CLINICAL STUDY REPORT

1. TITLE PAGE

Study Title:	A Phase 3, multicenter, randomized, double-blind, 24-week study of the clinical and antiviral effect of S-217622 compared with placebo in non-hospitalized participants with COVID-19
Study Number:	2117T1224 (ACTIV-2d/A5407)
Study Phase:	Phase 3
Study Design:	**Design:** Randomized, double-blind, study **Control**: Placebo **Duration of Study Treatment:** Days 1 through 5 **Dose:** 375 mg (3 tablets of 125 mg) for Day 1 and 125 mg (1 tablet of 125 mg) for Days 2 to 5 once daily **Participant Population:** Outpatient adults (≥ 18 years) with: a) documented positive SARS-CoV-2 nucleic acid or antigen test from a sample collected ≤ 72 hours (3 days) prior to randomization, b) onset of symptoms of COVID-19 ≤ 3 days prior to randomization, c) presence of 1 or more select COVID-19 signs/symptoms within 24 hours prior to randomization.
Product Name:	Ensitrelvir
Indication:	SARS-CoV-2 infection
Study Initiated:	03 Aug 2022
Study Completed:	02 Mar 2024
Sponsor: (Collectively referred to as "SHIONOGI")	Shionogi & Co., Ltd. (Head Office) 1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541-0045, Japan + 81-6-6202-2161
	Shionogi Inc. 400 Campus Drive Florham Park, NJ 07932, United States of America (USA) + 1-973-966-6900
	Shionogi B.V. Herengracht 464, 1017 CA, Amsterdam The Netherlands +44 (0)20 3053 4200 (UK office)
Sponsor's Responsible Medical Officer (Signer):	Sponsor's Chief Medical Officer Juan Carlos Gomez, MD

GCP Statement:	This study was conducted in accordance with Good Clinical Practice (GCP). Essential documents will be retained in accordance with GCP.
Date of Report:	21 Nov 2024

Confidentiality Statement

2. SYNOPSIS

Study Title: A Phase 3, multicenter, randomized, double-blind, 24-week study of the clinical and antiviral effect of S-217622 compared with placebo in nonhospitalized participants with COVID-19

Study Number:

2117T1224 (ACTIV 2d/A5407))

Compound:

Ensitrelvir

Trade Name: Not applicable

Sponsor:

SHIONOGI

Investigators and Study Sites: This study was a multicenter study conducted at 193 sites, including 48 in the United States (US), 34 sites in India, 16 sites in Brazil, 15 sites each in Argentina and South Africa, 10 sites each in Pakistan and Philippines, 9 sites in Cambodia, 8 sites in Mexico, 7 sites in Japan, 5 sites in Poland, 4 sites each in Thailand and Uganda, 3 sites each in Ghana and Malawi, and 2 sites in Kenya.

Publication (reference): Not applicable

Studied Period:

From 03 Aug 2022 to 02 Mar 2024

Phase of Development: Phase 3

Objectives:

Primary

- To determine if ensitrelvir reduced the time to sustained symptom resolution through Day 29 among outpatient adults with mild and moderate coronavirus disease 2019 (COVID-19) starting intervention within 3 days of symptom onset.

Secondary

Key Secondary Objectives

- To determine the effect of ensitrelvir compared with placebo on the change from baseline in quantitative $\log_{10}$ severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ribonucleic acid (RNA) levels by polymerase chain reaction (PCR) on nasopharyngeal (NP) swab at Day 4 among outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.
- To determine whether ensitrelvir reduced COVID-19-related hospitalization (adjudicated) and all deaths regardless of occurrence outside of hospital or during hospitalization (not adjudicated) through Day 29 among outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.

