# 2. SYNOPSIS

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| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>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 study conducted at 56 sites in Japan in Phase 2a Part.

**Publication (reference):** Not applicable

**Studied Period:** From 28 Sep 2021 to 27 Jan 2022 (Last observation date of the last participants in Phase 2a 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<br>– Time to the first negative SARS-CoV-2 viral titer<br>– Time to negative SARS-CoV-2 viral titers at 2 consecutive time points<br>– Time to sustained negative SARS-CoV-2 viral titer<br>– Proportion of participants with positive SARS-CoV-2 viral titer at each time point<br>– SARS-CoV-2 viral titer at each time point<br>– Relative change rate from baseline in SARS-CoV-2 viral titer at each time point |

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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| | – Area under the curve (AUC) of change in SARS-CoV-2 viral titer<br>• The following endpoints concerning reverse transcription polymerase chain reaction (RT-PCR) testing (nasopharyngeal swabs)<br>– Time to the first negative RT-PCR result<br>– Time to negative RT-PCR results at 2 consecutive time points<br>– Time to sustained negative RT-PCR results<br>– Proportion of participants with positive RT-PCR result at each time point<br>– Amount of SARS-CoV-2 viral RNA at each time point<br>– Change from baseline in the amount of SARS-CoV-2 viral RNA at each time point<br>– Relative change rate from baseline in the amount of SARS-CoV-2 viral RNA at each time point<br>– 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<br>– Symptomatic, no limitation of activities (Score 1)<br>– Symptomatic, limitation of activities (Score 2)<br>– Hospitalized, no oxygen therapy (Score 3)<br>– Hospitalized, with oxygen therapy (< 5 L/min) (Score 4)<br>– Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5)<br>– Hospitalized, with ventilation (Score 6)<br>– Death (Score 7) |

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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| • To investigate quality of life (QOL) following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.<br>• To confirm the pharmacokinetics (PK) following 5-day administration of S-217622 in participants with SARS-CoV-2 infection.<br>• 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<br>• Change from baseline in EuroQol 5 dimensions 5-level (EQ-5D-5L)<br>• Plasma concentration of S-217622 (Days 2, 6)<br>• 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]<br>• Time to first improvement of COVID-19 symptoms (duration of recovery, 72 hours [3 days] or longer)[b, c, d]<br>• Time to first improvement of COVID-19 symptoms (duration of recovery, 120 hours [5 days] or longer)[b, c, d]<br>• Time to first improvement of each COVID-19 symptom[b, c]<br>• Change from baseline in the total score of COVID-19 symptoms at each time point[b]<br>• Proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point[b, c]<br>• Proportion of participants with taste disorder or smell disorder at each time point<br>• 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]<br>• 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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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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| • To evaluate immunity in participants with SARS-CoV-2 infection.<br>• To evaluate the effect of 5-day administration of S-217622 on aggravation markers in participants with SARS-CoV-2 infection.<br>• 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)<br>• Change from baseline in aggravation markers[g]<br>• 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).<br>• 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]<br>• 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]<br>• Time to first improvement of COVID-19 symptoms (duration of recovery, 72 hours [3 days] or longer)[b, c, d]<br>• Time to first improvement of COVID-19 symptoms (duration of recovery, 120 hours [5 days] or longer)[b, c, d]<br>• Time to first improvement of each COVID-19 symptom[b, c] |

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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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]<br>• Proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point[b, c]<br>• Proportion of participants with taste disorder or smell disorder at each time point<br>• Time to resolution of fever (< 37.0°C)<br>• The following endpoints concerning SARS-CoV-2 viral titer<br>– Time to the first negative SARS-CoV-2 viral titer<br>– Time to negative SARS-CoV-2 viral titers at 2 consecutive time points<br>– Time to sustained negative SARS-CoV-2 viral titer<br>– Proportion of participants with positive SARS-CoV-2 viral titer at each time point<br>– SARS-CoV-2 viral titer at each time point<br>– Change from baseline in SARS-CoV-2 viral titer at each time point<br>– Relative change rate from baseline in SARS-CoV-2 viral titer at each time point<br>– AUC of change in SARS-CoV-2 viral titer<br>• The following endpoints concerning RT-PCR testing (nasopharyngeal swabs)<br>– Time to the first negative RT-PCR result<br>– Time to negative RT-PCR results at 2 consecutive time points<br>– Time to sustained negative RT-PCR results<br>– Proportion of participants with positive RT-PCR result at each time point<br>– Amount of SARS-CoV-2 viral RNA at each time point |

