form (ICF)/assent through the end of follow-up period. The severity and seriousness of an event was determined by the investigator according to the protocol-specified definitions. The relationship of an event to the study intervention was determined by the investigator.

Pharmacokinetics Assessment:

For the measurement of plasma S-217622 concentrations, blood samples were collected on Days 2 and 6.

Statistical Methods:

Efficacy Analyses:

In general, efficacy analyses were performed for ITT population (Phase 2a Part, and Phase 2b/3 Part), ITT1 population (Phase 2b Part), modified intention-to-treat (mITT) population, ie, ITT participants who had a positive SARS-CoV-2 viral titer at baseline (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). For Phase 3 Part, in principle, efficacy analyses were also performed for the ITT population or the mITT population. As for the primary endpoints of Phase 2a Part and Phase 2b Part, only the primary analyses were to be performed based on the PPS instead of the ITT population and ITT1 population, respectively, and based on the PPS or that with positive SARS-CoV-2 viral titer at baseline instead of the mITT population. In Phase 3 Part and Phase 2b/3 Part, the primary analyses and the key secondary analyses of the primary endpoint and the key secondary endpoint 1 (Phase 3 Part only) were performed based on the ITT1 population and the PPS instead of ITT population, and primary analysis and key secondary analysis of the key secondary endpoint 2 (Phase 3 Part only) were performed based on the ITT1 population and the PPS 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 was performed.

<u>Primary Endpoint in Phase 2a Part (Participants with Mild/Moderate or Asymptomatic SARS-CoV-2 infection)</u>

The primary endpoint in Phase2a Part, ie, the change from baseline in SARS-CoV-2 viral titer at each time point, was 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 were calculated using the mITT population for the participants with mild/moderate SARS-CoV-2 infection, the participants with asymptomatic SARS-CoV-2 infection, and the merged population separately. In addition, the van Elteren test was applied to the merged population of mild/moderate and asymptomatic SARS-CoV-2 infection for 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 condition of SARS-CoV-2 infection (mild/moderate or asymptomatic) was used. No multiplicity adjustment was performed in these pairwise comparisons.

Primary Endpoint in Phase 2b Part (Participants with Mild/Moderate SARS-CoV-2 Infection)

The primary efficacy endpoints in participants with mild/moderate SARS-CoV-2 infection in Phase 2b Part were 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.

As the primary analysis for this primary endpoint, pairwise comparison was performed between each S-217622 intervention group and the placebo group, analysis of covariance was 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 was 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 was performed between each S-217622 intervention group and the placebo group, analysis of covariance was applied with change from baseline on Day 4 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. The multiplicity adjustment was performed in these pairwise comparisons by using a fixed-sequence procedure.

Primary Endpoint in Phase 3 Part (Participants with Mild/Moderate SARS-CoV-2 Infection)

The primary endpoint in Phase 3 Part for participants with mild/moderate SARS-CoV-2 infection, ie, the time to resolution of 5 COVID-19 symptoms was 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 resolution of symptoms was defined in the footnotes to Objectives and Endpoints.

As the primary analysis for this primary endpoint, a comparison of the time to resolution of the 5 COVID-19 symptoms was 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 was performed in participants with mild/moderate SARS-CoV-2 infection of the ITT population. In this analysis, stratification by the time from the onset of

COVID-19 to randomization (< 72 hours, ≥ 72 hours) was included as well as SARS-CoV-2 vaccination history. The multiplicity adjustment was applied to the primary analysis and key secondary analyses of the primary endpoint.

As other analyses for this endpoint, the following analyses were 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 were performed in the ITT population. In that case, stratification by the time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) was included as well as SARS-CoV-2 vaccination history. The multiplicity adjustment planned for the primary analysis was not performed.

- Comparison was performed using the log-rank test stratified by time from the onset of COVID-19 to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history between the S-217622 125 mg group and the placebo group.
- Kaplan-Meier curves were plotted for each treatment group and the median time to resolution of the 5 COVID-19 symptoms and its 95% confidence interval (CI) were calculated. Moreover, the difference in median between treatment groups and its 95% CI were calculated.
- The hazard ratio of S-217622 125 mg group to the placebo group was 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 was estimated for each group and comparison between the S-217622 125 mg group and the placebo group was performed.

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

The primary endpoint in Phase 2b/3 Part in participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, ie, the proportion of participants with development/worsening of COVID-19 symptoms, was 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 of the 12 symptoms of COVID-19, taste disorder, or smell disorder by 14 days from the first administration of the study intervention. The development/worsening of symptoms was determined according to the protocol-specified rules.