- To determine if ensitrelvir reduced the time to sustained symptom resolution through Day 29 among all outpatient adults with SARS-CoV-2 (including participants enrolled within 5 days of symptom onset as permitted in versions 1.0, 2.0, and 3.0 of the protocol [Appendix 16.1.1]).
- To determine the effect of ensitrelvir compared with placebo on the change from baseline in quantitative $\log_{10}$ SARS-CoV-2 RNA levels by PCR on NP swab at Day 4 among all outpatient adults with SARS-CoV-2.
- To determine whether ensitrelvir reduced COVID-19-related hospitalization (adjudicated) and all deaths regardless of occurrence outside of hospital or during hospitalization (not adjudicated) through Day 29 among all outpatient adults with SARS-CoV-2.
- To determine the effect of ensitrelvir compared with placebo on the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12 among outpatient adults with SARS-CoV-2 starting intervention within 3 days of symptom onset.
- To determine the effect of ensitrelvir compared with placebo on the occurrence of persistent and/or late-onset symptoms of COVID-19 at Week 12 among all outpatient adults with SARS-CoV-2.

Other Secondary Objectives

- To determine if ensitrelvir reduced the time to sustained symptom resolution through Day 29 based on assessments for 2 consecutive days of 6 targeted symptoms (nasal obstruction or congestion, nasal discharge, sore throat, cough, feeling feverish, and fatigue), among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine if ensitrelvir reduced the time to sustained symptom resolution through Day 29 based on assessments for 2 consecutive days of all targeted symptoms excluding loss of taste and smell, among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine if ensitrelvir decreased the proportion of participants with detectable SARS-CoV-2 viral culture (unless viral culture is specified not to be performed at the investigative site) on NP swab at Day 4 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore differences between ensitrelvir and placebo in time to sustained symptom resolution through Day 29 among subgroups, including by high-risk vs. standard-risk at enrollment, by COVID-19 vaccination status, by receipt of COVID-19 treatments, and by time from symptom onset at enrollment among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore differences between ensitrelvir and placebo in the proportion of participants with detectable SARS-CoV-2 by viral culture from NP swab at Day 4 among subgroups, including by high-risk vs. standard-risk at enrollment, by COVID-19 vaccination status, by receipt of COVID-19 treatments, and by

time from symptom onset at enrollment among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.

- To determine whether ensitrelvir reduced all-cause hospitalization and all deaths through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine if ensitrelvir decreased the proportion of participants with detectable SARS-CoV-2 by viral culture from NP swab at Day 8 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the efficacy of ensitrelvir to increase the proportion of participants with NP SARS-CoV-2 RNA levels by quantitative PCR below the lower limit of quantification (LLoQ) on Days 4 and 8 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine whether ensitrelvir reduced levels of SARS-CoV-2 RNA by quantitative PCR in NP swabs from participants on Days 4 and 8 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine whether ensitrelvir resulted in a shorter time to return to pre COVID-19 health compared with placebo through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To evaluate the efficacy of ensitrelvir compared with placebo based on the assessment of symptoms using the World Health Organization (WHO) ordinal scale (1-8) (see Section 6.3.16 of the protocol [Appendix 16.1.1]) among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the efficacy of ensitrelvir to maintain pulse oximetry measurement of ≥ 96% through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the prevalence, severity, and types of persistent and/or late-onset symptoms in participants through end-of-study follow-up (Week 24) among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the prevalence, severity, and types of persistent and/or late-onset symptoms in participants through end-of-study follow-up (Week 24) among all outpatient adults with mild and moderate COVID-19.
- To determine the frequency of symptomatic viral rebound, defined as an increase in quantitative NP SARS-CoV-2 viral culture or NP SARS-CoV-2 RNA levels by quantitative PCR after Day 4 up to Day 29 in the setting of new or worsening clinical symptoms, in both study groups among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the frequency of symptomatic viral rebound, defined as an increase in quantitative NP SARS-CoV-2 viral culture or NP SARS-CoV-2

RNA levels by quantitative PCR after Day 4 up to Day 29 in the setting of new or worsening clinical symptoms, in both study groups among all outpatient adults with mild and moderate COVID-19.

