2. SYNOPSIS

Sponsor: Shionogi & Co., Ltd. Shionogi, Inc. *or* Shionogi B.V.	**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	**Page:**	

Study Title: A Phase 1, open-label, parallel-group study to assess the pharmacokinetics, safety, and tolerability of S-217622 in participants with mild, moderate, and severe renal impairment and healthy control participants

Investigators and Study Centers: This study was a multicenter study conducted at 4 sites in the United States (US).

Publication (reference): Not applicable

Studied Period:
From 19 Jul 2022 to 31 May 2023

Phase of Development: Phase 1

Objectives:

Primary

- To assess the pharmacokinetics (PK) of ensitrelvir after a single 375-mg oral administration of ensitrelvir in participants with mild, moderate, and severe renal impairment compared with control participants with normal renal function

Secondary

- To evaluate the safety and tolerability of ensitrelvir after a single 375-mg oral administration of ensitrelvir in participants with mild, moderate, or severe renal impairment and participants with normal renal function

Methodology:

This was a Phase 1, open-label, nonrandomized, parallel-group, matched healthy control cohort study in participants with mild renal impairment (Group A), moderate renal impairment (Group B), severe renal impairment (Group C), and normal renal function (Group D), as estimated by criteria at the Screening visit.

The study consisted of a Screening period (Days −28 to −2), including a Screening visit; a Confinement period (confinement in the clinical research unit [CRU] from Days −1 to 15, a single oral administration of ensitrelvir on Day 1, and discharge from the CRU on Day 15), and a Follow-up period (through Day 21 ± 2 days), including a Follow-up visit (at Day 21 ± 2 days) or an Early Termination visit.

On Day 1, a single 375-mg dose of ensitrelvir was administered in the fasted state. Blood samples for determination of plasma concentrations of ensitrelvir were collected at specified time points prior to study intervention and up to 336 hours postdose. Blood

samples for determination of plasma protein binding were also collected at 3 and 24 hours postdose. Urine samples for determination of urine concentrations of ensitrelvir were collected at specified time intervals up to 336 hours postdose.

In Group A, 8 eligible participants with mild renal impairment were planned to be enrolled.

In Group B, 8 eligible participants with moderate renal impairment were planned to be enrolled.

In Group C, 8 eligible participants with severe renal impairment were planned to be enrolled.

In Group D, 8 eligible participants with normal renal function were planned to be enrolled. All participants in Group D (normal renal function) were each demographically matched with a participant in Group B (moderate renal impairment); i.e., with respect to sex, age (± 5 years), and body mass index (BMI) (± 10%).

The sponsor could replace participants who did not complete the study.

Number of Participants (Planned and Analyzed):

Planned: Approximately 64 participants were planned to be screened to enroll 28 to 32 participants to receive study intervention for an estimated total of 4 to 8 evaluable participants per intervention group

Group Label	Ensitrelvir Dose	Renal Function of Study Participants	eGFR (mL/min)	Number of Planned Study Participants
Group A	375 mg	Mild impairment	60 to 89	8
Group B	375 mg	Moderate impairment	30 to 59	8
Group C	375 mg	Severe impairment	< 30*	8
Group D	375 mg	Normal**	≥ 90	8

eGFR: estimate of glomerular filtration rate based on the Modification of Diet in Renal Disease (MDRD) equation and multiplied by the participant's body surface area.

* Provided participant did not require hemodialysis

** Demographically matched with participants in Group B (moderate renal impairment) with respect to sex, age (± 5 years), and BMI (± 10%)

Screened: 54

Enrolled: 34

Treated: 32 (8 each in Groups A through D)

Analyzed for efficacy: Not applicable

Analyzed for safety: All treated participants; 32

Analyzed for PK: 32

Plasma and urine concentrations: 32

PK parameters: 32

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria

- 18 to ≤ 80 years of age inclusive, at the time of signing the informed consent
- Considered to be healthy (for healthy participants) or medically stable (for participants with renal impairment)

For participants with renal impairment

- Not undergoing hemodialysis and had mild, moderate, or severe renal impairment based upon their MDRD creatinine clearance estimate (eGFR) and the participant's body surface area (BSA) calculated at the Screening visit
  - Mild renal impairment: 60 to 89 mL/min
  - Moderate renal impairment: 30 to 59 mL/min
  - Severe renal impairment: < 30 mL/min
- A stable medication regimen within 14 days clinically stable laboratory test results for at least 3 months.
- Participants with hypertension had to have satisfactory control of blood pressure (eg, < 170 mm Hg systolic and < 100 mm Hg diastolic).