As the primary analysis for this primary endpoint, a comparison of the proportion of participants with development/worsening of COVID-19 symptoms was 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 participants with asymptomatic/mild symptoms only SARS-CoV-2 infection in the ITT population by applying the multiplicity adjustment in each pairwise comparison with Bonferroni's method.

As another analysis for this primary endpoint, the risk ratio and the risk difference of each S-217622 treatment group to the placebo group were estimated.

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

The key secondary endpoints in Phase 3 Part and Phase 2b/3 Part were 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).

The efficacy analyses of the key secondary endpoints 1 were performed for ITT population, those of the key secondary endpoints 2 were performed for mITT population. In participants with mild/moderate SARS-CoV-2 infection (Phase 3 Part), the population with < 72 hours from the COVID-19 symptom onset to randomization out of the ITT population of Phase 3 Part was used for the primary analysis.

The primary analyses for the key secondary endpoint 1 and the key secondary endpoint 2 were planned for participants with mild/moderate SARS-CoV-2 infection and those with asymptomatic/mild symptoms only SARS-CoV-2 infection separately. If only the comparison in the primary endpoint between the S-217622 125 mg group and the placebo group showed statistically significant at the given significant level, comparisons of the key secondary endpoints were performed between S-217622 125 mg group and the placebo group using analysis of covariance (for the key secondary endpoint 1), a log-rank test (for the key secondary endpoint 2). The analysis of covariance for the key secondary endpoint 1 was 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. The primary analysis population of the key secondary endpoint 1 was the population with < 72 hours from the COVID-19 symptom onset to randomization out of the ITT population for Phase 3 Part and ITT population for Phase 2b/3 Part. The stratification factors for log-rank test of the key secondary endpoint 2 were SARS-CoV-2 vaccination history for participants with mild/moderate SARS-CoV-2 infection; and the stratification factors for log-rank test of Phase 2b/3 Part were the SARS-CoV-2 vaccination history. The primary analysis population of the key secondary endpoint 2 was the population with < 72 hours from the COVID-19 symptom onset to randomization out of the mITT population for Phase 3 Part and mITT population for Phase 2b/3 Part. The log-rank test was at a one-sided significance level of 0.025. The multiplicity adjustment was applied to the primary analysis and key secondary analyses of the key secondary endpoints, and tests were performed in the order of the primary analysis of the primary endpoint, the primary analysis of the key secondary endpoint 1, the primary analysis of the key secondary endpoint 2, the key secondary analysis of the primary endpoint, the key secondary analysis of the key secondary endpoint 1, the key secondary analysis of the key secondary endpoint 2 using a fixed sequence procedure.

The other analyses were performed for the key secondary endpoints. The multiplicity adjustment planned for the primary analysis was not performed for statistical tests involving between-group comparisons that were performed in the other analyses.

Merged Analysis of Efficacy Endpoints

For each of participants with mild/moderate and asymptomatic/mild symptoms only SARS-CoV-2 infection, the merged analyses were conducted for the merged population of Phase 2a Part, Phase 2b Part, Phase 3 Part and Phase 2b/3 Part. The merged analyses of viral data were conducted for the merged population of Phase 3 Part and Phase 2b/3 Part.

Safety Analyses:

All safety analyses were performed in the safety analysis population for Phase 2a Part, Phase 2b Part, Phase 3 Part, and Phase 2b/3 Part, and these parts combined. In merged Parts, analyses were performed in the mild/moderate SARS-CoV-2 infection population, the asymptomatic/mild symptoms only SARS-CoV-2 infection population, and the merged population of these populations. Subgroup analyses for safety were also performed with respect to country (Japan) and age (<18, 18 to 64, ≥ 65) in the mild/moderate SARS-CoV-2 infection population, the asymptomatic/mild symptoms only SARS-CoV-2 infection population, and the merged population in merged Parts.

AEs were coded and classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0. The number and proportion of participants who experienced treatment-emergent adverse events (TEAEs), TEAEs with an outcome of death, serious TEAEs other than deaths, and TEAE leading to discontinuation of the study intervention were summarized by treatment group. The number and proportion of participants who experienced TEAEs in each category of severity and outcome were summarized by SOC and PT for each Part. Treatment-related TEAEs were summarized in the same manner as TEAEs.

For laboratory test values and vital signs, summary statistics of measurement values and their changes from baseline were calculated by treatment group for each scheduled time point. Qualitative laboratory data were summarized by the numbers of participants in the test categories at baseline and scheduled time points using shift tables.

