2. SYNOPSIS

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

Study Title:
A Phase 1 Drug-Drug Interaction Study of Ensitrelvir With Itraconazole or Carbamazepine in Healthy Adult Participants

Investigators and Study Centers: This study was conducted in 2 sites (1 site for each cohort) in Japan.

Publication (reference): Not applicable

Studied Period:
From 04 Aug 2023 (First participant informed consent obtained) to 07 Oct 2023 (Last participant last observation)

Phase of Development: Phase 1

Objectives and Endpoints:

Objectives	Endpoints
Primary	
● To investigate the effect of multiple doses of itraconazole on the pharmacokinetics (PK) of ensitrelvir in Japanese healthy adult participants. ● To investigate the effect of multiple doses of carbamazepine on the PK of ensitrelvir in Japanese healthy adult participants.	● Ensitrelvir: Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve over the dosing interval τ ($AUC_{0-\tau}$), and plasma concentration at 24 hours after administration (C_{24}) ● Itraconazole: C_{max}, T_{max}, $AUC_{0-\tau}$ ● Carbamazepine: C_{max}, T_{max}, $AUC_{0-\tau}$
Secondary	
● To investigate the safety and tolerability of coadministration of ensitrelvir and itraconazole in Japanese healthy adult participants. ● To investigate the safety and tolerability of coadministration of ensitrelvir and carbamazepine in Japanese healthy adult participants.	● Adverse events (AEs), physical examination, laboratory tests (hematology, blood chemistry, and urinalysis), vital signs (systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature), and 12-lead electrocardiography (ECG)

Methodology: This was a single-arm, open-label study in Japanese healthy adult participants. It consisted of Cohort A which investigated the effect of multiple doses of itraconazole (a strong cytochrome P450 [CYP] 3A inhibitor) on the PK of ensitrelvir and Cohort B which investigated the effect of multiple doses of carbamazepine (a strong CYP3A inducer) on the PK of ensitrelvir. In both cohorts, the safety and PK of ensitrelvir were confirmed first (Period 1), followed by the investigation of the effect of multiple doses of itraconazole or carbamazepine on the PK of ensitrelvir (Period 2).

<Cohort A>

Cohort A consisted of Screening Period (Days −28 to −1), Period 1 (Days −1 to 13 [±1]), and Period 2 (Days 25 to 42 [±1]); Periods 1 and 2 consisted of Hospitalization Period and Follow-up. In Period 1, Hospitalization Period was from Days −1 to 6 and Follow-up was performed on Day 13 (±1) (Follow-up 1). In Period 2, Hospitalization Period was from Days 25 to 35 and Follow-up was performed on Day 42 (±1) (Follow-up 2).

– Screening Period (Days −28 to −1):
  After obtaining informed consent, screening tests were performed to confirm the participant's eligibility for participation in the study.

Period 1

– Hospitalization Period (Days −1 to 6):
  Participants were admitted 1 day before the start of administration of ensitrelvir (Day −1), and were discharged on the 6th day after the administration on Day 1 (Day 6) (hospitalization period: 7 days and 6 nights).
  Participants who were determined to be eligible based on the screening tests were enrolled 1 day before the start of administration of ensitrelvir (Day −1). Participants received ensitrelvir 375 mg on Day 1 and multiple oral doses of ensitrelvir 125 mg once daily on Days 2 to 5 in the fasted state. Participants underwent the specified investigations and tests during hospitalization and were discharged after the investigations and tests scheduled on Day 6 were completed. All meals were normal meals.
– Follow-up 1 (Day 13 [±1]):
  Participants underwent specified investigations and tests on the 13th day (±1 day) after the start of administration of ensitrelvir (Day 1).

Period 2

– Hospitalization Period (Days 25 to 35):
  Participants were admitted 1 day before administration of itraconazole (Day 25), and were discharged on the 10th day after the administration on Day 26 (Day 35) (hospitalization period: 11 days and 10 nights).
  Participants received 2 doses of itraconazole (oral solution) 200 mg on Day 26 (the first dose in the fasted state and the second before a meal), and itraconazole (oral solution) 200 mg once daily on Days 27 to 34 in the fasted state. They received coadministration of ensitrelvir 375 mg on

Day 30 and ensitrelvir 125 mg once daily on Days 31 to 34. Participants underwent the specified investigations and tests during hospitalization and were discharged after the investigations and tests scheduled on Day 35 were completed. All meals were normal meals.

