2. SYNOPSIS

Sponsor: SHIONOGI	**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 ensitrelvir in participants with mild and moderate hepatic 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 30 Aug 2022 to 25 Apr 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 and moderate hepatic impairment compared with control participants with normal hepatic function

Secondary

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

Methodology:

This was a Phase 1, open-label, nonrandomized, parallel-group, matched healthy control cohort study in participants with mild hepatic impairment (Group A), moderate hepatic impairment (Group B), and normal hepatic function (Group C), 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), including a Follow-up visit (Day 21 ± 2) 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 hepatic impairment who had a Child-Pugh classification system score of Class A at the Screening visit were planned to be enrolled.

In Group B, 8 eligible participants with moderate hepatic impairment who had a Child-Pugh classification system score of Class B at the Screening visit were planned to be enrolled.

In Group C, 8 eligible participants with normal hepatic function were planned to be enrolled. All participants in Group C (normal hepatic function) were to be demographically matched with each participant in Group B (moderate hepatic function).

Every effort was to be made to match the normal hepatic function participants in Group C with both the mild and moderate hepatic impairment participants in Groups A and B with respect to sex, age (± 5 years), and body mass index (BMI) (± 10%). If this was not possible, the priority was to match the participants in Group C (normal hepatic function) with each participant in Group B (moderate hepatic impairment).

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

Number of Participants (Planned and Analyzed):

Planned: Approximately 48 participants were planned to be screened to enroll 24 participants to receive study intervention, for an estimated total of 8 evaluable participants per intervention group (as tabulated below)

Group Label	Ensitrelvir Dose	Hepatic Function of Study Participants	Number of Planned Study Participants
Group A	375 mg	Mild impairment	8
Group B	375 mg	Moderate impairment	8
Group C	375 mg	Normal	8

Screened: 52

Enrolled: 27 (2 participants were discontinued prior to receiving study intervention)

Treated: 25 (9 in Group A [including 1 replacement participant] and 8 each in Groups B and C)

Analyzed for efficacy: Not applicable

Analyzed for safety: All treated participants; 25

Analyzed for PK: All treated participants; 25

Plasma and urine concentrations: All treated participants; 25

PK parameters: All treated participants; 25

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 hepatic impairment)

For participants with hepatic impairment

- A diagnosis of clinically stable hepatic disease for at least 1 month prior to the Screening visit, confirmed by medical history or previous confirmation of hepatic cirrhosis by liver biopsy or medical imaging technique (including laparoscopy, computerized tomography [CT] scan, magnetic resonance imaging [MRI], or ultrasonography).
- Mild or moderate hepatic impairment based on the Child-Pugh classification score at the Screening visit to determine eligibility:
  - Mild (Class A) hepatic impairment (Child-Pugh classification score 5 to 6)
  - Moderate (Class B) hepatic impairment (Child-Pugh classification score 7 to 9)

For healthy participants

- Matched to each participant with moderate (and mild when possible) hepatic impairment with respect to sex, age (± 5 years), and BMI (± 10%).

Exclusion criteria

For participants with hepatic 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
  - Platelet: < 50,000/μL
- Estimated GFR < 80 mL/min/1.73 m^2.
- 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.
- History of or current gall bladder or bile-duct disease with the exception of Gilbert's syndrome or asymptomatic gallstones.
- Biliary liver cirrhosis (including primary biliary cholangitis and primary sclerosing cholangitis) or preliminary diagnosed biliary obstruction.

- Esophageal varices with a history of bleeding within 2 months prior to the Screening visit.
- Trans-jugular intrahepatic portosystemic shunt placement.

For healthy participants:

- Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
- 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%).
- Estimated glomerular filtration rate (eGFR) < 80 mL/min/1.73 m^2.
- 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 × 125-mg tablets) to be taken orally.

The tablets were to be taken after an overnight fast of at least 10 hours.

3. Packaging Lot Number:

[redacted]

Duration of Treatment:

A single oral dose was 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 (Feu), 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 the concentration listing.

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

In total, 52 participants were screened and there were 25 screen failures. A total of 27 participants were enrolled in the study. Of these 27 participants, 25 (92.6%) were treated with a single dose of ensitrelvir, 9 participants in Group A (including 1 replacement participant) and 8 participants each in Groups B and C. In total, 23 participants (85.2%) completed the study. Four participants (14.8%) did not complete the study. Two participants were discontinued prior to receiving study intervention and the reason for discontinuation were reported as "other": "subject was an alternative" and "healthy match no longer needed"; ie, no further participants were required for inclusion in Group C. There were 2 participant withdrawals (one in Group A and one in Group B) in the study after receiving study intervention.

Only 1 major protocol deviation (PD) was reported (Group C): the informed consent process was conducted using an outdated consent form from 10 June 2022 instead of the updated version from 05 December 2022.

Overall, the mean age (SD) at informed consent was 57.0 years (9.48). The majority of participants were male (60.0%). Most participants were White (80.0%) and most were Hispanic or Latino (56.0%). The mean (SD) height was 167.85 cm (10.18). The mean (SD) weight was 80.31 kg (15.79). The mean (SD) BMI was 28.42 kg/m^2 (4.43).

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

Efficacy:

Not applicable

Safety:

The safety of ensitrelvir was assessed in 25 participants treated in this study. All participants were treated with a single oral dose of ensitrelvir (375 mg).

In total, TEAEs were reported in 4 participants (16.0%): 2 participants (22.2%) in Group A [mild impairment], 1 participant (12.5%) in Group B [moderate impairment], and 1 participant (12.5%) in Group C [normal function].