For ECGs (Phase 2a Part only), summary statistics for ECG interpretations (normal, abnormal but not clinically significant, or abnormal and clinically significant) at each scheduled time point after randomization (including baseline) were calculated for each treatment group.

PK Analyses:

For the PK concentration population, plasma S-217622 concentrations were listed for each 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 trough concentrations (C_{24}) defined as plasma S-217622 concentrations within 20 to 28 hours after the first dose on Day 2 were summarized by treatment group and part with N, mean (Mean), standard deviation (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}$^{1/2}$ × 100, where sd was the SD of natural log-transformed values), median (Median), minimum (Min), and maximum (Max) each for Phase 2a Part, Phase 2b Part, Phase 3 Part and Phase 2b/3 Part. If possible, C_{24} were summarized by age group (12 to 18 years old, 19 to 64 years old, and over 65 years old). The data were not to be summarized for a group with N less than 3. The plasma concentrations of S-217622 versus the time from the last dosing of study intervention prior to blood sampling were graphically presented at the linear scale by treatment group.

Summary of Results:

Phase 3 Part was conducted in participants with mild/moderate SARS-CoV-2 infection.

Efficacy (Phase 3 Part):

This section focuses on the results of the S-217622 125 mg group used to evaluate the efficacy.

Data Sets Analyzed

- Of the ITT population of Phase 3 Part (603 participants in the S-217622 125 mg group and 600 participants in the placebo group), the population with < 72 hours from the onset of COVID-19 to randomization, which was the primary analysis population, consisted of 347 participants in the S-217622 125 mg group and 343 participants in the placebo group.
- Of the mITT population of Phase 3 Part (318 participants in the S-217622 125 mg group and 334 participants in the placebo group), the population with < 72 hours from the onset of COVID-19 to randomization, which was the primary analysis population, consisted of 203 participants in the S-217622 125 mg group and 214 participants in the placebo group.

Demographics and Other Baseline Characteristics

- For the ITT population with < 72 hours from the onset of COVID-19 to randomization, male participants accounted for 55.6% (193/347) in the S-217622 125 mg group and 50.7% (174/343) in the placebo group (hereafter in the same order). The median age (range) was 34.0 (14–67) years and 32.0 (12–68) years, respectively. Minor participants and participants aged 65 years or older were enrolled in both intervention groups. All participants were Asians except for 2 participants each in the S-217622 125 mg group and the placebo group. A great majority of participants had received SARS-CoV-2 vaccination: 92.8% (322/347) and 91.8% (315/343), respectively.
- The demographic and other baseline characteristics of the ITT population were similar to those of the ITT population with < 72 hours from the onset of COVID-19 to randomization. The percentage of participants with ≥ 72 hours from the onset of COVID-19 to randomization was 42.5% (256/603) and 42.8% (257/600) of the whole ITT population, respectively.
- There were no significant differences in demographics or other baseline characteristics between the intervention groups in either population.

Primary Endpoint

- The primary endpoint of Phase 3 Part was the time to resolution of 5 COVID-19 symptoms. The median time to resolution of 5 COVID-19 symptoms in the ITT population with < 72 hours from the onset of COVID-19 to randomization (95% CI), which means the time for 50% of participants to recover from the 5 COVID-19 symptoms, was 167.9 (145.0, 197.6) hours in the S-217622 125 mg group and 192.2 (174.5, 238.3) hours in the placebo group, with the median being shorter by 24.3 hours (approximately 1 day) in the S-217622 125 mg group compared with the placebo group. There was a statistically significant difference between the intervention groups (Peto-Prentice's stratified generalized Wilcoxon test, one-sided p = 0.0204).
- In a similar analysis in the ITT population performed as the key secondary analysis of the primary endpoint, the median time to resolution of 5 COVID-19 symptoms in the ITT population (95% CI) was 189.7 (161.6, 216.0) hours in the S-217622 125 mg group and 200.3 (180.8, 235.2) hours in the placebo group, with no significant difference between the intervention groups. The median time to resolution of 5 COVID-19 symptoms was numerically shorter by 10.6 hours in the S-217622 125 mg group compared with the placebo group.