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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| | – Change from baseline in the amount of SARS-CoV-2 viral RNA at each time point<br>– Relative change rate from baseline in the amount of SARS-CoV-2 viral RNA at each time point<br>– 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<br>– Symptomatic, no limitation of activities (Score 1)<br>– Symptomatic, limitation of activities (Score 2)<br>– Hospitalized, no oxygen therapy (Score 3)<br>– Hospitalized, with oxygen therapy (< 5 L/min) (Score 4)<br>– Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5)<br>– Hospitalized, with ventilation (Score 6)<br>– Death (Score 7)<br>• $SpO_2$ 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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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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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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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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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]<br>• Time to first improvement of COVID-19 symptoms (duration of recovery, 120 hours [5 days] or longer)[b, c, d]<br>• Time to first improvement of each COVID-19 symptom[b, c]<br>• 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]<br>• Change from baseline in total score of COVID-19 symptoms at each time point[b]<br>• Proportion of participants with improvement of COVID-19 symptoms and each symptom at each time point[b, c]<br>• Proportion of participants with taste disorder or smell disorder at each time point<br>• 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<br>– Time to negative SARS-CoV-2 viral titers at 2 consecutive time points<br>– Time to sustained negative SARS-CoV-2 viral titer<br>– Proportion of participants with positive SARS-CoV-2 viral titer at each time point<br>– SARS-CoV-2 viral titer at each time point<br>– Change from baseline in SARS-CoV-2 viral titer at each time point |

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| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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| | – Relative change rate from baseline in SARS-CoV-2 viral titer at each time point<br>– AUC of change in SARS-CoV-2 viral titer<br>• The following endpoints concerning RT-PCR testing (nasopharyngeal swabs)<br>– Time to the first negative RT-PCR result<br>– Time to negative RT-PCR results at 2 consecutive time points<br>– Time to sustained negative RT-PCR results<br>– Proportion of participants with positive RT-PCR result at each time point<br>– Amount of SARS-CoV-2 viral RNA at each time point<br>– Change from baseline in the amount of SARS-CoV-2 viral RNA at each time point<br>– Relative change rate from baseline in the amount of SARS-CoV-2 viral RNA at each time point<br>– 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<br>– Symptomatic, no limitation of activities (Score 1)<br>– Symptomatic, limitation of activities (Score 2)<br>– Hospitalized, no oxygen therapy (Score 3)<br>– Hospitalized, with oxygen therapy (< 5 L/min) (Score 4)<br>– Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5) |

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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| | – Hospitalized, with ventilation (Score 6)<br>– Death (Score 7)<br>• $SpO_2$ 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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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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. | • Proportion of participants with development of COVID-19 symptoms[e, f]<br>• 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<br>– Time to negative SARS-CoV-2 viral titers at 2 consecutive time points<br>– Time to sustained negative SARS-CoV-2 viral titer<br>– Proportion of participants with positive SARS-CoV-2 viral titer at each time point<br>– SARS-CoV-2 viral titer at each time point<br>– Change from baseline in SARS-CoV-2 viral titer at each time point<br>– Relative change rate from baseline in SARS-CoV-2 viral titer at each time point |

