2. SYNOPSIS

Study Title:
A Phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of S-217622 in the prevention of symptomatic SARS-CoV-2 infection in household contacts of an individual with symptomatic COVID-19

Study Number:
2206T1331

Compound:
S-217622

Trade Name: Not applicable

Sponsor:
Shionogi & Co., Ltd./Shionogi Inc./Shionogi B.V.

Investigators and Study Sites: This study was a multicenter study conducted at 178 contracted sites, including 95 sites in the US, 67 sites in Japan, 2 sites in Vietnam, 11 Sites in Argentina, and 3 sites in South Africa.

Publication (reference): Not applicable

Studied Period:
From 09 Jun 2023 to 18 Sep 2024

Phase of Development: 3

Objectives, Endpoints, and Estimands:

Objective	Endpoint
Primary	
• To compare ensitrelvir with placebo in the prevention of symptomatic SARS-CoV-2 infection in participants with a negative screening SARS-CoV-2 infection who are household members (hereinafter referred to as "participants") of SARS-CoV-2-infected patients (hereinafter referred to as "index patients") through Day 10 (using the mITT analysis set)	• Proportion of participants in the mITT analysis set with a negative screening SARS-CoV-2 infection (CLC-negative RT-PCR test) who are infected with SARS-CoV-2 (CLC-positive RT-PCR test) and have COVID-19 symptoms onset[a] through Day 10
Key secondary	
• To compare ensitrelvir with placebo in the prevention of symptomatic SARS-CoV-2 infection in participants with a negative screening SARS-CoV-2 infection who are household members of SARS-CoV-2-infected index patients through Day 10 (using the ITT analysis set)	• Proportion of participants in the ITT analysis set with a negative screening SARS-CoV-2 infection (local laboratory-confirmed negative test) who are infected with SARS-CoV-2 (CLC-positive RT-PCR test) and have COVID-19 symptoms onset[a] through Day 10
Secondary	

• To compare ensitrelvir with placebo in the prevention of SARS-CoV-2 infection in participants (defined as CLC-positive RT-PCR test)	• Proportion of participants who are infected with SARS-CoV-2 (CLC-positive RT-PCR test) through Days 10, 15, 21, or 28, regardless of occurrence of COVID-19 symptoms
• To compare ensitrelvir with placebo to determine if ensitrelvir reduces levels of SARSCoV-2 in NP swabs in participants who test positive for SARSCoV-2 through Day 10	SARS-CoV-2 viral RNA endpoints: • Time to the first CLC-positive RT-PCR result • Proportion of participants with CLC-positive RT-PCR result at each timepoint • AUC of change in amount of SARS-CoV-2 viral RNA
• To compare ensitrelvir with placebo to evaluate how ensitrelvir affects COVID-19 symptoms resolution and improvement through Day 28 in participants who test positive (CLC-positive RT-PCR test) for SARS-CoV-2 through Day 10	• Proportion of participants who are infected with SARS-CoV-2 (CLC-positive RT-PCR test) and have no COVID-19 symptoms onset[a] through Day 10 • Proportion of participants who are infected with SARS-CoV-2 (CLC-positive RT-PCR test) and have no COVID-19 symptoms through Day 10 • Proportion of participants with sustained resolution[b] of all COVID-19 symptoms through Day 28 • Proportion of participants with sustained resolution of the 5 key COVID-19 symptoms (nasal congestion or runny nose, sore throat, cough, fever, and fatigue) through Day 28 • Proportion of participants with sustained resolution[b] of each COVID-19 symptom through Day 28 • Change in total[c] score of COVID19 symptoms at each timepoint • Change in total score of the 5 key COVID-19 symptoms at each timepoint • Time from first confirmed SARS-CoV-2 (CLC-positive RT-PCR test) until at least 1 COVID-19 symptom through Day 28 • Time from first confirmed SARS-CoV-2 (CLC-positive RT-PCR test) until COVID-19 symptoms onset[a] through Day 28 • AUC of the daily total[c] symptom score associated with COVID-19 over time from COVID-19 symptoms onset[a] through Day 28 • AUC of the daily total symptom score for the 5 key COVID-19 symptoms over time from onset[a] of the 5 key COVID-19 symptoms through Day 28