Key Secondary Endpoints

- One of the key secondary endpoints was the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA. For the ITT population with < 72 hours from the onset of COVID-19 to randomization, the mean change (SD) from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA (log_{10} [copies/mL]) was −2.737 (1.085) in the S-217622 125 mg group and −1.235 (1.528) in the placebo group. The least squares (LS) mean of the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA showed a significantly greater decrease by 1.47 log_{10} (copies/mL) in the S-217622 125 mg group compared with the placebo group (p < 0.0001).
- In a similar analysis in the ITT population performed as the key secondary analysis of the key secondary endpoint, the mean change (SD) from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA (log_{10} [copies/mL]) was −2.646 (1.097) in the S-217622 125 mg group and −1.419 (1.423) in the placebo group. The LS mean of the change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA showed a greater decrease by 1.2 log_{10} (copies/mL) in the S-217622 125 mg group compared with the placebo group.
- The other key secondary endpoint was the time to the first negative SARS-CoV-2 viral titer. The median time to the first negative SARS-CoV-2 viral titer in the mITT population with < 72 hours from the onset of COVID-19 to randomization (95% CI), which means the time for 50% of participants to show the first negative SARS-CoV-2 viral titer, was 36.2 (23.4, 43.2) hours in the S-217622 125 mg group and 65.3 (62.0, 66.8) hours in the placebo group, with the median being shorter by 29.1 hours (approximately 1 day) in the

S-217622 125 mg group compared with the placebo group. There was a statistically significant difference between the intervention groups ($p < 0.0001$).

- In a similar analysis in the mITT population performed as the key secondary analysis of the key secondary endpoint, the median time to the first negative SARS-CoV-2 viral titer (95% CI) was 24.5 (22.8, 38.4) hours in the S-217622 125 mg group and 62.0 (45.0, 64.0) hours in the placebo group, with the median being shorter by 37.5 hours (approximately 1.5 day) in the S-217622 125 mg group compared with the placebo group.

Other Secondary Endpoints

For the ITT population with < 72 hours from the onset of COVID-19 to randomization, the median time to resolution of 12 and 14 COVID-19 symptoms was shortened by 34.0 hours (approximately 1.5 days) and 44.1 hours (approximately 2 days), respectively, in the S-217622 125 mg group compared with the placebo group.

Safety (Phase 3 Part):

This section describes on the results of both of the S-217622 125 mg group and 250 mg group to evaluate the safety.

- Of the 1821 randomized participants, 13 participants did not receive the study intervention and were excluded from the safety analysis population. A total of 1808 participants (604 participants in the S-217622 125 mg group, 599 participants in the S-217622 250 mg group, 605 participants in the placebo group) were included in the safety analysis population of Phase 3 Part.
- Male participants accounted for 52.8% (319/604) in the S-217622 125 mg group, 54.3% (325/599) in the S-217622 250 mg group, and 51.4% (311/605) in the placebo group (hereafter in the same order). The median age (range) was 35.0 (14–69) years, 34.0 (13–68) years and 33.0 (12–69) years, respectively. Minor participants and participants aged 65 years or older were enrolled in all intervention groups. A great majority of participants were Asian: 99.7% (602/604), 99.7% (597/599) and 99.7% (603/605), respectively. There were no significant differences in demographics or other baseline characteristics among the intervention groups.
- The incidence of TEAE in the safety analysis population was 44.2% (267/604) in the S-217622 125 mg group, 53.6% (321/599) in the S-217622 250 mg group, and 24.8% (150/605) in the placebo group (hereafter in the same order). The incidence of treatment-related TEAEs was 24.5% (148/604), 36.2% (217/599), and 9.9% (60/605), respectively. The incidences of TEAEs and treatment-related TEAEs were higher in the S-217622 125 mg and 250 mg groups than in the placebo group. The incidences of both TEAEs and treatment-related TEAEs were lower in the S-217622 125 mg group than in the S-217622 250 mg group.
- No deaths were reported in any of the intervention groups. Other serious TEAEs, which occurred in 1 participant in the S-217622 125 mg group (heavy menstrual bleeding) and 1 participant in the placebo group (cholecystitis

acute), were considered unrelated to the study intervention. TEAEs leading to discontinuation of study intervention were reported in 4 participants (4 events: 1 with mild eczema, 1 with mild vomiting, 1 with moderate rash, and 1 with moderate hypertension) in the S-217622 125 mg group, 6 participants (7 events: 1 with mild rash, 1 with mild headache, 1 with moderate rash, 1 with moderate nausea, 1 with moderate vomiting, 1 with moderate abdominal pain and moderate presyncope) in the S-217622 250 mg group, and 2 participants (3 events: 1 with mild headache, 1 with mild muscular weakness and moderate hypoaesthesia) in the placebo group. Of these events, eczema and vomiting reported in the S-217622 125 mg group, mild and moderate rash reported in the S-217622 250 mg group, and muscular weakness and hypoaesthesia reported in the placebo group were considered related to the study intervention, but all these events were resolved or resolving after discontinuation of study treatment.