For healthy participants

- Clinical laboratory tests within normal reference range or abnormal but considered not clinically significant and normal renal function (ie, eGFR > 90 mL/min).
- Matched to each participant with moderate renal impairment with respect to sex, age (± 5 years), and BMI (± 10%).

Exclusion criteria

Participants with renal impairment:

- Participant with clinically significant laboratory values or outside the following ranges or limits:
  - Hemoglobin: < 9 g/dL
  - WBC count: < 2500/μL or > 15,000/μL
  - Aspartate aminotransferase (AST): > 300 U/L
  - Alanine aminotransferase (ALT): > 300 U/L
  - Total bilirubin: > 4.5 mg/dL
  - Prothrombin time-international normalized ratio: > 3
  - Platelets: < 50,000/μL
- Systolic blood pressure outside the range of 90 to 170 mm Hg, diastolic blood pressure outside the range of 50 to 100 mm Hg, or pulse rate outside the range of 40 to 100 beats per minute
- QTc > 500 msec.
- Current or anticipated need for hemodialysis during the study.

Healthy participants:

- History or presence of/significant history of or current renal disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.
- ALT or AST > 1.5 × the upper limit of normal range (ULN); alkaline phosphatase or bilirubin ≥ 1.5 × ULN (isolated bilirubin > 1.5 × ULN was acceptable if bilirubin was fractionated and direct bilirubin is < 35%).
- Systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or considered ineligible by the investigator or subinvestigator based on blood pressure at the Screening visit or upon admission to the CRU.
- QTc > 450 msec for male participants or > 470 msec for female participants at the Screening visit or upon admission to the CRU (QTc was the QT interval corrected for heart rate according to Fridericia's formula [QTcF]).

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

1. Test Product

Ensitrelvir

2. Dose and Mode of Administration

A single dose of 375 mg (3 x 125-mg tablets) to be taken orally.

The tablets were to be taken after an overnight fast of at least 10 hours. The tablets were to be swallowed whole and not chewed, broken, or crushed.

3. Packaging Lot Number:

[redacted]

Duration of Treatment:

A single oral dose administered on Day 1 of this study.

Participants were confined in the CRU from Day -1 to Day 15 (day of discharge). Participants were followed through Day 21 ± 2 days, including a Follow-up visit (at Day 21 ± 2 days) or an Early Termination visit.

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

Not applicable

Criteria for Evaluation:

Efficacy Assessment:

Efficacy parameters were not evaluated in this study.

Safety Assessment:

The assessment of safety was based on the reporting of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs; specifically, rash), clinical laboratory assessments, vital sign measurements, physical examinations, and electrocardiography (ECG).

Pharmacokinetics Assessments:

Based on the plasma and urine concentrations of ensitrelvir, the following PK parameters were calculated by using noncompartmental analysis: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under curve (AUC) from time zero to the time of the last quantifiable concentration after dosing ($AUC_{0\text{-last}}$), AUC extrapolated from time zero to infinity ($AUC_{0\text{-inf}}$), terminal elimination half-life ($t_{1/2,z}$), terminal elimination rate constant (λ_z), mean residence time (MRT), apparent total clearance (CL/F), apparent volume of distribution in the terminal elimination phase (V_z/F), renal clearance (CL_R), fraction of dose excreted in urine (F_{eu}), and plasma unbound fraction (Fu).

Pharmacodynamics Assessments:

Pharmacodynamic parameters were not evaluated in this study.

Statistical Methods:

Efficacy Analyses:

Not applicable.