• To compare ensitrelvir with placebo in reducing the number of hospitalizations and death in participants who test positive for SARS-CoV-2 infection (CLC-positive RT-PCR test) during the study	• Proportion of participants with hospitalization[d] or death from any cause through Day 28
• To confirm the pharmacokinetics of ensitrelvir in participants following multiple doses ensitrelvir for 5 days	• Plasma concentration of ensitrelvir at Visits 2, 3, and Event-driven Visit
• To compare ensitrelvir with placebo and the effect on safety and tolerability in participants	• Number and proportion of participants with TEAEs, deaths, other serious TEAEs, and TEAEs leading to discontinuation of study intervention
Exploratory	
• To compare ensitrelvir with placebo in reducing the number of days of hospital and intensive care unit stay in participants who test positive for SARS-CoV-2 infection during the study	• Number of days of hospital and intensive care unit stay in participants with SARS-CoV-2-related hospitalization through Day 28 as reported by the sites
• To explore the association between the index patient's amount of viral RNA and the participant's positive central laboratory-confirmed RT-PCR test	• Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the CLC-positive RT-PCR reported cases in the household
• To investigate the relation between the index patient's amount of SARS-CoV-2 viral RNA and the events of SARS-CoV-2 infection in household contacts	• Correlation between the index patient's amount of SARS-CoV-2 viral RNA and the incidence of SARS-CoV-2 ill case within their household contacts
• To identify SARS-CoV-2 variants in NP swabs for participants who test positive for SARSCoV-2 and for index patients corresponding to test-positive participants through Day 28	• SARS-CoV-2 variant based on NP swab spike gene sequence
• To investigate treatment-emergent amino acid substitutions in protease (NSP5) and its cleavage site using NP swabs of participants who test positive for SARS-CoV-2 through Day 28	• Treatment-emergent amino acid substitutions based on NP swab NSP5 and its cleavage site gene sequence
• To evaluate antiviral activity of ensitrelvir against SARS-CoV-2 clinical isolates derived from NP swabs of participants who have confirmed treatment-emergent amino acid substitutions in protease (NSP5) and its cleavage site through Day 28	• Phenotypic assay (EC_{50}) of ensitrelvir against SARS-CoV-2 clinical isolates derived from the NP swabs that have confirmed treatment-emergent amino acid substitutions in protease (NSP5) and its cleavage site
• To compare ensitrelvir with placebo on the effect on QOL in participants	• Change from baseline in EQ-5D-5L • Proportion of participants who achieve baseline or better health through Day 28
• To compare ensitrelvir with placebo on the effect on Global Impression Questionnaire in participants who test positive for SARS-CoV-2 infection during the study	• Change from baseline in Global Impression Questionnaire • Proportion of participants who achieve baseline or better health through Day 28

• To investigate coinfection with influenza and SARS-CoV-2 using NP swabs of participants who test positive for SARS-CoV-2 through Day 28	• Proportion of participants who are coinfected with influenza and SARS-CoV-2
• To investigate SARS-CoV-2 RNA and/or COVID-19 symptom rebound during the study	• Proportion of participants who have viral RNA rebound from Day 6 up to Day 28 • Proportion of participants who have COVID-19 symptomatic rebound after the sustained resolution of COVID-19 through Day 28

AUC = area under the curve; CLC = central laboratory-confirmed; COVID-19 = coronavirus disease 2019; EC_{50} = 50% effective concentration; EQ5D5L = EuroQol 5 Dimensions 5 Levels; ITT = intention-to-treat; mITT = modified intention-to-treat; NP = nasopharyngeal; NSP5 = nonstructural protein 5; PK = pharmacokinetic(s); QOL = quality of life; RTPCR = reverse transcription polymerase chain reaction; SARSCoV2 = severe acute respiratory syndrome coronavirus 2; TEAE = treatment-emergent adverse event

COVID-19 symptoms were defined as: (1) fever (defined as body temperature ≥ 38.0°C per tympanic or rectal thermometer or ≥ 37.5°C per axillary, oral, or forehead/temporal thermometer; see Section 9.5.1.3.3), (2) shortness of breath or difficulty breathing, (3) cough, (4) sore throat, (5) nasal congestion or runny nose, (6) chills, (7) fatigue, (8) body or muscle pain or aches, (9) headache, (10) nausea, (11) vomiting, (12) diarrhea, (13) change in sense of taste, and (14) change in sense of smell.

a COVID-19 symptoms onset in study participants was defined as the occurrence (or worsening [increasing a symptom score from baseline] in the case of pre-existing COVID-19-like symptoms) of ≥ 1 of the 14 specified COVID-19 symptoms for at least 48 hours.

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

c Total symptom score was the sum of scores for the targeted symptoms in the participant's study diary (each individual symptom score is 0 = none, 1 = mild, 2 = moderate, and 3 = severe; see Section 9.5.1.2.2.1 for definitions).

