2. SYNOPSIS

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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 88 sites in Japan (62 sites) and South Korea (26 sites) in Phase 2b Part.

Publication (reference): Not applicable

Studied Period: From 03 Jan 2022 (Enrollment date of the first participant in Phase 2b Part) to 10 Mar 2022 (Last observation date of the last participant in Phase 2b 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 participants with SARS-CoV-2 infection.	• 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 – Relative change rate from baseline in SARS-CoV-2 viral titer at each time point

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	– 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 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)

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• To investigate quality of life (QOL) following 5-day administration of S-217622 in participants with SARS-CoV-2 infection. • To confirm the pharmacokinetics (PK) following 5-day administration of S-217622 in participants with SARS-CoV-2 infection. • To investigate the safety and tolerability following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Saturation of percutaneous oxygen (SpO_2) at each time point • Change from baseline in EuroQol 5 dimensions 5-level (EQ-5D-5L) • Plasma concentration of S-217622 (Days 2, 6) • 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]	

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• 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.	• 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). • 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.	• 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] • 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]

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

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	– 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

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• 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) following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) 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 mild/moderate SARS-CoV-2 infection who have at least 3 moderate symptoms, based on the time to improvement of COVID-19 symptoms.	• Time to first improvement of COVID-19 symptoms[b,c]
Key Secondary	
• 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.	• Time to the first negative SARS-CoV-2 viral titer
• To compare the effect in improving clinical symptoms following 5-day administration	• Time to first improvement of COVID-19 symptoms[b,c]

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of S-217622 with that of placebo in participants with mild/moderate SARS-CoV-2 infection who have at least 1 moderate symptoms, based on the time to improvement of COVID-19 symptoms.[i]	
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 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] • 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] • 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 endpoints concerning 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

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	– 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 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)

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	– 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) following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) 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

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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, h]
Key secondary	
• 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.	• 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 endpoints concerning 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

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• 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.	– 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 • 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

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• 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) following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.	• Gene sequence of 3CL protease (nsp5) 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

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 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

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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 COVID-19 onset and considered by the participant to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline has improved to moderate or better, or moderate symptoms at baseline has improved to mild or better for 24 hours.
- Pre-existing symptoms that were present prior to COVID-19 onset and considered by the participant not to have worsened at baseline (pre-treatment examination): Severe symptoms at baseline has remained severe or improved, or moderate symptoms at baseline has remained moderate or improved for 24 hours.
- Symptoms other than the above (Symptoms that had not occurred before COVID-19 onset, occurred 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 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 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, or shortness of breath (difficulty breathing): Severity of none at baseline has worsened to mild or worse, mild symptoms at baseline has worsened to moderate or worse, or moderate symptoms at baseline has 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 has worsened to mild or worse, mild symptoms at baseline has worsened to moderate or worse, or moderate symptoms at baseline has 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 Of the 14 symptoms in COVID-19, taste disorder and smell disorder are 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 are 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 had symptoms meeting any of the following criteria.

- The scores for taste disorder or 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

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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 worsen to mild or worse, mild symptoms at baseline worsen to moderate or worse, or moderate symptoms at baseline worsen 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 worsens to mild or worse, mild symptoms at baseline worsen to moderate or worse, or moderate symptoms at baseline worsen 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).

i Participants who have one or two moderate (COVID-19 score: 2) symptoms may have been included according to the master protocol.

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 administrated 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 administrated 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

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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) will be established for the interim analyses of the primary endpoint and the key secondary endpoint of each of Phase 3 Part and Phase 2b/3 Part for the purpose of decision on stopping the study for efficacy reasons. It will control such unblinded information as the key codes and the results of analysis which may have an impact on the conduct or evaluation of Phase 3 Part and 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 have at least 1 moderate symptom were to be enrolled in 3 groups (145 participants/group).