- To determine the frequency of viral rebound in both treatment groups, defined as an increase in quantitative NP SARS-CoV-2 viral culture or NP SARS-CoV-2 RNA levels by quantitative PCR after Day 4 up to Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine the frequency of viral rebound in both treatment groups, defined as an increase in quantitative NP SARS-CoV-2 viral culture or NP SARS-CoV-2 RNA levels by quantitative PCR after Day 4 up to Day 29 among all outpatient adults with mild and moderate COVID-19.
- To evaluate the safety of ensitrelvir.
- To explore measures of psychological health, functional health, and health-related quality of life in participants through end-of-study follow-up (Week 24) among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To determine whether ensitrelvir reduced death due to any cause through end-of-study follow-up (Week 24).
- To determine the pharmacokinetics (PK) of ensitrelvir.

<u>Exploratory</u>

- To evaluate whether ensitrelvir reduced a COVID-19 Severity Ranking Scale score based on COVID-19-associated symptom burden (severity and duration), hospitalization, and death through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore the impact of ensitrelvir on participant-reported rates of new SARS-CoV-2 positivity of household contacts through Day 29 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore whether baseline and follow-up laboratory markers were associated with clinical and virologic outcomes in relation to ensitrelvir use among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore baseline and emergent viral resistance to ensitrelvir through Day 16 among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore differences between ensitrelvir and placebo in NP SARS-CoV-2 RNA levels among subgroups, including by high-risk vs. standard-risk at enrollment, by COVID-19 vaccination status, by receipt of COVID-19 treatments, and by time from symptom onset at enrollment among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore possible predictors of outcomes, including death and hospitalization, across the study population, including by time from symptom onset, symptoms

at baseline, sex assigned at birth, demographic characteristics, geographic region, and vaccination status among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.

- To explore and develop a model for the interrelationships between virologic outcomes and clinical outcomes in each study group among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore the association between viral genotypes and phenotypic susceptibility to ensitrelvir and clinical outcomes and virologic response to ensitrelvir among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore relationships between exposure of ensitrelvir with laboratory markers and clinical outcomes among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To evaluate the safety of ensitrelvir in the high-risk and standard-risk subpopulations.
- To explore differences between ensitrelvir and placebo in death due to any cause through end-of-study follow-up (Week 24) in the high-risk and standard-risk subpopulations.
- To explore differences between ensitrelvir and placebo to reduce levels of SARS-CoV-2 RNA by quantitative PCR in NP swabs from participants on Days 4 and 8 among participants who have a positive culture at baseline among outpatient adults with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.
- To explore differences between ensitrelvir and placebo for Weeks 12 and 24 endpoints censured by a positive response to “return to normal health.”

Methodology:

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of ensitrelvir for the treatment of symptomatic high-risk and standard-risk nonhospitalized adults with SARS-CoV-2 infection.

The study consisted of a Screening visit; a Study Entry/Randomization visit (Day 1); and visits on Days 4, 8, 16, and 29, and Weeks 12 and 24. Additionally, there was an event-driven evaluation visit for worsening symptoms between Days 6 to 29, premature discontinuation visits for discontinuations before Day 29 and after Day 29, and an event-driven evaluation visit for SARS-CoV-2 reinfection, as applicable.

Overall, 2093 eligible adult participants were randomized to receive 1 of the following 2 regimens:

- Ensitrelvir at a dose of 375 mg (3 tablets) for Day 1 and 125 mg (1 tablet) for Days 2 to 5 once daily

  OR

- Placebo for ensitrelvir administered once daily for 5 days (Days 1 to 5 [3 tablets on Day 1 and 1 tablet on Days 2 to 5])

Participants must have begun study intervention (on Day 1) no more than 3 days from self-reported onset of COVID-19-related symptoms. Participants completed the study diary every day from Day 1 through Day 29 and were followed up through the Week 24 visit. The study evaluated ensitrelvir for safety, as well as for activity in reducing the time to sustained symptom resolution, SARS-CoV-2 viral levels by quantitative PCR, and the proportion of participants with viral culture positivity at Day 4, the prevalence, severity, and types of persistent and/or late-onset symptoms, in addition to adjudicated COVID-19 related hospitalization, all-cause hospitalization, all-cause mortality, and clinical status on an ordinal scale as compared with placebo control. The National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) data safety monitoring board (DSMB) reviewed interim safety results on a regular basis as recommended by the DSMB. The DSMB could recommend early termination of randomization to ensitrelvir if there were safety concerns.