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

Methodology: This was a randomized, double-blind, multicenter, parallel-group, placebo-controlled comparative study in participants who were household members of symptomatic severe acute respiratory syndrome coronavirus (SARS-CoV-2)-infected index patients. Participants were randomly assigned in a 1:1 ratio to receive study intervention (ensitrelvir or placebo).

Number of Participants (Planned and Analyzed):

Planned: Based on the assumptions, enrollment in the study was planned to remain open until 92 events (ie, the number of participants with a negative screening SARS-CoV-2 infection [central laboratory-confirmed negative reverse transcription polymerase chain reaction (RT-PCR) test] who were infected with SARS-CoV-2 [central laboratory-confirmed positive RT-PCR test] and have coronavirus disease 2019 (COVID-19) symptoms onset through Day 10) were achieved. Assuming 7.0% of placebo-treated participants and 3.5% of ensitrelvir-treated participants have an event, it was estimated that approximately 2200 participants would have to be randomized to

achieve this number of events. However, the total number of participants enrolled may have been adjusted to achieve this number of events. For example, if the event rate is as low as 5.90% and 2.95%, respectively, it was estimated that approximately 2600 participants would have to be randomized to achieve this number of events.

Randomized: 2387 (1194 in the ensitrelvir group, 1193 in the placebo group)

Analyzed for efficacy:

- Modified intention-to-treat (mITT) analysis set: 2041 (1030 in the ensitrelvir group, 1011 in the placebo group)
- Intention-to-treat (ITT) analysis set: 2387 (1194 in the ensitrelvir group, 1193 in the placebo group)
- Per protocol analysis set: 2027 (1026 in the ensitrelvir group, 1001 in the placebo group)

Analyzed for safety:

- Safety analysis set: 2377 (1190 in the ensitrelvir group, 1187 in the placebo group)

Analyzed for pharmacokinetics (PK):

- PK analysis set: 1180 in the ensitrelvir group

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

- Index patient (patient of any age with SARS-CoV-2 Infection, 1 per household)
    - Must have had at least 1 COVID-19 symptom as listed below within 24 hours before the index patient provided informed consent. COVID-19 symptom(s) must have been deemed by the investigator as related to the current SARS-CoV-2 infection (not related to pre-existing comorbidities) or deemed as pre-existing and worsened due to SARS-CoV-2 infection.
        - Fever (defined as body temperature ≥ 38.0°C per tympanic or rectal thermometer or ≥ 37.5°C per axillary, oral, or forehead/temporal thermometer)
        - Shortness of breath or difficulty breathing
        - Cough
        - Sore throat
        - Nasal congestion or runny nose
        - Chills
        - Fatigue
        - Body or muscle pain or aches
        - Headache
        - Nausea
        - Vomiting

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

- Must have had a positive SARS-CoV-2 test (a nucleic acid amplification test or antigen test) from any respiratory tract specimen (eg, oropharyngeal, NP or nasal swab, or saliva) from a sample collected ≤ 72 hours prior to randomization of the participant
- Must have a potential study participant who can participate in the study within 72 hours after onset of COVID-19 symptoms in an index patient

- Study participants (multiple study participants from the same household were allowed to be enrolled):
  - Must have been ≥ 12 years of age
  - Must have had a negative screening for SARS-CoV-2 infection as determined by SARS-CoV-2 test
  - Must have lived in a household with the index patient and continued to live in same household and shared common areas such as dining rooms and bathrooms from within 72 hours after onset of COVID-19 symptoms in the index patient through the end of the study
  - Must not have been considered by the investigator to have had SARS-CoV-2 infection and:
    - had no measured fever at Screening
    - had no COVID-19 symptoms at Screening
  - Were capable and willing to complete a participant diary

2. Exclusion criteria
- Index patients were excluded if the following applied:
  - Had documented respiratory infection other than COVID-19 within 14 days prior to the Screening visit
- Study participants were excluded if the following applied:
  - Had documented respiratory infection other than COVID-19 within 14 days prior to the Screening visit
  - Tested positive for SARS-CoV-2 in the last 6 months
  - Had an underlying disease requiring systemic corticosteroids (excluding topical) or antipyretics/analgesics
  - Known renal impairment
  - Had severe liver dysfunction, such as known history of cirrhosis or liver decompensation

Test Product, Dose and Mode of Administration, Lot Number:

1. Test Product

Ensitrelvir (S-217622)

2. Dose and Mode of Administration

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

IMP = investigational medicinal product; NIMP = noninvestigational medicinal product

3. Packaging Lot Number

The packaging lot numbers and expiration dates of the study intervention used in this study are provided in Table 9-2.