- TEAEs reported in at least 2% in any of the invention groups were high density lipoprotein decreased (31.1% [188/604]), blood triglycerides increased (8.1% [49/604]), blood bilirubin increased (6.0% [36/604]), blood cholesterol decreased (3.3% [20/604]), bilirubin conjugated increased (2.5% [15/604]), blood creatine phosphokinase increased (2.3% [14/604]), and headache (2.2% [13/604]) in the S-217622 125 mg group, high density lipoprotein decreased (38.6% [231/599]), blood triglycerides increased (12.4% [74/599]), blood bilirubin increased (9.3% [56/599]), blood cholesterol decreased (4.7% [28/599]), headache and bilirubin conjugated increased (3.3% [20/599] each), and blood lactate dehydrogenase increased (2.5% [15/599]) in the S-217622 250 mg group, blood triglycerides increased (5.3% [32/605]), high density lipoprotein decreased (3.8% [23/605]), headache (2.3% [14/605]), diarrhoea and aspartate aminotransferase increased (2.0% [12/605] each) in the placebo group, respectively. Treatment-related TEAEs reported in at least 2% in any of the invention groups were high density lipoprotein decreased (18.4% [111/604]), blood bilirubin increased (2.8% [17/604]), blood triglycerides increased (2.6% [16/604]) in the S-217622 125 mg group, high density lipoprotein decreased (26.2% [157/599]), blood triglycerides increased (6.2% [37/599]), blood bilirubin increased (5.8% [35/599]), headache (2.2% [13/599]), blood cholesterol decreased (2.0% [12/599]) in the S-217622 250 mg group, and blood triglycerides increased (2.8% [17/605]) only in the placebo group.
- TEAEs reported in at least 2% in the S-217622 125 mg group were related to laboratory tests except for headache, which occurred at an incidence similar to that in the placebo group. The incidence of blood creatine phosphokinase increased, one of the TEAEs related to laboratory tests, in the S-217622 125 mg group was similar to that in the placebo group.
- Most of the TEAEs were categorized as mild. Reported severe TEAEs were heavy menstrual bleeding in 1 participant in the S-217622 125 mg group, headache in 1 participant in the S-217622 250 mg group, and diarrhoea and cholecystitis acute in 1 participant each in the placebo group. Except for headache, none of the TEAEs were considered related to the study

intervention. The headache in the S-217622 250 mg group occurred on Day 1 and was resolved on Day 4 by administration of paracetamol, while the study treatment was continued.

- Most of the TEAEs were resolved or resolving at the time of last evaluation. Except for an event of mild, non-serious rash reported in the S-217622 250 mg group, all of the unresolved TEAEs considered related to study intervention were related to laboratory tests and were mild and non-serious.
- The incidences of TEAEs on Day 6-7 were higher in the S-217622 125 mg and 250 mg groups than in the placebo group. This difference is explained by the fact that most of the TEAEs related to laboratory tests were reported on Day 6 (allowance +1), probably because the laboratory test measurements were scheduled on Days 1 (pre-dose), 6, 14, and 28. Excluding the TEAEs related to laboratory tests, the incidence of TEAEs over time was similar in the S-217622 groups and the placebo group.
- Among the laboratory test parameters, decreases in high density lipoprotein, increases in triglycerides, increases in total bilirubin and direct bilirubin, increases in serum iron, and decreases in unsaturated iron binding capacity (UIBC) were more frequently observed in the S-217622 125 mg and 250 mg groups compared with the placebo group. However, these changes were temporary.

CONCLUSIONS

Efficacy Conclusions (Phase 3 Part):

Clinical improvement and antiviral effect were verified in the ITT or mITT population with < 72 hours from the onset of COVID-19 to randomization in the S-217622 125 mg group. Numerical reduction in the median time to resolution of clinical symptoms, and reductions in viral RNA levels and in duration of positive viral titer were observed in the whole ITT or mITT population as well. In addition to resolution of the 5 COVID-19 symptoms evaluated as the primary endpoint, S-217622 also improved the 12 and 14 COVID-19 symptoms, indicating S-217622 is effective for a wider range of COVID-19 symptoms.

Safety Conclusions (Phase 3 Part):

No new safety concerns were observed in Phase 3 Part of this study. Consistent with the safety evaluation based on the results of Phase 2a Part and Phase 2b Part, the results suggested no particular safety concerns and indicated that once daily oral doses of S-217622 for 5 days (375 mg on Day 1, 125 mg on Days 2 through 5) were well tolerated in participants with SARS-CoV-2 infection.

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