Number of Participants (Planned and Analyzed):

Planned: Approximately 2000 participants were planned to be enrolled into the study and randomized equally to ensitrelvir and placebo groups.
Randomized:

- All randomized participants (RND) set: 2093 (1042 in the ensitrelvir group, 1051 in the placebo group)

Analyzed for efficacy:

- Modified intent-to-treat (mITT) set: 1888 (945 in the ensitrelvir group, 943 in the placebo group)
- Modified intent-to-treat 1 (mITT1) set: 2085 (1038 in the ensitrelvir group, 1047 in the placebo group)
- Viral culture (VC) set: 601 (309 in the ensitrelvir group, 292 in the placebo group)

Analyzed for safety:

- Safety Analysis set (SAF): All treated participants; 2085 (1038 in the ensitrelvir group, 1047 in the placebo group)

Analyzed for PK:

- PK set: 287 (222 in the ensitrelvir group, 65 in the placebo group)

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

<u>For all participants</u>

- Age ≥ 18 years

  Documentation of laboratory-confirmed active SARS-CoV-2 infection, as determined by a nucleic acid (eg, reverse-transcriptase PCR) or antigen test from any respiratory tract specimen (eg, oropharyngeal, NP or nasal swab, or saliva) collected ≤ 72 hours (3 days) prior to randomization. (Earlier versions of the study protocol [versions 1.0 to 3.0, Appendix 16.1.1] allowed participants to

begin study intervention up to 5 days from self-reported date of onset of any of the COVID-19-related symptoms).

- Participants were expected to begin study intervention ≤ 3 days from self-reported date of onset of any of the COVID-19-related symptoms from the following list:
  - Cough
  - Shortness of breath or difficulty breathing
  - Feeling feverish
  - Chills
  - Fatigue
  - Body pain or muscle pain or aches
  - Diarrhea
  - Nausea
  - Vomiting
  - Headache
  - Sore throat
  - Nasal obstruction or congestion
  - Nasal discharge
  - Loss of taste
  - Loss of smell
- One or more of the following signs/symptoms present within 24 hours prior to randomization (all criteria above except loss of taste or loss of smell):
  - Cough
  - Shortness of breath or difficulty breathing
  - Feeling feverish
  - Chills
  - Fatigue
  - Body pain or muscle pain or aches
  - Diarrhea
  - Nausea
  - Vomiting
  - Headache
  - Sore throat
  - Nasal obstruction or congestion
  - Nasal discharge
- Oxygenation saturation of ≥ 92% on room air adjusted for altitude and obtained at rest by study staff within 24 hours prior to randomization; for a potential participant who regularly received chronic supplementary oxygen for an underlying lung condition, oxygen saturation measured while on their standard home oxygen supplementation level was to be ≥ 92%.

<u>For high-risk participants (excluded in the US)</u>

Participants at higher risk of progression to severe COVID-19 were defined as follows:

- Age ≥ 65 years
- Age ≥ 18 with 1 of the following:

- Obesity (body mass index [BMI] ≥ 30 kg/m^2); BMI was rounded to the nearest whole number, for example 29.5 kg/m^2 was rounded to 30 kg/m^2
- Diabetes mellitus
- Hypertension requiring daily prescribed therapy
- Cardiovascular disease requiring daily prescribed therapy or congenital heart disease
- Chronic lung disease (eg, chronic obstructive pulmonary disease [COPD], moderate to severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension) requiring daily prescribed therapy
- Chronic kidney disease, defined as known current kidney impairment with a creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 within the past 12 months prior to randomization, as long as the participant does not have known CrCl < 30 mL/min by Cockcroft-Gault or require dialysis
- Down syndrome
- Sickle cell disease
- One of the following immunocompromising conditions or immunosuppressive treatments:
  - Receiving chemotherapy or other therapies for cancer
  - Hematologic malignancy (active or in remission)
  - History of a hematopoietic stem cell or a solid organ transplant
  - HIV infection: not on antiretroviral therapy or with CD4+ cell count < 200 cells/mm^3
  - Combined primary immunodeficiency disorder
  - Taking immunosuppressive medications (eg, drugs to suppress rejection of transplanted organs or to treat rheumatologic and gastrointestinal conditions, such as antitumor necrosis factor agents, mycophenolate, and rituximab); current use of some corticosteroids was exclusionary, due to concern for possible drug-drug interaction (DDI) with ensitrelvir