For Phase 3 Part, 1260 eligible participants with mild/moderate SARS-CoV-2 infection who have at least 3 moderate symptoms will be enrolled in 3 groups (420 participants/group). In the case no interim analysis is performed for the purpose of decision on stopping the study for efficacy reasons, 1215 eligible participants will be randomly assigned to each of these intervention groups (405 participants/group).

For Phase 2b/3 Part, 600 eligible participants with asymptomatic/mild symptoms only SARS-CoV-2 infection will be enrolled in 3 groups (200 participants/group). In the case no interim analysis is performed for the purpose of decision on stopping the study for efficacy reasons, 570 eligible participants will be randomly assigned to each of these intervention groups (190 participants/group).

Randomized (Phase 2b Part):

Analyzed for efficacy (Phase 2b Part):
Participants with mild/moderate SARS-CoV-2 infection

- Intention-to-treat 1 (ITT1) population:
  341 participants (114 in the S-217622 125 mg group, 116 in the S-217622 250 mg group, and 111 in the placebo group)

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Analyzed for safety (Phase 2b Part):

- Safety analysis population
  421 participants (140 in the S-217622 125 mg group, 140 in the S-217622 250 mg group, and 141 in the placebo group)

Diagnosis and Main Criteria for Inclusion:

The inclusion and exclusion criteria were common for all Parts.

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 20 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 symptoms of moderate (COVID-19 symptom score: 2) or severe out of the 12 symptoms due to COVID-19 infection within 2 weeks before randomization (excluding symptoms present prior to COVID-19 onset).

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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 2b Part):

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

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

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Reference Therapy, Dose and Mode of Administration, Lot Number (Phase 2b Part):

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

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 viral 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

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- 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.

- Biomarkers (aggravation markers)
- SARS-CoV-2 lineage
- Polymorphisms of 3CL Protease (nsp5)
- Proportion of amino acid substitution in 3CL protease (nsp5) gene
- Drug antiviral activity
- Immunity (SARS-CoV-2 neutralizing antibody titers)

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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), ITT1 population (Phase 2b Part), ITT2 population (Phase 3 Part, Phase 2b/3 Part), or mITT population, ie, ITT or ITT2 participants who had a positive SARS-CoV-2 viral titer at baseline (common for Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part). As for the primary endpoints of Phase 2a Part and Phase 2b Part, and the primary and key secondary endpoints of Phase 3 Part and Phase 2b/3 Part, only the primary analyses were to be performed based on the PPS instead of ITT, ITT1, and ITT2 population, respectively, and based on the PPS with positive SARS-CoV-2 viral titer at baseline instead of mITT population for Phase 2a Part, Phase 3 Part, and Phase 2b/3 Part and ITT1 population for Phase 2b Part.

<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

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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 COVID-19 onset 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 COVID-19 onset 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 improvement of 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 improvement of symptoms is defined in the footnotes to Objectives and Endpoints.

As the primary analysis for this primary endpoint, a pairwise comparison of the time to improvement of COVID-19 symptoms will be performed between each S-217622 treatment group and the placebo group using a log-rank test stratified by the time from

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COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history at a one-sided significance level of 0.025 in the participants with mild/moderate SARS-CoV-2 infection population of participants who have at least 3 moderate symptoms in the ITT2 population. In addition, in the mild/moderate SARS-CoV-2 infection population of participants who have at least 1 moderate symptom in the ITT2 population, a similar analysis will be performed as a key secondary analysis. The multiplicity adjustment will be applied to the primary analysis. The following analyses will be performed as other analyses.

- Pairwise comparison using the generalized Wilcoxon test stratified by time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history between each S-217622 treatment group and the placebo group will be performed.
- Kaplan-Meier curves will be plotted for each treatment group and the median time to improvement of 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 each S-217622 treatment group to the placebo group will be estimated using a Cox proportional hazard model stratified by time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history.
- Restricted mean survival time (RMST) with a 21-day investigation period will be estimated for each treatment group and pairwise comparison between each S-217622 treatment group and the placebo group will be performed.