There were no notable differences in TEAEs by treatment group. There were no significant safety concerns identified in participants with mild or moderate hepatic impairment (Groups A and B, respectively). On the preferred term (PT) level, each TEAE was reported by only 1 participant overall (4.0% of all participants). The PTs were: back pain, diarrhoea, dysuria, glomerular filtration rate decreased, headache, and myalgia. Only 1 treatment-related TEAE was reported in the mild or moderate hepatic impairment groups: 1 participant from Group A (glomerular filtration rate decreased).

There were no severe TEAEs or severe treatment-related TEAEs reported. There were no deaths, no SAEs, no AESIs, and no adverse events (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, and temperature), ECG examinations, or physical examinations.

Pharmacokinetics:

As tabulated below, T_{max} was similar among participants with mild or moderate hepatic impairment and the control population. There was a tendency of decrease in exposure to ensitrelvir based on C_{max} and AUC with increased severity of hepatic impairment. Geometric mean Fu at 3- and 24-hour postdose was similar across groups (around 1.1% to 1.6%). V_Z/F was, on average, numerically higher in participants with hepatic impairment, with a trend suggesting an increase in value with increased severity of hepatic impairment. $t_{1/2,z}$ and MRT were numerically higher in participants with hepatic impairment, and similar across groups by severity of hepatic impairment.

Summary of PK Parameters by Study Group

	Group C Normal hepatic function (N = 8)	Group A Mild hepatic impairment (N = 8)	Group B Moderate hepatic impairment (N = 8)
T_{max} [h]			
Median	2.00	2.00	3.00
Range	1.00-8.00	1.50-6.00	2.00-6.00
C_{max} [µg/mL]			
Geometric mean	20.5	18.2	15.3
Geometric CV%	15.1	17.0	30.4
$AUC_{0\text{-last}}$ [µg·h/mL]			
Geometric mean	1130	1137	979.4
Geometric CV%	24.7	31.6	25.2
$AUC_{0\text{-inf}}$ [µg·h/mL]			
Geometric mean	1150	1180	1003
Geometric CV%	24.4	30.1	24.6
λ_z [1/h]			
Geometric mean	0.0158	0.0146	0.0146
Geometric CV%	16.9	19.6	23.0
$t_{1/2,z}$ [h]			
Geometric mean	43.9	47.6	47.5
Geometric CV%	16.9	19.6	23.0
CL/F [L/h]			
Geometric mean	0.326	0.318	0.374
Geometric CV%	24.4	30.1	24.6

CL_R [L/h]			
Geometric mean	0.0525	0.0518	0.0623
Geometric CV%	24.0	30.1	49.6
Fu at 3 h			
Geometric mean	0.0147	0.0138	0.0159
Geometric CV%	109.5	18.8	16.6
Fu at 24 h			
Geometric mean	0.0114	0.0133	0.0161
Geometric CV%	14.2	25.1	53.0
V_z/F [L]			
Geometric mean	20.7	21.8	25.6
Geometric CV%	12.8	32.7	29.6
MRT [h]			
Geometric mean	67.4	75.1	74.3
Geometric CV%	20.9	20.1	22.2
Total cumulative A_{eu} [mg]			
Geometric mean	59.3	60.8	61.0
Geometric CV%	38.4	35.9	50.8
Total cumulative Feu, [%]			
Geometric mean	15.8	16.2	16.3
Geometric CV%	38.4	35.9	50.8

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, 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 $t_{½,z}$ in participants with mild and moderate hepatic impairment (Groups A and B) against the normal control group (Group C) is summarized below. Results of analysis of variance indicated that geometric mean ratios (corresponding 90% confidence intervals [CIs]) in participants with mild, and moderate hepatic impairment compared to healthy control participants (with normal hepatic function) were 1.0263 (0.8149 to 1.2925) and 0.8724 (0.7053 to 1.0792), respectively for $AUC_{0\text{-inf}}$, and were 0.8856 (0.7724 to 1.0153) and 0.7425 (0.6036 to 0.9134), respectively for C_{max}, suggesting hepatic impairment tends to decrease the exposures of ensitrelvir with increased severity of hepatic function.

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 hepatic impairment)			
C_{max}	0.8856	0.7724	1.0153

$AUC_{0\text{-last}}$	1.0059	0.7923	1.2771
$AUC_{0\text{-inf}}$	1.0263	0.8149	1.2925
$t_{1/2,z}$	1.0833	0.9274	1.2655
Group B (moderate impairment) versus control (no hepatic impairment)			
C_{max}	0.7425	0.6036	0.9134
$AUC_{0\text{-last}}$	0.8665	0.6977	1.0760
$AUC_{0\text{-inf}}$	0.8724	0.7053	1.0792
$t_{1/2,z}$	1.0811	0.9069	1.2888

$AUC_{0\text{-inf}}$ = 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; GeoMean = geometric mean; LSMean = least squares mean; Ref = reference (Group C); $t_{1/2;z}$ = terminal elimination half-life; test (Group A or B)

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 or moderate hepatic impairment compared with healthy control participants with normal hepatic function were 1.0263 (0.8149 to 1.2925) and 0.8724 (0.7053 to 1.0792), respectively.

Geometric mean ratios (90% CI) for the C_{max} of ensitrelvir in participants with mild or moderate hepatic impairment compared with healthy control participants with normal hepatic function were 0.8856 (0.7724 to 1.0153) and 0.7425 (0.6036 to 0.9134), respectively.

The geometric mean Fu of ensitrelvir was similar across groups (around 1.1% to 1.6%), suggesting that hepatic impairment did not affect the degree of ensitrelvir protein binding.

Some differences were observed in the PK of ensitrelvir after a single 375-mg oral dose in participants with mild or moderate hepatic impairment, when compared with participants with normal hepatic function, however, these were not considered to be clinically meaningful.

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

Date of Report: 30 Nov 2023