<u>For standard-risk participants</u>

Standard-risk participants could be enrolled at any site globally. At US sites only standard-risk participants were planned to be enrolled. Participants at standard-risk for progression to severe COVID-19 were defined as ≥ 18 to < 65 years of age and meeting all inclusion criteria for all participants, with none of the risk factors in inclusion criteria for high-risk participants.

2. Exclusion criteria

- History of hospitalization for the current SARS-CoV-2 infection (ie, prior hospitalization for a prior episode of SARS-CoV-2 infection was allowable)
- For the current SARS-CoV-2 infection, any positive SARS-CoV-2 molecular (nucleic acid) or antigen test from any respiratory tract specimen (eg, oropharyngeal, NP or nasal swab, or saliva) collected > 72 hours (3 days) prior to randomization. Participants with reinfection, defined as prior SARS-CoV-2 infection that began > 90 days prior to the current onset of

symptoms with interval resolution of symptoms were eligible as long as the current infection had not been present for more than 3 days prior to randomization

- Current need for hospitalization or immediate medical attention in the opinion of the investigator
- Currently pregnant or breastfeeding
- Individuals who had used Paxlovid or any other oral, inhaled, or injectable medication intended to treat the current SARS-CoV-2 infection before randomization were excluded
- Known allergy/sensitivity or any hypersensitivity to components of ensitrelvir or placebo for ensitrelvir
- Known (within 12 months prior to randomization) renal impairment, defined as CrCl < 30 mL/min by Cockcroft-Gault or requiring dialysis
- Known history of cirrhosis or liver decompensation (including ascites, variceal bleeding, or hepatic encephalopathy)

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

1. Test Product

Ensitrelvir

2. Dose and Mode of Administration

Participants were randomized to receive 1 of the following 2 regimens:

- Ensitrelvir at a dose of 375 mg (3 tablets of 125 mg) for Day 1 and 125 mg (1 tablet of 125 mg) for Days 2 to 5 once daily

  OR

- Placebo for ensitrelvir administered once daily for 5 days (Days 1 to 5 [3 tablets on Day 1 and 1 tablet on Days 2 to 5])

Ensitrelvir was administered as 125-mg tablets or matching placebo. Ensitrelvir/placebo tablets could be taken without food restrictions. The tablets were to be swallowed whole and not chewed, broken, or crushed. If a dose was delayed, it was to be taken as soon as possible, but no more than 12 hours later than expected. If the delay was greater than 12 hours, the dose was to be skipped and the next dose taken as scheduled. If a participant vomited after dosing, the dose was not to be repeated on the same day. Dosing was to be started the following day if the course was not completed. Dosing was not to be extended beyond Day 5.

3. Packaging Lot Number

Packaging Lot numbers for ensitrelvir and placebo were 31599.2, 31599.10, 31599.15, and 31599.21.

Duration of Treatment:

5 days

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

Not applicable

Statistical Methods:

Efficacy Analyses:

For the primary efficacy outcome, based on the estimand definition for the symptom duration outcome, time (days) from the start of intervention (ensitrelvir or placebo) until sustained resolution was compared using restricted mean symptom duration up to Day 28, to provide an estimate of the difference in restricted mean symptom durations for treatment (ensitrelvir vs. placebo), along with a 95% confidence interval (CI) and 2-sided p-value.

Following testing of the primary efficacy endpoint, key secondary efficacy endpoints were tested sequentially at the 2-sided 5% alpha level, as part of the statistical hierarchy described in the statistical analysis plan (SAP). Sensitivity and/or supplementary analyses for the key secondary endpoints were performed in line with methods outlined in the SAP. Subgroup analyses for the key secondary endpoints were applied as for the primary efficacy endpoint.