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

The primary endpoint in Phase 2b/3 Part for participants with asymptomatic/mild symptoms only SARS-CoV-2 infection, ie, 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 ITT2 population with development/worsening of any of the 12 symptoms of COVID-19, taste disorder, or smell disorder by 14 days after the first administration of the study intervention. The development/worsening of symptoms is determined according to the protocol-specified rules.

As the primary analysis for this primary endpoint, a pairwise comparison of the proportion of participants with development/worsening of COVID-19 symptoms will be performed between each S-217622 treatment group and the placebo group using

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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 ITT2 population. The multiplicity adjustment 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.

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

The key secondary endpoint in Phase 3 Part and Phase 2b/3 Part, ie, the time to the first negative SARS-CoV-2 viral titer, is defined as the time from the start of the study intervention to the first confirmed drop of SARS-CoV-2 viral titer 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 SARS-CoV-2 virus titer or the time of the last evaluation of SARS-CoV-2 virus titer before the first administration of protocol-specified prohibited concomitant drug, whichever is earlier.

The primary analysis for this key secondary endpoint is planned for participants with mild/moderate SARS-CoV-2 infection and those with asymptomatic/mild symptoms only SARS-CoV-2 infection separately. Pairwise comparison of the time to the first negative SARS-CoV-2 viral titer will be performed between each S-217622 treatment group and the placebo group using a log-rank test stratified by the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history at a one-sided significance level of 0.025 in participants with mild/moderate SARS-CoV-2 infection in mITT population of each Phase 3 Part and Phase 2b/3 Part. Pairwise comparison of the time to the first negative SARS-CoV-2 viral titer will be compared between each S-217622 treatment 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 the mITT population. The multiplicity adjustment will be applied to the primary analysis.

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

- Pairwise comparison will be performed using the generalized Wilcoxon test stratified by the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history between each S-217622

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treatment group and the placebo group in the participants with mild/moderate SARS-CoV-2 infection. Pairwise comparison will be performed using the generalized Wilcoxon test stratified by the SARS-CoV-2 vaccination history between each S-217622 treatment group and the placebo group in the participants with asymptomatic/mild symptoms only SARS-CoV-2 infection.

- For participants with mild/moderate SARS-CoV-2 infection and those with asymptomatic/mild symptoms only SARS-CoV-2 infection, 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 each S-217622 treatment group to the placebo group will be estimated using a Cox proportional hazard model stratified by the time from COVID-19 onset to randomization (< 72 hours, ≥ 72 hours) and SARS-CoV-2 vaccination history in the participants with mild/moderate SARS-CoV-2 infection. The hazard ratio of each S-217622 treatment group to the placebo group will be estimated using a Cox proportional hazard model stratified by SARS-CoV-2 vaccination history in the participants with asymptomatic SARS-CoV-2 infection.
- For participants with mild/moderate SARS-CoV-2 infection and those with asymptomatic/mild symptoms only SARS-CoV-2 infection, RMST with a 21-day investigation period will be estimated for each treatment group, and a pairwise comparison between each S-217622 treatment group and the placebo group will be performed.

Safety Analyses:

All safety analyses were to be 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 will be 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.

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

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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 $\{\exp[sd^2] - 1\}^{1/2} \times 100$, 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 to18 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.

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Summary of Results:

Efficacy (Phase 2b Part):

The primary objective of Phase 2b Part is to evaluate the improvement of clinical symptoms up to Day 6 and the antiviral effect against SARS-CoV-2 on Day 4 in participants with mild/moderate SARS-CoV-2 infection. In Phase 2b Part, unblinding was performed when the observation on Day 6 had been completed in the last participant of Phase 2b Part, and the efficacy of S-217622 was evaluated with co-primary endpoints (time-weighted average change in total score of the 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) based on the results collected up to Day 6 of all participants. Efficacy and safety data continued to be collected through Day 7 and thereafter, and an exploratory evaluation of the efficacy was performed when the observation on Day 21 had been completed in all participants. In this CSR, the efficacy up to the unblinding is mainly described but the data collected after the unblinding are also included.