Safety Analyses:

Safety data were summarized using descriptive statistics.

Pharmacokinetic Analyses:

The PK concentration population included all participants who received ensitrelvir and had at least 1 evaluable concentration of ensitrelvir in plasma or urine. This population was used for summarizing plasma concentrations.

The PK parameter population included all participants with at least 1 PK parameter estimated appropriately and was used for PK parameter listings and summaries.

The estimated PK parameters except for T_{max} were summarized by group with N, mean, standard deviation (SD), coefficient of variation (CV%, calculated by SD/mean × 100), geometric mean and coefficient of variation for geometric mean (geometric CV%), and median, minimum, and maximum values at each sampling time. The geometric CV% was calculated according to a formula geometric CV% = $[\exp(sd^2)-1]^{1/2} \times 100$, where sd was the standard deviation for natural log (ln)-transformed data. The T_{max} was summarized by group with N, mean, SD, CV%, median, minimum, and maximum values. If the number of PK parameter data was < 3, the data were not summarized.

If the number of data points used to calculate λ_z was < 3 or the calculated coefficient of determination (R^2) value for λ_z is < 0.800, then that study participant's λ_z, and $AUC_{0\text{-inf}}$, $t_{1/2,z}$, MRT, CL/F, and V_z/F derived from λ_z were to be flagged in the data listing, and excluded from the descriptive and statistical analysis. If λ_z could not be determined, then $AUC_{0\text{-inf}}$, $t_{1/2,z}$, MRT, CL/F, and V_z/F were not to be estimated.

In addition to the parameters listed above, the extrapolated percent of $AUC_{0\text{-inf}}$, calculated as AUC_{extr} (%) = 100 × ($AUC_{0\text{-inf}} - AUC_{0\text{-last}}$)/$AUC_{0\text{-inf}}$, were determined. If the AUC_{extr} was greater than 20%, then $AUC_{0\text{-inf}}$, MRT, CL/F, and V_z/F derived from $AUC_{0\text{-inf}}$ would be flagged in the data listing and excluded from the descriptive statistics and statistical analysis.

For summaries of plasma concentrations, plasma concentrations below the lower limit of quantification (BLQ) were treated as 0 for calculations of mean, SD, CV%, median, minimum, and maximum values and treated as missing for calculation of geometric mean and geometric CV% mean values. Time course profiles for cumulative Feu were prepared.

Summary of Results:

A total of 34 participants enrolled in the study. Most participants (32 participants, 94.1%) were treated with a single dose of ensitrelvir and all 32 treated participants completed the study. Two participants (5.9%) were withdrawn from the study, both participants were in Group B and were withdrawn prior to treatment because the group of participants with moderate renal impairment was already complete (reason: "Other: Moderate Group Completed"). Only 1 major protocol deviation was reported: a pharmacogenomics sample was collected prior to signing the pharmacogenomics consent (participant inadvertently forgot to sign the relevant page before the sample was collected).

One major protocol deviation was reported. For a participant in Group A, a pharmacogenomics sample was collected prior to signing the pharmacogenomics consent. The participant inadvertently did not sign the appropriate page of the form at time of consenting, but subsequently signed the consent form.

Overall, the mean age at informed consent was 64.2 years (SD 10.15). The majority of participants were male (65.6%). Participants were White (84.4%) or Black or African American (15.6%). Just over half of the population was Hispanic or Latino (56.3%). Mean height was 167.2 cm (SD 9.68), mean weight was 81.1 kg (SD 13.21), and mean BMI was 29.0 kg/m^2 (SD 3.90).

No substantial differences in demographic characteristics were observed among treatment groups.

Efficacy:

Not applicable.

Safety:

All treated participants (32 participants, 94.1% of enrolled patients) were included in the Safety Population. All treated participants received a single oral dose of ensitrelvir (375 mg).

Ensitrelvir was well tolerated in participants with renal impairment.