For analyses of secondary and exploratory efficacy outcomes, statistical inferences were based on 95% CIs for effects comparing ensitrelvir to placebo and associated 2-sided tests of no difference between groups using a 5% type I error rate.

Safety Analyses:

Safety data were summarized using descriptive statistics.

Pharmacokinetic Analyses:

The PK objectives of the study were to determine and summarize the PK of ensitrelvir. The PK concentrations were summarized and presented with the PK analysis set. The individual plasma ensitrelvir concentrations were listed by study participants, along with the time elapsed from the previous dose before blood sampling. In addition, the time elapsed from the previous dose and the plasma ensitrelvir concentration were graphically presented. Plasma concentrations of ensitrelvir after the previous dose were summarized for data at 60 and 90 minutes postdose on Day 1 and predose on Day 4 (C_{24hr}) by time and day with number of participants (N), mean, standard deviation (SD), and coefficient of variation (CV%, calculated by SD/mean × 100); geometric mean (Geometric Mean) and CV% for geometric mean (CV% Geometric Mean); and median, minimum (min), and maximum (max) values. The C_{24hr} is defined as the plasma concentration of ensitrelvir within 20 to 28 hours after the previous dose.

Summary of Results:

	Ensitrelvir Group n (%)	Placebo Group n (%)	Total n (%)
Participants screened			2445
Participants randomized	1042	1051	2093
Week 12 (primary analysis)	1042	1051	2093
Participants who had completed the study (up to Week 24)*	666 (63.9)	672 (63.9)	1338 (63.9)
Participants withdrawn from the study	59 (5.7)	54 (5.1)	113 (5.4)
Participants in primary analysis (mITT set)	945	943	1888
Week 24 (final analysis)	1042	1051	2093
Participants completed the study	980 (94.0)	994 (94.6)	1974 (94.3)

Participants withdrawn from the study	62 (6.0)	57 (5.4)	119 (5.7)
Participants in final safety analysis	1038	1047	2085

* Number of participants who had already completed the Week 24 visit at the time of the primary analysis, which took place after completion of the Week 12 visit by the last participant.

Demographics:

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

For the 1888 participants in the mITT set (defined as all participants who received at least 1 dose of ensitrelvir or placebo and who started intervention within 3 days of symptom onset; the primary analysis set for this study), the mean age (SD) was 40.4 (13.68) years in the ensitrelvir group and 40.1 (13.80) years in the placebo group. The mean BMI (SD) was 25.95 (4.571) kg/m^2 in the ensitrelvir group and 26.17 (4.587) kg/m^2 in the placebo group. The ensitrelvir group was 57.1% female and the placebo group was 53.7% female.

The COVID-19 vaccination status was comparable between treatment groups with 71.4% of participants in the ensitrelvir group having completed last vaccine > 3 months prior to enrollment and 75.7% of participants in the placebo group. Overall, 25.9% of participants were not vaccinated in the ensitrelvir group and 22.1% in the placebo group. Most participants (73.6%) had completed a primary series of vaccinations, with their last vaccine > 3 months prior to enrollment.

Efficacy:

This study did not meet its primary efficacy endpoint of a statistically significant reduction in time to sustained resolution (symptoms completely absent for at least 2 days) of 15 common COVID-19 related symptoms for once daily treatment with ensitrelvir compared to placebo when treatment was initiated within 3 days of symptom onset.

A predefined supportive analysis of resolution (symptoms completely absent for at least 1 day) of 6 symptoms yielded a nominal difference ($p < 0.05$) in the time to resolution of symptoms. Numerical reductions in mean viral RNA levels and a higher proportion of participants with negative viral cultures on Day 4 were observed in the ensitrelvir group compared with placebo although the results should be interpreted in an exploratory manner. Symptomatic viral rebound did not occur in this study.