The results up to the unblinding are summarized below.

Data Sets Analyzed

- A total of 428 participants with mild/moderate SARS-CoV 2 infection were randomized to one of the treatment groups.
- The ITT1 population consisted of 341 participants (114 in the S-217622 125 mg group, 116 in the S-217622 250 mg group, and 111 in the placebo group).

Demographics and Other Baseline Characteristics

For participants in the ITT1 population:

- The proportion of male participants was greater in the placebo group than in either of the S-217622 treatment groups; male participants accounted for 53.5% (61/114) in the S-217622 125 mg group, 56.9% (66/116) in the S-217622 250 mg group, and 64.9% (72/111) in the placebo group (hereafter in the same order). The median age (range) was 32.0 years (14–68), 34.0 years (12–69), and 37.0 years (16–68), respectively; the age was comparable across the treatment groups. Participants under 20 years and over 65 years of age were enrolled in each treatment group. All participants except for 1 each in the S-217622 250 mg and placebo groups were Asian (339/341), most of whom were Japanese (335/339). The time from disease onset to enrollment was ≥ 72 hours in approximately half of participants in all treatment groups: 51.8%

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(59/114), 54.3% (63/116), and 51.4% (57/111), respectively. A great majority of participants had received COVID-19 vaccination in all treatment groups: 85.1% (97/114), 83.6% (97/116), and 87.4% (97/111), respectively.

Primary Endpoint

For participants in the ITT1 population:

- The time-weighted average change in total score of the 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6) (SD) was −5.95 (4.02) in the S-217622 125 mg group and −4.92 (3.25) in the placebo group, and there was no statistically significant difference between the S-217622 125 mg group and the placebo group. However, the least squares (LS) means of the time-weighted average changes were greater in the S-217622 125 mg group than in the placebo group. The mean (SD) change from baseline in SARS-CoV-2 viral titer on Day 4 (log_{10} [$TCID_{50}$/mL]) was −1.69 (0.84) in the S-217622 125 mg group and −1.06 (0.99) in the placebo group. The LS means of the change from baseline in SARS-CoV-2 viral titer on Day 4 showed a statistically significantly greater decrease by 0.41 log_{10} ($TCID_{50}$/mL) in the S-217622 125 mg group compared with the placebo group ($p < 0.0001$).
- In the comparison in the co-primary endpoints between S-217622 125 mg group and the placebo group, one of these endpoints failed to show a statistically significant difference. Therefore, in the context of the fixed-sequence procedure for multiplicity adjustment, it has been interpreted that the co-primary endpoints also failed to show a statistical significance in the comparison between S-217622 250 mg group and the placebo group. The following results of comparisons in the co-primary endpoints between S-217622 250 mg group and the placebo group should be interpreted as secondary analyses. The time-weighted average change in total score of the 12 COVID-19 symptoms from initiation of administration (Day 1) up to 120 hours (Day 6) (SD) was −5.42 (3.70) in the S-217622 250 mg group and −4.92 (3.25) in the placebo group, and there was no statistically significant difference between the S-217622 250 mg group and the placebo group. However, the LS means of the time-weighted average changes were greater in the S-217622 250 mg group than in the placebo group. The mean (SD) change from baseline in SARS-CoV-2 viral titer on Day 4 (log_{10} [$TCID_{50}$/mL]) was −1.43 (0.83) in the S-217622 250 mg group and −1.06 (0.99) in the placebo group. The LS means of the change from baseline in SARS-CoV-2 viral titer

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on Day 4 showed a statistically significantly greater decrease by 0.4 $\log_{10}$ ($TCID_{50}$/mL) in the S-217622 250 mg group compared with the placebo group ($p < 0.0001$).