In total, TEAEs were reported in 5 participants (15.6%): TEAEs were reported in 3 participants (37.5%) in Group A and 2 participants (25.0%) in Group B. No participants in Group C (severe renal impairment) or Group D (normal renal function) experienced TEAEs.

Only 1 preferred term (PT) (vessel puncture site haemorrhage) was reported for > 1 participant overall (2 participants, 6.3% [1 each from Group A and 1 from Group B]). All other TEAEs by PT were each reported by only 1 participant overall (3.1%). Two TEAEs were reported, each in a single participant (PTs dry mouth and glomerular filtration rate decreased).

There were no severe TEAEs or treatment-related TEAEs. There were also no deaths, no SAEs, no AESIs, and no AEs leading to withdrawal from the study.

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

Pharmacokinetics:

As tabulated below, T_{max} was shorter in participants with renal impairment than in the control population (with normal renal function), but similar in all groups of participants with renal impairment (mild, moderate or severe). Exposure to ensitrelvir, based on C_{max} and AUC parameters, was, on average, numerically higher in participants with renal impairment, suggesting an increase in exposure with increased severity of renal impairment. Consistent with this increased exposure, λ_z and CL/F were, on average, numerically lower, and $t_{1/2,z}$ and MRT were longer in participants with renal impairment. There was no pattern of change in V_z/F, cumulative amount excreted in urine (A_{eu}), or cumulative Feu across the groups with increased severity of renal impairment compared with the control group. The geometric mean CL_R was lower in the groups with renal impairment than in the control group, but there was no pattern of change in CL_R across the groups with increased severity of renal impairment. The geometric mean Fu was similar across groups (approximately 1% to 2%) of participants with normal renal function and renal impairment at 3- and 24-hours postdose, suggesting that protein binding was independent of ensitrelvir concentration over the range of concentrations evaluated in this study.

Summary of PK Parameters by Study Group

	Group D Normal renal function (N = 8)	Group A Mild renal impairment (N = 8)	Group B Moderate renal impairment (N = 8)	Group C Severe renal impairment (N = 8)
T_{max} [h]				
Median	4.25	2.25	2.50	2.75
Range	2.00-8.00	1.50-8.00	1.00-12.0	2.00-6.00
C_{max} [µg/mL]				
Geometric mean	15.5	20.5	20.5	17.2
Geometric CV%	34.7	18.9	12.6	19.8
$AUC_{0\text{-last}}$ [µg·h/mL]				
Geometric mean	977.3	1398	1445	1512
Geometric CV%	25.9	20.7	24.5	23.4
$AUC_{0\text{-inf}}$ [µg·h/mL]				
Geometric mean	996.0	1432	1483	1596
Geometric CV%	26.0	20.8	26.0	26.1
λ_z [1/h]				
Geometric mean	0.0158	0.0133	0.0127	0.0098
Geometric CV%	27.3	30.1	25.9	28.5
$t_{1/2,z}$ [h]				
Geometric mean	44.0	52.1	54.7	70.7
Geometric CV%	27.3	30.1	25.9	28.5
CL/F [L/h]				
Geometric mean	0.376	0.262	0.253	0.235
Geometric CV%	26.0	20.8	26.0	26.1
CL_R [L/h]				
Geometric mean	0.0561	0.0327	0.0406	0.0325
Geometric CV%	17.2	44.7	29.1	18.3
Fu at 3 h				
Geometric mean	0.0130	0.0143	0.0125	0.0172
Geometric CV%	12.7	41.0	26.4	21.8
Fu at 24 h				
Geometric mean	0.0118	0.0128	0.0141	0.0165
Geometric CV%	10.1	15.8	53.1	25.7
V_z/F [L]				
Geometric mean	23.9	19.7	19.9	24.0
Geometric CV%	27.6	35.7	22.7	22.7
MRT [h]				
Geometric mean	69.0	80.8	87.5	105
Geometric CV%	20.7	21.8	21.7	27.5
Total cumulative A_{eu} 0-336 h [mg]				
Geometric mean	54.8	45.7	58.6	49.2
Geometric CV%	29.5	44.7	20.6	26.5
Total cumulative Feu 0-336 h [%]				
Geometric mean	14.6	12.2	15.6	13.1
Geometric CV%	29.5	44.7	20.6	26.5