– Follow-up 2 (Day 42 [±1]):
Participants underwent specified investigations and tests on Day 42 (±1).

The administration in Period 2 (Day 26) started at least 21 days after the end of administration in Period 1 (Day 5).

<Cohort B>

Cohort B consisted of Screening Period (Days −28 to −1), Period 1 (Days −1 to 13 [±1]), and Period 2 (Days 25 to 51 [±1]); Periods 1 and 2 consisted of Hospitalization Period and Follow-up. In Period 1, Hospitalization Period was from Days −1 to 6 and Follow-up was performed on Day 13 (±1) (Follow-up 1). In Period 2, Hospitalization Period was from Days 25 to 44 and Follow-up was performed on Day 51 (±1) (Follow-up 2).

– Screening Period (Days −28 to −1):
After obtaining informed consent, screening tests were performed to confirm the participant's eligibility for participation in the study.

Period 1

– Hospitalization Period (Days −1 to 6):
Participants were admitted 1 day before the start of administration of ensitrelvir (Day −1), and were discharged on the 6th day after the administration on Day 1 (Day 6) (hospitalization period: 7 days and 6 nights).
Participants who were determined to be eligible based on the screening tests were enrolled 1 day before the start of administration of ensitrelvir (Day −1). Participants received ensitrelvir 375 mg on Day 1 and multiple oral doses of ensitrelvir 125 mg once daily on Days 2 to 5 in the fasted state. Participants underwent the specified investigations and tests during hospitalization and were discharged after the investigations and tests scheduled on Day 6 were completed. All meals were normal meals.

– Follow-up 1 (Day 13 [±1]):
Participants underwent specified investigations and tests on the 13th day (±1 day) after the start of administration of ensitrelvir (Day 1).

Period 2

– Hospitalization Period (Days 25 to 44):
Participants were admitted 1 day before administration of carbamazepine (Day 25), and were discharged on the 19th day after the administration on Day 26 (Day 44) (hospitalization period: 20 days and 19 nights).
They received carbamazepine 100 mg twice daily on Days 26 to 28, carbamazepine 200 mg twice daily on Days 29 to 32, and carbamazepine

300 mg twice daily on Days 33 to 43 before a meal. They received coadministration of ensitrelvir 375 mg on Day 39 and ensitrelvir 125 mg once daily on Days 40 to 43. Participants underwent the specified investigations and tests during hospitalization and were discharged after the investigations and tests scheduled on Day 44 were completed. All meals were normal meals.

– Follow-up 2 (Day 51 [±1]):
Participants underwent specified investigations and tests on Day 51 (±1).

The administration in Period 2 (Day 26) started at least 21 days after the last dose in Period 1 (Day 5).

Number of Participants (Planned and Analyzed):

Planned: 28

Enrolled: 28

Analyzed for PK:

- PK concentration population: 28
- PK parameter population: 28

Analyzed for safety (safety analysis population): 28

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

- Male and female participants who had Japanese parents and were 18 to 55 years of age, inclusive, at the time of signing the informed consent.
- Body mass index (BMI) within the range of 18.5 to 30.0, inclusive.

2. Exclusion criteria

- History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the investigational intervention; or interfering with the interpretation of data.
- (Cohort B only) Either of the following abnormalities at screening or on admission (Day −1):
  – Lenticular opacities
  – Intraocular pressure: > 21 mmHg
- Positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (nucleic acid amplification or antigen test) during the screening period.
- Sensitivity to the investigational intervention, or components thereof, or drug or other allergy that, in the opinion of the investigator, contraindicated participation in the study (except for those with seasonal allergy).
- (Cohort B only) Participants with either of the following human leukocyte antigen (HLA) gene sequence as determined by HLA genotyping at screening:
  – HLA-A*31:01
  – HLA-B*15:02