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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| | – AUC of change in SARS-CoV-2 viral titer<br>• The following endpoints concerning RT-PCR testing (nasopharyngeal swabs)<br>– Time to the first negative RT-PCR result<br>– Time to negative RT-PCR results at 2 consecutive time points<br>– Time to sustained negative RT-PCR results<br>– Proportion of participants with positive RT-PCR result at each time point<br>– Amount of SARS-CoV-2 viral RNA at each time point<br>– Change from baseline in the amount of SARS-CoV-2 viral RNA at each time point<br>– Relative change rate from baseline in the amount of SARS-CoV-2 viral RNA at each time point<br>– 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<br>– Symptomatic, no limitation of activities (Score 1)<br>– Symptomatic, limitation of activities (Score 2)<br>– Hospitalized, no oxygen therapy (Score 3)<br>– Hospitalized, with oxygen therapy (< 5 L/min) (Score 4)<br>– Hospitalized, with oxygen therapy (≥ 5 L/min) (Score 5)<br>– Hospitalized, with ventilation (Score 6)<br>– Death (Score 7)<br>• $SpO_2$ at each time point |

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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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 **Error! Reference source not found.**9.3.1.2 but did not meet exclusion criterion #1 to #5 in Section **Error! Reference source not found.**9.3.2.2.

b The following 12 symptoms were evaluated: low energy or tiredness, muscle or body aches, headache, chills

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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 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 has 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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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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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| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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 are 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 2a Part):**

**Analyzed for efficacy (Phase 2a Part):**

1. Participants with mild/moderate SARS-CoV-2 infection
   - Intention-to-treat (ITT) population:
     40 participants (14 in the S-217622 125 mg group, 12 in the S-217622 250 mg group, and 14 in the placebo group)

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

- Modified intention-to-treat (mITT) population:
  37 participants (13, 12, and 12)
- Per protocol set (PPS):
  33 participants (13, 9, and 11)

2. Participants with asymptomatic SARS-CoV-2 infection
   - ITT population:
     7 participants (2 in the S-217622 125 mg group, 2 in the S-217622 250 mg group, and 3 in the placebo group)
   - mITT population:
     6 participants (2, 2, and 2)
   - PPS:
     7 participants (2, 2, and 3)

**Analyzed for safety (Phase 2a Part):**

- Safety analysis population
  68 participants (21 in the S-217622 125 mg group, 23 in the S-217622 250 mg group, and 24 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)

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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).

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 2a Part):**

| Study Intervention Name | Packaging Lot No. |
|---|---|
| S-217622 tablet 250 mg | Day1, [redacted] |
| S-217622 tablet 125 mg | 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

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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

| Study Intervention Name | Packaging Lot No. |
|---|---|
| S-217622 tablet Placebo-D | Day1, [redacted] |
| S-217622 tablet Placebo-B | 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 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

   - $SpO_2$

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

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

- 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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| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

**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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| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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 are 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 will be performed between each S-217622 intervention group and the placebo group, analysis of covariance will be applied with time-weighted average change as response, and by time from 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 is one or higher at the initiation of administration (Day 1) in the ITT1 population. In addition, as the primary analysis for change from baseline on Day 4 in SARS-CoV-2 viral titer, pairwise comparison will be performed between each S-217622 intervention group and the placebo group, analysis of covariance will be 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 will be 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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| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

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 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.

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

**Summary of Results:**

**Efficacy (Phase 2a Part):**

Data Sets Analyzed

- A total of 69 participants were randomized to one of the treatment groups.
- For all participants (with mild/moderate and asymptomatic SARS-CoV-2 infection combined), the mITT population consisted of 43 participants (15 in the S-217622 125 mg group, 14 in the S-217622 250 mg group, and 14 in the placebo group) (hereafter in the same order), while the ITT population consisted of 47 participants (16, 14, and 17).
- As for participants with mild/moderate SARS-CoV-2 infection, the mITT population consisted of 37 participants (13, 12, and 12), while the ITT population consisted of 40 participants (14, 12, and 14).
- As for participants with asymptomatic SARS-CoV-2 infection, the mITT population consisted of 6 participants (2, 2, and 2), while the ITT population consisted of 7 participants (2, 2, and 3).