Duration of Treatment:

5 days

Reference Therapy, Dose and Mode of Administration, Lot Number:

Not applicable

Statistical Methods:

Efficacy Analyses:

The primary analysis for the primary endpoint compared the proportion of participants who were infected with SARS-CoV-2 (central laboratory-confirmed [CLC]-positive RT-PCR test) and had COVID-19 symptoms onset through Day 10 between the 2 treatment arms and expressed the effect by risk ratio in the mITT analysis set. The comparison was based on a model providing analysis set-averaged estimates using a generalized estimating equations (GEE) approach for a Poisson regression and accounting for clustering within households and the stratification factors of time from symptom onset in the index patient to time of enrollment of the study participant (< 48 hours, ≥ 48 hours) and pooled geographic region (North America, Japan, Rest of World). Under this Poisson regression model, risk ratio of ensitrelvir group to placebo group was estimated, 95% confidence interval (CI) of the risk ratio and the p-value for testing the null hypothesis that the risk ratio is 1 was calculated using the Poisson

regression model. As the key secondary analysis of the primary endpoint, the same analysis as that of the primary analysis was conducted in the ITT analysis set using a fixed-sequence method of type I error control. Sensitivity and/or supplementary analyses for the primary endpoint were performed in line with methods outlined in the Section 9.7.1.2.1.1 and in the statistical analysis plan (SAP).

All analyses of secondary objectives were performed twice: first in the mITT analysis set, and then repeated in the ITT analysis set. A total of 16 secondary endpoints were analyzed. All endpoints that evaluated proportions of participants were performed according to the analysis of the primary endpoint. For time-to-event analyses, Kaplan-Meier methods were used and for area under the curve (AUC) secondary endpoints, AUC was calculated by the trapezoidal method as described in Section 8.2 in the SAP.

All 13 exploratory endpoints were analyzed in line with methods outlined in the SAP. No type I error control methods were used for hypothesis tests in pursuit of secondary or exploratory objectives.

Safety Analyses:

All safety analyses were performed using the safety analysis set. Participants were analyzed with the ensitrelvir arm if they received any doses of the active treatment, while participants in the placebo group received placebo for all doses.

Pharmacokinetic Analyses:

The PK objective of the study was to confirm the PK of ensitrelvir in participants following multiple doses of ensitrelvir for 5 days. For the PK analysis set, plasma concentrations of ensitrelvir were listed by participants and visit along with the time elapsed from the last dosing of study intervention prior to blood sampling. Plasma concentrations of ensitrelvir within 20 to 28 hours after the previous dose on Day 2 and prior to dose on Day 3 were summarized as plasma trough concentration (C_{trough}) on Day 3 with N, mean, standard deviation (SD), coefficient of variation (CV%, calculated as SD/mean × 100), geometric mean and its CV% geometric mean, median, minimum and maximum values. The CV% geometric mean was calculated according to the following formula: CV% geometric mean = $[\exp(SD^2) - 1]^{1/2} \times 100$, where SD is the standard deviation for natural log (ln)transformed data. C_{trough} was also summarized by the age and/or body weight group.

Summary of Results:

A total of 2524 participants were screened in the study. Of those participants, 2387 participants were randomized/enrolled and 2377 participants were treated in total. The mITT analysis set consisted of 1030 participants in the ensitrelvir group and 1011 participants in the placebo group. The ITT analysis set consisted of 2387 participants, including 1194 participants in the ensitrelvir group and 1193 participants in the placebo group.

Demographics:

There were no substantial differences in demographic and other baseline characteristics between the treatment groups.

For the 2387 participants in the mITT analysis set, the mean age (SD) was 41.8 (16.95) years in the ensitrelvir group and 43.0 (16.13) years in the placebo group

(same order, hereinafter). The mean body mass index (SD) was 26.44 (5.671) and 26.56 (5.306). The percentage of male participants was 43.3% and 38.0%.

The COVID-19 vaccination status was comparable between treatment groups with 69.9% of participants in the ensitrelvir group having a history of COVID-19 vaccination and 69.9% of participants in the placebo group. Overall, 59.8% of participants reported having received 2 vaccine doses in the ensitrelvir group and 60.4% in the placebo group.

Efficacy:

The SCORPIO-PEP study met its primary and key secondary endpoints. Ensitrelvir demonstrated a statistically significant reduction in the risk of symptomatic COVID-19 through Day 10 in participants with a confirmed central or local negative SARS-CoV-2 test at baseline in the mITT and ITT analysis sets. Sensitivity and supplementary analyses were consistent with the primary and key secondary results. These data indicate a robust reduction in confirmed events of COVID-19.