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

1. Test Product

Study Intervention Name	Ensitrelvir fumarate	Itraconazole	Carbamazepine
Type	Drug	Drug	Drug
Dosage Form	Tablet	Syrup	Tablet
Unit Dose Strengths	Each tablet contains 125 mg of ensitrelvir.	1 mL of the solution contains 10 mg of itraconazole.	Each tablet contains 100 mg of carbamazepine.
Dosage Levels	<Cohort A> Administered 3 tablets of ensitrelvir 125 mg on Day 1, and 1 tablet of ensitrelvir 125 mg on Days 2 to 5 once daily in the fasted state. Administered 3 tablets of ensitrelvir 125 mg on Day 30, and 1 tablet of ensitrelvir 125 mg on Days 31 to 34 once daily in the fasted state. <Cohort B> Administered 3 tablets of ensitrelvir 125 mg on Day 1, and 1 tablet of ensitrelvir 125 mg on Days 2 to 5 once daily in the fasted state. Administered 3 tablets of ensitrelvir 125 mg on Day 39, and 1 tablet of ensitrelvir 125 mg on Days 40 to 43 once daily in the fasted state.	<Cohort A> Administered itraconazole 200 mg twice daily on Day 26 (the first dose in the fasted state and the second before a meal), and itraconazole 200 mg once daily on Days 27 to 34 in the fasted state.	<Cohort B> Administered carbamazepine 100 mg twice daily on Days 26 to 28, carbamazepine 200 mg twice daily on Days 29 to 32, and carbamazepine 300 mg twice daily on Days 33 to 43 before a meal. The first dose of carbamazepine on Days 39 to 43 was administered in the fasted state similarly to ensitrelvir.
Route of Administration	Oral	Oral	Oral
Use	Experimental	Concomitant drug	Concomitant drug
Investigational Intervention or Non-investigational Intervention/ Auxiliary Medicinal Product	Investigational intervention	Non-investigational intervention	Non-investigational intervention
Sourcing	Provided centrally by the sponsor.	Purchased by the study site.	
Packaging and Labeling	Each tablet was packed in a press through package sheet, and 7 sheets were packed in an individual carton. Each carton was	Each carton was labeled as required per Japanese requirement.	

	labeled as required per Japanese requirement.	

2. Dose and Mode of Administration

The study interventions were administrated as shown in the table above.

3. Packaging Lot Number

Ensitrelvir: [redacted]

Itraconazole: [redacted]

Carbamazepine: [redacted]

Duration of Treatment:

5 days in each Period

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

Not applicable

Criteria for Evaluation:

Pharmacokinetic Assessment:

As the PK parameters of ensitrelvir, C_{max}, T_{max}, $AUC_{0-\tau}$, and C_{24} were determined after the first and fifth doses. As the PK parameters of itraconazole and carbamazepine, C_{max}, T_{max}, and $AUC_{0-\tau}$ were determined on the first day of coadministration with ensitrelvir (Day 30 and Day 39, respectively).

Safety Assessment:

Adverse events, physical examinations, clinical laboratory test, vital signs, and 12-lead ECG.

All AEs/SAEs were collected from the date of informed consent until the end of study participation.

Statistical Methods:

Pharmacokinetic Analyses:

Pharmacokinetic analyses were performed on the PK concentration population or the PK parameter population.

The plasma concentrations of ensitrelvir, itraconazole, and carbamazepine were tabulated for each agent, each study intervention period, and each time point of measurement.

In Cohort A, the effects of multiple doses of itraconazole on the PK of ensitrelvir were investigated. PK parameters of ensitrelvir after administration alone (Day 1 and Day 5) and coadministration with itraconazole (Day 30 and Day 34) were compared using analysis of variance with dosing conditions (administered alone or in combination with itraconazole) as a fixed effect and participant as a random effect, using the MIXED procedure in SAS, separately for the first and fifth doses of ensitrelvir. The primary parameters were C_{max} and $AUC_{0-\tau}$. If the 90% confidence intervals (CIs) for the geometric least squares mean ratios of these parameters were

within the range of 0.8000 and 1.2500, it was considered that multiple doses of itraconazole did not affect the PK of ensitrelvir.