Secondary Endpoints

For participants in the ITT1 population:

- The 12 COVID-19 symptoms were categorized into the following 5 symptom subsets: acute symptoms (sore throat, cough, and feeling hot or feverish); main clinical symptoms (stuffy or runny nose, sore throat, cough, chills or shivering, and feeling hot or feverish); respiratory symptoms (stuffy or runny nose, sore throat, cough, and shortness of breath [difficulty breathing]); systemic symptoms (low energy or tiredness, muscle or body aches, headache, chills or shivering, and feeling hot or feverish); and gastrointestinal symptoms (nausea, vomiting, or diarrhoea). The time-weighted average changes were analyzed for the subtotal of symptom scores for each of the 5 symptom subsets from initiation of administration (Day 1) up to 120 hours (Day 6). The respiratory symptoms showed a significant improvement in either the S-217622 125 mg or 250 mg group compared with the placebo group ($p = 0.0153$ and $p = 0.0033$, respectively). The main clinical symptoms and acute symptoms were significantly improved in the S-217622 250 mg group compared with the placebo group ($p = 0.0149$ for the main clinical symptoms and $p = 0.0070$ for the acute symptoms), while they tended to be improved in the S-217622 125 mg group compared with the placebo group without a significant difference. Compared to these symptom groups, the systemic symptoms or the gastrointestinal symptoms did not show a significant difference between either of the S-217622 treatment groups and the placebo group. Although the LS mean of the changes in the systemic symptoms did not show a significant difference between either of the S-217622 treatment groups and the placebo group, a decrease in symptom scores was observed over time. The gastrointestinal symptoms did not produce sufficient symptoms at the baseline to evaluate the difference between each of the S-217622 treatment groups and the placebo group.
- The changes from baseline in total score of the 12 COVID-19 symptoms (SD) 12 hours post-dose were −3.4 (3.9) in the S-217622 125 mg group, −2.6 (3.2) in the S-217622 250 mg group, and −2.6 (3.3) in the placebo group (hereafter in the same order), −4.5 (4.1), −3.8 (3.8), and −3.5 (3.5) 24 hours post-dose, −6.0 (4.8), −5.7 (4.3), and −4.7 (3.6) 48 hours post-dose, −6.7 (4.3), −6.8

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(4.2), and −5.9 (3.8) 72 hours post-dose, −7.4 (4.4), −7.5 (4.2), and −6.5 (3.9) 96 hours post-dose, and −8.3 (4.7), −7.9 (4.1), and −7.2 (3.9) 120 hours post-dose, respectively. There was no significant difference between either of the S-217622 treatment groups and the placebo group at any time point. However, the LS mean of the changes from baseline in total score of the 12 COVID-19 symptoms was numerically greater in the S-217622 125 mg group than in the placebo group from 12 hours post-dose onward, and in the S-217622 250 mg group than in the placebo group from 48 hours post-dose onward.

- The change from baseline in taste disorder score showed a significant difference between the S-217622 125 mg group and the placebo group at all the time points from 12 hours post-dose onward through 120 hours post-dose except for 84 hours post-dose, with the greatest p-value of 0.0347, and between the S-217622 250 mg group and the placebo group at all the time points from 24 hours post-dose onward through 120 hours post-dose except for 60 and 72 hours post-dose, with the greatest p-value of 0.0498. The change from baseline in smell disorder score showed a significant difference between the S-217622 125 mg group and the placebo group 48 to 72, 96, and 108 hours post-dose, with the greatest p-value of 0.0242, and between the S-217622 250 mg group and the placebo group 72 and 120 hours post-dose, with the greatest p-value of 0.0403.

Safety (Phase 2b Part):
In Phase 2b Part, unblinding was performed when the observation on Day 6 had been completed in the last participant of Phase 2b Part, and the safety of S-217622 was evaluated based on the results collected up to the unblinding. Efficacy and safety data continued to be collected through Day 7 and thereafter, an exploratory evaluation of the safety was performed when the observation of the follow-up period on Day 28 had been completed in all participants. In this CSR, the safety up to the unblinding is mainly described but the data collected after the unblinding are also included.