Primary Efficacy Endpoint:

The number of participants with sustained resolution of all targeted symptoms alive and without hospitalization by Day 29 in the mITT set was 768 (81.3%) in the ensitrelvir group and 755 (80.1%) in the placebo group. The estimate of the difference in restricted mean symptom duration (95% CI) for ensitrelvir vs placebo group in the mITT set was -0.6 days (-1.38, 0.19) with a 2-sided $p = 0.1397$ that did not achieve statistical significance.

The secondary analyses of the primary efficacy endpoint, conducted in the mITT2 and mITT3 sets and the mITT subset of participants starting study intervention within 2 days of symptom onset, as well as the sensitivity analyses excluding late entered diary data, showed similar results to the primary analysis.

In the supportive analysis of the time to resolution (symptoms completely absent for at least 1 day) of all 15 targeted symptoms for a day and being alive and without hospitalization by Day 29 the estimate of the difference in restricted mean symptom durations (95% CI) for ensitrelvir vs placebo group in the mITT set was -0.8 days (-1.54, 0.01) with 2-sided nominal p = 0.0530.

Key Secondary Endpoints:

The mean change from baseline (min, max) in quantitative log_{10} SARS-CoV-2 RNA levels in NP swab at Day 4 was -2.7435 (-8.301, 4.600) for the ensitrelvir group and -1.9630 (-7.660, 7.600) for the placebo group. In the analysis of covariance (ANCOVA), the adjusted estimate (95% CI) of the difference in LS mean change from baseline between ensitrelvir and placebo was -0.72 (-0.90, -0.55), nominal $p < 0.0001$.

For the first sensitivity analysis of the change from baseline in quantitative log_{10} SARS-CoV-2 RNA levels at Day 4, the main analysis was repeated without baseline log_{10} SARS-CoV-2 RNA in the model and an unadjusted estimate and associated 95% CI was obtained. In the mITT1 set, the adjusted estimate (95% CI) of the difference in mean change from baseline between ensitrelvir and placebo was -0.65 (-0.82, -0.49), nominal $p < 0.0001$.

For the second sensitivity analysis of the change from baseline in quantitative log_{10} SARS-CoV-2 RNA levels at Day 4, the main analysis was repeated with missing data on Day 4 having change from baseline treated as zero. In the mITT set, the adjusted estimate (95% CI) of the difference in mean change from baseline between ensitrelvir and placebo was -0.65 (-0.82, -0.48), nominal $p < 0.0001$.

For the third sensitivity analysis of the change from baseline in quantitative log_{10} SARS-CoV-2 RNA levels at Day 4, the main analysis was repeated restricting only to participants with baseline SARS-CoV-2 RNA $\geq$ LLoQ. In the mITT set, the adjusted estimate (95% CI) of the difference in mean change from baseline between ensitrelvir and placebo was -0.83 (-1.03, -0.64), nominal $p < 0.0001$.

The number of participants with hospitalization due to COVID-19 or death due to any cause through Day 29 in the mITT set was 3 (0.3%) in the ensitrelvir group and 1 (0.1%) in the placebo group. The risk ratio estimate comparing the probability of hospitalization (95% CI) for ensitrelvir vs placebo group in the mITT set was 2.9937 (0.3120, 28.7278) with 2-sided nominal p = 0.6246.

The number of alive participants with sustained resolution (symptoms completely absent for at least 2 days) of all targeted symptoms without hospitalization for any reason in the mITT1 set was 841 (81.0%) in the ensitrelvir group and 832 (79.5%) in the placebo group. The estimate of the difference in restricted mean symptom duration up to Day 28 (95% CI) for ensitrelvir vs placebo group in the mITT1 set was -0.6 days (-1.34, 0.16) with 2-sided nominal p = 0.1235.

The number of participants with persistent and/or late-onset symptoms of COVID-19 (Week 12) in the mITT set was 227 (24.0%) in the ensitrelvir group and 221 (23.4%) in the placebo group. The estimated risk ratio (95% CI) for ensitrelvir vs placebo group in the mITT set was 1.02 (0.872, 1.205) with nominal p = 0.7869.