In Cohort B, the effects of multiple doses of carbamazepine on the PK of ensitrelvir were investigated. PK parameters of ensitrelvir after administration alone (Day 1 and Day 5) and coadministration with carbamazepine (Day 39 and Day 43) were compared using analysis of variance with dosing conditions (administered alone or in combination with carbamazepine) as a fixed effect and participant as a random effect, using the MIXED procedure in SAS, separately for the first and fifth doses of ensitrelvir. The primary parameters were C_{max} and $AUC_{0-\tau}$. If the 90% CIs for the geometric least squares mean ratios of these parameters were within the range of 0.8000 and 1.2500, it was considered that multiple doses of carbamazepine did not affect the PK of ensitrelvir.

Safety Analyses:

All safety analyses were performed on the safety analysis population.

Adverse events were classified by System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA), Version 26.0. The number and proportion of participants who experienced treatment-emergent adverse events (TEAEs), deaths, other serious TEAEs, and TEAEs leading to discontinuation of administration were summarized.

For clinical laboratory test, vital signs, and 12-lead ECG parameters, summary statistics were calculated for measured values and changes from baseline at each measurement time point scheduled after enrollment.

Summary of Results:

Pharmacokinetics:

- The C_{max}, $AUC_{0-\tau}$ and C_{24} of ensitrelvir coadministered with itraconazole increased by approximately 1.05-, 1.10-, and 1.27-fold, respectively, on the initial dose of ensitrelvir and approximately 1.24-, 1.31-, and 1.40-fold, respectively, on the last dose of ensitrelvir, compared to those of ensitrelvir administered alone, suggesting that itraconazole (a strong CYP3A inhibitor) had no clinically meaningful effect on the PK of ensitrelvir.
- The C_{max}, $AUC_{0-\tau}$ and C_{24} of ensitrelvir coadministered with carbamazepine at the scheduled dose decreased by approximately 8%, 21%, and 35%, respectively, on the initial dose of ensitrelvir and approximately 38%, 46%, and 52%, respectively, on the last dose of ensitrelvir, compared to those of ensitrelvir administered alone.
- As a result of integrated analyses of all participants who completed the study as planned and those with adjusted carbamazepine dose in Cohort B, the exposures of ensitrelvir when coadministered with carbamazepine decreased by around 40% to 50% of those when ensitrelvir was administered alone regardless of the dose of carbamazepine, suggesting that carbamazepine (a strong CYP3A inducer) had a clinically meaningful effect on the PK of ensitrelvir.

Safety:

- No deaths or serious TEAEs were reported during the study. All TEAEs reported in this study were mild or moderate and resolved during the study.
- In Cohort A, a TEAE leading to discontinuation of study intervention was reported in 1 participant (nasopharyngitis) in Stage 1 and considered not related to ensitrelvir.
- In Cohort B, TEAEs leading to discontinuation of study intervention were reported in 6 participants; 1 participant (COVID-19) in Stage 1 and 5 participants (erythema in 2 participants, erythema and pruritus in 2 participants, and erythema, pruritus and C-reactive protein increased in 1 participant) in Stage 2. Erythema, pruritus, and C-reactive protein increased are known adverse drug reactions of carbamazepine and were considered not related to ensitrelvir.
- No clinically significant abnormal results were observed in laboratory tests, vital signs, or 12-lead ECGs in the study.

CONCLUSIONS

Pharmacokinetics Conclusions:

Itraconazole (a strong CYP3A inhibitor) was suggested to have no clinically meaningful effect on the PK of ensitrelvir, whereas carbamazepine (a strong CYP3A inducer) was suggested to have a clinically meaningful effect on the PK of ensitrelvir.

Safety Conclusions:

Coadministration of ensitrelvir and itraconazole in Cohort A was not considered to cause any significant safety issues. In Cohort B in which carbamazepine was coadministered, there were participants withdrawn from the study due to adverse drug reactions of carbamazepine, but no AEs which were assessed as related to ensitrelvir were reported.

Date of Report: 28 Dec 2023