Of the 428 randomized participants (419 were Japanese), 7 participants did not receive the study intervention and was excluded from the safety analysis population. A total of 421 participants (140 each in the S-217622 125 mg and 250 mg groups and 141 in the placebo group) were included in the safety analysis population in Phase 2b Part. The safety data reported up to the unblinding (Day 6 of the last participant) of Phase 2b Part are summarized below.

- The overall incidence of TEAEs in Phase 2b Part was 26.4% (37/140) in the S-217622 125 mg group, 34.3% (48/140) in the S-217622 250 mg group, and 24.1% (34/141) in the placebo group.
- The overall incidence of treatment-related TEAEs in Phase 2b Part was 9.3% (13/140) in the S-217622 125 mg group, 18.6% (26/140) in the S-217622 250 mg group, and 5.0% (7/141) in the placebo group.
- The incidences of TEAEs were comparable between the S-217622 125 mg and placebo groups, while those were greater in the S-217622 250 mg group than in the placebo group.
- The incidences of treatment-related TEAEs were greater in either of the S-217622 treatment groups than in the placebo group.
- The incidences of TEAEs and treatment-related TEAEs were smaller in the S-217622 125 mg group than in the S-217622 250 mg group.
- The TEAEs reported in at least 2% in any of the three groups of Phase 2b Part were high density lipoprotein decreased (16.4% [23/140]) in the S-217622 125 mg group, high density lipoprotein decreased (20.0% [28/140]) and headache, diarrhoea, back pain, and hypertriglyceridaemia (2.1% [3/140] each) in the S-217622 250 mg group, and rash and high density lipoprotein decreased (2.1% [3/141] each) in the placebo group. The treatment-related TEAE reported in at least 2% in any of the three groups was high density lipoprotein decreased (5.7% [8/140] and 12.1% [17/140] in the S-217622 125 mg and 250 mg groups, respectively) only. No treatment-related TEAEs with an incidence of at least 2% were reported in the placebo group.
- No deaths or serious TEAEs were reported in the S-217622 treatment groups. Serious TEAEs were reported in 2 participants in the placebo group, both of which were considered unrelated to the study intervention.
- Three TEAEs leading to discontinuation of study intervention were reported in 2 participants in the S-217622 125 mg group, all of which were considered related to the study intervention.

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While the incidences of TEAEs and treatment-related TEAEs slightly increased in the safety data reported up to Day 28 of the last participant of Phase 2b Part compared with the data up to the unblinding, the safety profile of S-217622 was considered to be unchanged.

CONCLUSIONS

This CSR mainly reports the efficacy and safety in participants with mild/moderate SARS-CoV-2 infection using data up to the unblinding (Day 6 of the last participant) of Phase 2b Part of this study.

Efficacy Conclusions (Phase 2b Part):

Of the co-primary endpoints in Phase 2b Part, the change from baseline in SARS-CoV-2 viral titer on Day 4 demonstrated a statistically significantly greater decrease. However, the 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) failed to demonstrate a significant difference between either of the S-217622 treatment groups and the placebo group; therefore the primary objective of Phase 2b Part failed to be achieved. This could be attributed to the low baseline scores of many of the 12 COVID-19 symptoms (ie, mild symptoms with a score of less than 1) in the participants in Phase 2b Part, which made it difficult to demonstrate a significant difference between the S-217622 treatment groups and the placebo group. The following symptoms with a score of 1 or higher were considered to be specific in the participants in Phase 2b Part: low energy or tiredness, feeling hot or feverish, stuffy or runny nose, sore throat, and cough. The respiratory symptoms including some of these symptoms showed a significant improvement in either of the S-217622 treatment groups compared with the placebo group.

Safety Conclusions (Phase 2b Part):

In Phase 2b Part, no deaths or serious TEAEs were reported in the S-217622 treatment groups, and no specific safety issues were identified with oral administration of once-daily for 5 days (375 mg or 750 mg on Day 1 and 125 mg or 250 mg on Days 2 through 5). S-217622 was well tolerated in Phase 2b Part as well as Phase 2a Part. The safety profile of S-217622 was considered to be unchanged.

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