Demographics and Other Baseline Characteristics

- All 69 randomized participants of Phase 2a Part were Japanese.
- As for participants with mild/moderate SARS-CoV-2 infection in the ITT population, the proportion of male participants was greater in the placebo group than in the S-217622 treatment groups; male participants accounted for 42.9% (6/14) in the S-217622 125 mg group, 50.0% (6/12) in the S-217622 250 mg group, and 78.6% (11/14) in the placebo group (hereafter in the same order). The median age (range) was 34.5 years (22–59), 37.5 years (23–63), and 35.0 years (16–61), respectively, being comparable across the treatment groups. No participants under 20 years of age were enrolled in the S-217622 treatment groups. The time from disease onset to enrollment was ≥ 72 hours in the majority of participants in all treatment groups: 64.3% (9/14), 58.3% (7/12), and 64.3% (9/14), respectively. A great majority of participants had received COVID-19 vaccination in all treatment groups: 85.7% (12/14), 83.3% (10/12), and 71.4% (10/14), respectively.
- As for participants with asymptomatic SARS-CoV-2 infection in the ITT population, all participants were male except for one in the placebo group. The age was 41 and 47 years in the S-217622 125 mg group, 37 and 41 years in the S-217622 250 mg group, and 37, 45, and 51 years in the placebo group, being comparable across the treatment groups. No participants under 20 years of age

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

were enrolled in any treatment groups. All participants except for one in the placebo group had received COVID-19 vaccination.

Primary Endpoint

For all participants (with mild/moderate and asymptomatic SARS-CoV-2 infection combined) in the mITT population:

- The mean (SD) change from baseline in SAR-CoV-2 viral titer ($log_{10}$ [$TCID_{50}$/mL]) was −1.05 (1.17) in the S-217622 125 mg group, −2.03 (1.21) in the S-217622 250 mg group, and −0.86 (0.93) in the placebo group on Day 2 (hereafter in the same order), −2.42 (1.42), −2.81 (1.21), and −1.54 (0.74) on Day 4, and −2.56 (1.35), −2.76 (1.19), and −2.08 (0.91) on Day 6, respectively.
- Compared with the placebo group, the change from baseline in SARS-CoV-2 viral titers showed greater decrease by approximately 1 $log_{10}$ ($TCID_{50}$/mL) in the S-217622 250 mg group on Day 2, and by approximately 1 $log_{10}$ ($TCID_{50}$/mL) in both the S-217622 125 mg and 250 mg groups on Day 4. The change from baseline in SARS-CoV-2 viral titers on Days 2 and 4 was statistically significant in the S-217622 250 mg group, compared with the placebo group ($p = 0.0212$ and $p = 0.0083$ each).
- In the post hoc analysis using ANCOVA model, the least squares (LS) means of the change from baseline in SARS-CoV-2 viral titers showed greater decrease by approximately 1 $log_{10}$ ($TCID_{50}$/mL) in the S-217622 250 mg group on Day 2, and by approximately 1 $log_{10}$ ($TCID_{50}$/mL) in either of the S-217622 125 mg or 250 mg groups on Day 4, compared with the placebo group. The difference in the LS means of change from baseline in SARS-CoV-2 viral titers on Day 2 was statistically significant in the S-217622 250 mg group, compared with the placebo group ($p = 0.0129$). The difference in the LS means of change from baseline in SARS-CoV-2 viral titers on Day 4 was statistically significant in either the S-217622 125 mg group or 250 mg group, compared with the placebo group ($p = 0.0018$ and $p = 0.0004$ each).

Secondary Endpoints (Common to Participants with Mild/Moderate and with Asymptomatic SARS-CoV-2 Infection)

- For all participants (with mild/moderate and asymptomatic SARS-CoV-2 infection combined) in the mITT population, the median time to first negative SARS-CoV-2 viral titer (the time to when 50% of participants had a negative SARS-CoV-2 viral titer) was shorter in the S-217622 125 mg and 250 mg

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

groups than in the placebo group by approximately 50 hours and 48 hours (2 days), respectively.