In the mITT1 set, the number of participants with persistent and/or late-onset symptoms of COVID-19 (Week 12) was 256 (24.7%) in the ensitrelvir group and 253 (24.2%) in the placebo group. The estimated risk ratio (95% CI) for ensitrelvir vs placebo group in the mITT1 set was 1.02 (0.878, 1.187) with nominal p = 0.7990.

Pharmacokinetics:

A total of 287 participants (222 participants in the ensitrelvir group, 65 in the placebo group) were included in the PK analysis set. Although plasma concentrations in some participants were much higher than previously obtained plasma concentrations, the plasma concentrations for almost all participants were similar to those previously obtained.

Safety:

The safety of ensitrelvir was assessed in 2085 participants treated in this study (1038 in the ensitrelvir group and 1047 in the placebo group). The mean duration of study intervention was 4.9 days in the ensitrelvir and 5.0 days in the placebo group for participants in the safety set.

The number and percentage of participants who reported at least one treatment-emergent adverse event (TEAE) was 638 (61.5%) in the ensitrelvir group and 635 (60.6%) in the placebo group in the study period through Day 29. The most common TEAEs in both treatment groups were hypertriglyceridaemia, creatinine renal clearance decreased, blood triglycerides increased, hyperglycaemia and low density lipoprotein increased (all in at least 5.9% of participants).

Up to Week 24 (final analysis), the number and percentage of participants who reported at least one TEAE increased slightly in both treatment groups (719 [69.3%] participants in the ensitrelvir group and 732 [69.8%] in the placebo group). Similar incidence rates were reported for all but one of the most common TEAEs. The incidence rate of the system organ class (SOC) infections and infestations was more than twice as high in both treatment groups as in the study period up to Day 29.

The incidence of TEAEs with onset from Day 30 through Week 24 was 311 (30.0%) participants in the ensitrelvir group and 348 (33.2%) participants in the placebo group.

In total, treatment-related TEAEs were reported in 86 (8.3%) participants in the ensitrelvir group and 74 (7.1%) participants in the placebo group up to Day 29. The incidence rates were similar in the study period up to Week 24.

Potentially life-threatening (Grade 4) and severe (Grade 3) TEAEs were reported in 14 of 1037 participants (1.4%) and 102 of 1037 (9.8%) in the ensitrelvir group and in 24 of 1048 participants (2.3%) and 127 of 1048 participants (12.1%) in the placebo group in the study period up to Day 29. All potentially life-threatening AEs were considered to be unrelated to treatment. The incidence of severe treatment-related TEAEs was reported with 4 participants (0.4%) in the ensitrelvir group and with 11 of 1048 participants (1.0%) in the placebo group. Similar incidence rates were reported for the study period up to Week 24.

There were no deaths in the ensitrelvir treatment group; 2 deaths were reported in the placebo treatment group in the study period up to Week 24.

In the study period through Day 29, nonfatal serious TEAEs were reported in 5 (0.5%) participants in the ensitrelvir group and 6 (0.6%) participants in the placebo group. All nonfatal serious preferred terms (PTs) were reported in one single participant. Incidence rates maintained low with 1.1% in the ensitrelvir group and 1.2% in the placebo group in the study period up to Week 24 (final analysis).

There was no difference in the incidence of skin and subcutaneous tissue related TEAEs of special interest in the treatment period up to Day 29. All PTs defined as adverse events (AEs) of special interest (AESI) occurred with an incidence below 0.5% in both treatment groups. Similar results were obtained for the study period up to Week 24.

There were no clinically relevant changes in laboratory values. No clinically relevant abnormal findings were reported in vital signs (blood pressure, pulse rate, respiratory rate, and temperature) or physical examinations.

As described above, the incidence of TEAEs in the ensitrelvir group was similar to that of the placebo group, and there were no notable differences in the types of TEAEs in both study periods. Therefore, ensitrelvir was considered to have no significant safety issues.

CONCLUSIONS

The primary efficacy endpoint was not met. There was a consistent numerical reduction in duration of symptoms for ensitrelvir compared with placebo. An antiviral effect was observed for both RNA and viral culture.

The safety and tolerability profile of ensitrelvir was similar to placebo. There were no treatment-related serious AEs or deaths.

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