A_{eu} = amount excreted in urine; $AUC_{0\text{-inf}}$ = AUC extrapolated from time zero to infinity; $AUC_{0\text{-last}}$ = AUC from time zero to the time of the last quantifiable concentration after dosing; CL/F = apparent total clearance; CL_R = renal clearance; C_{max} = maximum plasma concentration; CV% = percentage coefficient of variation, Feu = fraction of dose excreted in urine; Fu = plasma unbound fraction; λ_z = terminal elimination rate constant; MRT = mean residence time; SD = standard deviation; $t_{1/2,z}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration; V_z/F = apparent volume of distribution in the terminal elimination phase

A statistical analysis of the PK parameters of ensitrelvir comparing C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and $t_{1/2,z}$ in participants with mild, moderate, and severe renal impairment (Groups A, B, and C) against the normal control group (Group D) is summarized below. Results of analysis of variance indicated that geometric mean ratios (corresponding 90% CI) in participants with mild, moderate, and severe renal impairment compared to healthy control participants (with normal renal function) were 1.4374 (1.1716 to 1.7636), 1.4885 (1.1883 to 1.8646), and 1.6021 (1.2782 to 2.0080), respectively, for $AUC_{0\text{-inf}}$, and 1.3239 (1.0409 to 1.6837), 1.3274 (1.0608 to 1.6611), and 1.1141 (0.8737 to 1.4206), respectively for C_{max}.

Statistical Analysis of the PK Parameters

Comparison	Ratio Test/Ref [a]	90% CI [b] Lower	90% CI [b] Upper
Group A (mild impairment) versus control (no renal impairment)			
C_{max}	1.3239	1.0409	1.6837
$AUC_{0\text{-last}}$	1.4303	1.1668	1.7532
$AUC_{0\text{-inf}}$	1.4374	1.1716	1.7636
$t_{1/2,z}$	1.1855	0.9252	1.5190
Group B (moderate impairment) versus control (no renal impairment)			
C_{max}	1.3274	1.0608	1.6611
$AUC_{0\text{-last}}$	1.4780	1.1882	1.8385
$AUC_{0\text{-inf}}$	1.4885	1.1883	1.8646
$t_{1/2,z}$	1.2434	0.9874	1.5658
Group C (severe impairment) versus control (no renal impairment)			
C_{max}	1.1141	0.8737	1.4206
$AUC_{0\text{-last}}$	1.5475	1.2494	1.9167
$AUC_{0\text{-inf}}$	1.6021	1.2782	2.0080
$t_{1/2,z}$	1.6072	1.2627	2.0457

$AUC_{0\text{-inf}}$ = AUC extrapolated from time zero to infinity; $AUC_{0\text{-last}}$ = AUC from time zero to the time of the last quantifiable concentration after dosing; CI = confidence interval; C_{max} = maximum plasma concentration; Ref = reference (Group D); $t_{1/2,z}$ = terminal elimination half-life; test (Group A; B; or C)

a Geometric mean (Test)/geometric mean (Ref). Geometric mean was based on least squares mean.

b 90% CI.

Conclusions:

Geometric mean ratios (90% CI) for the $AUC_{0\text{-inf}}$ of ensitrelvir in participants with mild, moderate, or severe renal impairment compared with healthy control participants with normal renal function were 1.4374 (1.1716 to 1.7636), 1.4885 (1.1883 to 1.8646), and 1.6021 (1.2782 to 2.0080), respectively.

The geometric mean Fu of ensitrelvir was similar across groups (1.18% to 1.72%), suggesting that renal impairment did not affect the degree of ensitrelvir protein binding.

There were no clinically meaningful differences in PK in participants with mild, moderate, or severe renal impairment, compared with participants with normal renal function.

A single 375-mg oral dose of ensitrelvir was well tolerated in participants with mild to severe renal impairment and in those with normal renal function.

Date of Report: 30 Nov 2023