- For all participants (with mild/moderate and asymptomatic SARS-CoV-2 infection combined) in the mITT population, the proportion of participants with a positive SARS-CoV-2 viral titer on Day 2 was 86.7% (13/15) in the S-217622 125 mg group, 71.4% (10/14) in the S-217622 250 mg group, and 78.6% (11/14) in the placebo group (hereafter in the same order), 26.7% (4/15), 14.3% (2/14), and 71.4% (10/14) on Day 4, and 0.0% (0/15), 14.3% (2/14), and 30.8% (4/13) on Day 6, respectively. The proportion of participants with a positive SARS-CoV-2 viral titer was smaller in the S-217622 125 mg and 250 mg groups than in the placebo group from Day 4 onward, excepting the S-217622 125 mg group on Day 14.
- For all participants (with mild/moderate and asymptomatic SARS-CoV-2 infection combined) in the ITT population, the median time to first negative RT-PCR result (the time to when 50% of participants had a negative RT-PCR) was approximately 120 hours (5 days) shorter numerically in either the S-217622 125 mg or 250 mg groups than in the placebo group, although some participants needed a long time to become RT-PCR negative in all treatment groups.
- For all participants (with mild/moderate and asymptomatic SARS-CoV-2 infection combined) in the ITT population, the proportion of participants with a positive RT-PCR result on Day 4 was 93.3% (14/15) in the S-217622 125 mg group, 78.6% (11/14) in the S-217622 250 mg group, and 94.1% (16/17) in the placebo group (hereafter in the same order), 66.7% (10/15), 57.1% (8/14), and 75.0% (12/16) on Day 6, and 42.9% (6/14), 53.8% (7/13), and 66.7% (10/15) on Day 9, respectively. The proportion of participants with a positive RT-PCR result was numerically smaller in the S-217622 125 mg and 250 mg groups than in the placebo group on Days 6 and 9.
- For all participants (with mild/moderate and asymptomatic SARS-CoV-2 infection combined) in the ITT population, the mean (SD) change from baseline in the amount of SARS-CoV-2 viral RNA ($log_{10}$ [copies/mL]) on Day 2 was −1.109 (0.774) in the S-217622 125 mg group, −1.147 (1.325) in the S-217622 250 mg group, and −0.542 (0.848) in the placebo group (hereafter in the same order), −2.677 (1.063), −2.761 (1.291), and −1.269 (1.228) on Day 4, and −3.114 (1.025), −3.122 (1.194), and −1.924 (1.114) on Day 6, respectively. The decreases in the amount of SARS-CoV-2 viral RNA

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

were greater in the S-217622 125 mg and 250 mg groups than in the placebo group from Day 2 onward. The decreases in the amount of SARS-CoV-2 viral RNA were greater by approximately 1.4 $\log_{10}$ (copies/mL) in either the S-217622 125 mg or 250 mg groups compared with the placebo group on Day 4, and by approximately 1.2 $\log_{10}$ (copies/mL) on Day 6. In the post hoc analysis using ANCOVA model, the LS means of the change from baseline in the amount of SARS-CoV-2 viral RNA showed greater decrease by approximately 1 $\log_{10}$ (copies/mL) in either the S-217622 125 mg or 250 mg groups on Day 4, and by approximately 0.7 $\log_{10}$ (copies/mL) in the S-217622 125 mg group and approximately 0.8 $\log_{10}$ (copies/mL) in the S-217622 250 mg group on Day 6 compared with the placebo group.

- For participants with mild/moderate SARS-CoV-2 infection in the ITT population, whose baseline 8-Point Ordinal Scale was < 3 (hospitalized, no oxygen therapy), there was no participant whose score was aggravated to ≥ 3 in the 8-Point Ordinal Scale in either the S-217622 125 mg or 250 mg groups while there were 2 in the placebo group. The score was not aggravated to ≥ 4 (hospitalized, with oxygen therapy [< 5 L/min]) in any participants. For participants with asymptomatic SARS-CoV-2 infection in the ITT population, there was no participant whose score was aggravated to ≥ 1 (symptomatic, no limitation of activities) in the 8-Point Ordinal Scale in both the S-217622 125 mg and 250 mg groups while there was only 1 in the placebo group. The score was not aggravated to ≥ 2 (symptomatic, limitation of activities) in any participants.