Primary Efficacy Endpoint

The proportion of participants (95% CI) who were infected with SARS-CoV-2 (CLC-positive RT-PCR test) and had COVID19 symptoms onset through Day 10 in the mITT analysis set was 2.9% (1.97, 4.13) in the ensitrelvir group and 9.0% (7.31, 10.94) in the placebo group. The risk ratio (95% CI) of symptomatic COVID-19 in participants randomized to ensitrelvir compared to participants randomized to placebo was 0.33 (0.22, 0.49) based on the GEE Poisson regression model, indicating superiority of the ensitrelvir group over the placebo group ($p < 0.0001$).

Key Secondary Endpoint

The proportion of participants (95% CI) with symptomatic COVID-19 through Day 10 in the ITT analysis set was 4.4% (3.27, 5.67) in the ensitrelvir group and 10.2% (8.56, 12.09) in the placebo group. The risk ratio (95% CI) of symptomatic COVID-19 in participants randomized to ensitrelvir compared to participants randomized to placebo was 0.43 (0.32, 0.59) based on the GEE Poisson regression model, indicating superiority of ensitrelvir over placebo ($p < 0.0001$).

For the supplementary analysis on the risk for symptomatic COVID 19 through Days 15, 21, and 28, the proportion of participants (95% CI) with symptomatic COVID-19 through Day 28 in the mITT analysis set was 5.8% (4.47, 7.43) in the ensitrelvir group and 12.2% (10.21, 14.34) in the placebo group. The risk ratio (95% CI) of symptomatic COVID-19 through Day 28 in participants randomized to ensitrelvir compared to participants who randomized to placebo was 0.48 (0.36, 0.64) in the mITT analysis set. In the ITT analysis set, the risk ratio of symptomatic COVID-19 through Day 28 was 0.56 (0.45, 0.71).

The results of the other sensitivity and supportive analyses were in accordance with the primary and key secondary results.

Safety:

The safety of ensitrelvir was assessed in 2377 participants treated in this study (1190 in the ensitrelvir group and 1187 in the placebo group). Of the participants who received ensitrelvir, 1175 (98.7%) participants completed the treatment course.

The number and percentage of participants who reported at least 1 treatment-emergent adverse event (TEAE) was 180 (15.1%) in the ensitrelvir group and 184 (15.5%) in the placebo group. The most common TEAEs (≥ 1.0%) in both treatment groups were headache, diarrhea, influenza, oropharyngeal pain, nasopharyngitis, cough, and fatigue (all reported in less than 3% of participants).

In total, treatment-related TEAEs were reported in 19 participants in the ensitrelvir group and 21 participants in the placebo group.

There were 6 (0.5%) severe TEAEs reported in the ensitrelvir group and 5 (0.4%) severe TEAEs in the placebo group.

There were no deaths reported in the study.

Nonfatal serious TEAEs were reported in 2 (0.2%) participants in the ensitrelvir group and in 2 (0.2%) participants in the placebo group. None of them were classified as treatment-related.

Treatment-emergent AEs leading to discontinuation of study intervention were reported in 1 (< 0.1%) participant in the ensitrelvir group (drug eruption) and in 1 (< 0.1%) participant in the placebo group (pyrexia). One TEAE led to withdrawal from the study in 1 ensitrelvir participant.

There were no clinically important differences in laboratory values observed between the ensitrelvir and the placebo groups and no clinically important abnormal findings in vital signs (blood pressure, pulse rate, respiratory rate, and temperature), electrocardiography examinations, or physical examinations.

As described above, the TEAE incidence of the ensitrelvir group was similar to that of the placebo group, and there were no notable differences in the types of TEAE. No new or unexpected safety concerns were observed in the SCORPIO-PEP study. Therefore, ensitrelvir was considered to have no significant safety issue in this study and was well tolerated.

Pharmacokinetics:

A total of 1180 participants in the ensitrelvir group were included in the PK analysis set. The geometric mean (CV%) ensitrelvir C_{trough} in the PK analysis set was 12.8 (61.4) µg/mL.

CONCLUSIONS

The SCORPIO-PEP study met its primary and key secondary endpoints demonstrating that once-daily ensitrelvir led to a statistically significant reduction in the risk of symptomatic COVID-19 in household contacts of an individual with symptomatic COVID-19 compared to placebo treatment.

The safety and tolerability profile of ensitrelvir was similar to placebo and no new or unexpected safety concerns were identified. Therefore, ensitrelvir was considered to have no significant safety issues in this study and was well tolerated.

Date of Report: 26 Feb 2025