<u>Secondary Endpoints (Participants with Mild/Moderate SARS-CoV-2 Infection Only)</u>

- For participants with mild/moderate SARS-CoV-2 infection in the ITT population, the median time to first improvement of COVID-19 symptoms (the time to when COVID-19 symptoms were improved in 50% of participants) was 40.6 hours (95%CI, 12.2 to 76.5) in the S-217622 125 mg group, 55.2 hours (10.3 to 109.2) in the S-217622 250 mg group, and 36.7 hours (0.1 to 190.7) in the placebo group (hereafter in the same order). No differences were observed in the median time to first improvement of COVID-19 symptoms between either of the S-217622 treatment groups and the placebo group. The estimated RMST was 57.9 hours, 81.6 hours, and 80.9 hours, respectively. Although the median time to first improvement of COVID-19 symptoms was similar between either of the S-217622 treatment groups and the placebo group, there was a numerical tendency for RMST with

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|---|---|---|
| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

a 21-day investigation period to be numerically shorter in the S-217622 125 mg group compared with the placebo group.

- For participants with mild/moderate SARS-CoV-2 infection in the ITT population, the mean (SD) change from baseline in the total score of COVID-19 symptoms 12 hours post-dose was −4.4 (4.3) in the S-217622 125 mg group, −2.6 (3.4) in the S-217622 250 mg group, and −2.1 (1.6) in the placebo group (hereafter in the same order), −4.8 (3.8), −4.2 (3.5), and −1.6 (1.8) 24 hours post-dose, and −5.8 (5.6), −4.1 (4.1), and −2.9 (2.1) 48 hours post-dose, respectively. The decreases in the total score of COVID-19 symptoms were numerically greater in either the S-217622 125 mg or 250 mg groups than in the placebo group from 12 hours post-dose onward.
- For participants with mild/moderate SARS-CoV-2 infection in the ITT population, the proportion of participants with improvement of COVID-19 symptoms 12 hours post-dose was 25.0% (3/12) in the S-217622 125 mg group, 27.3% (3/11) in the S-217622 250 mg group, and 54.5% (6/11) in the placebo group (hereafter in the same order), 45.5% (5/11), 45.5% (5/11), and 54.5% (6/11) 24 hours post-dose, 72.7% (8/11), 54.5% (6/11), and 63.6% (7/11) 48 hours post-dose, 83.3% (10/12), 63.6% (7/11), and 60.0% (6/10) 72 hours post-dose, 81.8% (9/11), 72.7% (8/11), and 63.6% (7/11) 96 hours post-dose, respectively. The proportion of participants with improvement of COVID-19 symptoms tended to be numerically greater in the S-217622 125 mg group than in the placebo group from 72 hours post-dose onward.
- For participants with mild/moderate SARS-CoV-2 infection in the ITT population, the median time to resolution of fever (the time to reach 50% for the proportion of participants whose fever had resolved to < 37.0°C) was numerically shorter in the S-217622 125 mg and 250 mg groups than in the placebo group by 42 hours (nearly 2 days) and 64 hours (2.5 days), respectively, although the number of participants who had fever ( ≥ 37.0°C) at baseline was small.

<u>Secondary Endpoint (Participants with Asymptomatic SARS-CoV-2 Infection Only)</u>

- The number of participants with asymptomatic SARS-CoV-2 infection was too small to discuss any trends by dose of the proportion of participants with development of COVID-19.

**Safety (Phase 2a Part):**

Of the 69 randomized participants, 1 participant did not receive the study intervention and was excluded from the safety analysis population. A total of 68 participants with mild/moderate or asymptomatic SARS-CoV-2 infection (21 in the S-217622 125 mg group, 23 in the S-217622 250 mg group, and 24 in the placebo group) were included in the safety analysis population in Phase 2a Part.

No deaths, serious TEAEs, or TEAEs leading to discontinuation of study intervention were reported during the Phase 2a Part of the study. All TEAEs reported in this Part for participants with mild/moderate or asymptomatic SARS-CoV-2 infection are summarized below.

- The overall incidence of TEAEs in Phase 2a Part for the safety analysis population was 52.4% (11/21) in the S-217622 125 mg group, 69.6% (16/23) in the S-217622 250 mg group, and 37.5% (9/24) in the placebo group.
- The overall incidence of treatment-related TEAEs in Phase 2a Part was 23.8% (5/21) in the S-217622 125 mg group, 43.5% (10/23) in the S-217622 250 mg group, and 0% (0/24) in the placebo group.
- The incidences of TEAEs and treatment-related TEAEs were greater in either of the S-217622 treatment groups than in the placebo group, and were smaller in the S-217622 125 mg group than in the S-217622 250 mg groups.
- TEAEs reported in at least 3 participants in any of the treatment groups of Phase 2a Part were high density lipoprotein decreased (14.3% [3/21] and 52.2% [12/23] in the S-217622 125 mg and 250 mg groups, respectively), headache and blood triglycerides increased (13.0% [3/23] each in S-217622 250 mg group). No TEAEs were reported in 3 or more participants in the placebo group. The only treatment-related TEAE reported in at least 3 participants in any of the treatment groups was high density lipoprotein decreased (14.3% [3/21] and 34.8% [8/23] in the S-217622 125 mg and 250 mg groups, respectively).
- No severe TEAEs were reported, and most of TEAEs were categorized as mild. The moderate TEAEs were nasopharyngitis (1 participant in the S-217622 125 mg group), headache and vomiting (one and the same participant in the S-217622 250 mg group). All these moderate events were considered unrelated to the study intervention.
- Most of the TEAEs were resolved or resolving at the last observation. The TEAEs that were not resolved were urine ketone body present (1 participant in the S-217622 125 mg group), hyperbilirubinaemia (1 participant in the S-217622 250 mg group), gamma-glutamyltransferase increased, alanine aminotransferase increased, blood uric acid increased, and protein urine present (1 participant each in the placebo group). All of these events were mild and non-serious, and considered unrelated to the study intervention excluding hyperbilirubinaemia. One TEAE (presyncope) reported in the placebo group and considered unrelated to the study intervention was resolved with sequelae.
- No TEAEs occurred on the loading dose day, and most of the TEAEs occurred on Day 2-7. TEAEs observed from Day 15 onwards were nasopharyngitis (2

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| **Name of Finished Product**<br>Not applicable | **Volume:** | : |
| **Name of Active Ingredient:**<br>S-217622 | **Page:** | |

participants), insomnia, fatigue, pyrexia, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased (1 participant each) in the S-217622 125 mg group, and headache (2 participants), nausea, and diarrhoea (1 participant each) in the S-217622 250 mg group, all of which were considered unrelated to S-217622.

**CONCLUSIONS**

**Efficacy Conclusions (Phase 2a Part):**

The oral administration of S-217622 once-daily for 5 days (375 mg or 750 mg on Day 1, 125 mg or 250 mg on Days 2 through 5) demonstrated an antiviral effect in participants with mild/moderate or asymptomatic SARS-CoV-2 infection, and was suggested to be clinically effective in patients with mild/moderate SARS-CoV-2 infection, based on the data of 69 participants in Phase 2a Part (40 participants in the ITT population and 37 participants in the mITT population for participants with mild/moderate SARS-CoV-2 infection, 7 participants and 6 participants for participants with asymptomatic SARS-CoV-2 infection, respectively).

**Safety Conclusions (Phase 2a Part):**

Overall, S-217622 was safe and well tolerated 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) based on the data of 68 participants in Phase 2a Part.

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