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Pharmacokinetics, Safety, and Tolerability of Ensitrelvir, a Novel Oral Inhibitor of 3C-like Protease of SARS-CoV-2, in Participants with Hepatic Impairment

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Introduction and Purpose

- Ensitrelvir is a novel oral inhibitor of 3C-like protease of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- Ensitrelvir received emergency approval for use in Japan on November 2022 and standard approval in March 2024 as an oral antiviral drug against SARS-CoV-2 infection regardless of risk factors, with a dose regimen for the treatment of COVID-19 of 5-day oral dose once daily of 375 mg on Day 1 and 125 mg on Days 2 to 5 [1].
- The urinary recovery of ensitrelvir ranged from 12.9% to 21.8% after single dose [2], suggesting contribution of liver to the clearance of ensitrelvir.
- The aim of this study was to assess the pharmacokinetics (PK), safety, and tolerability of ensitrelvir in participants with hepatic impairment and healthy control participants.

Methods

- This was a phase 1, open-label, parallel-group study conducted in US.
- Participants with mild and moderate (Child-Pugh class A and B, respectively) hepatic impairment and healthy control participants matched based on sex, age, and body mass index (BMI) were enrolled.
- The participants received a single oral dose of ensitrelvir 375 mg (the same dose as a loading dose on Day 1 approved in Japan).
- The PK of ensitrelvir was compared between participants with mild and moderate hepatic impairment and healthy control participants.
- The safety and tolerability were assessed in the participants.

Results: Demographics

- Twenty-five participants received ensitrelvir and all treated participants were included in the safety and PK population.
- The baseline characteristics of the participants are summarized in Table 1.

Table 1 Baseline Participant Characteristics

Characteristics	Normal (N = 8)	Mild (N = 9)	Moderate (N = 8)
Age [years]; mean (SD)	59.3 (9.57)	53.7 (10.82)	58.4 (7.78)
Sex; n (%)			
Male	4 (50.0)	7 (77.8)	4 (50.0)
Female	4 (50.0)	2 (22.2)	4 (50.0)
Ethnicity; n (%)			
Hispanic or Latino	4 (50.0)	6 (66.7)	4 (50.0)
Not Hispanic or Latino	4 (50.0)	3 (33.3)	4 (50.0)
Race; n (%)			
White	5 (62.5)	9 (100)	6 (75.0)
Black or African American	3 (37.5)	0	1 (12.5)
American Indian or Alaska Native	0	0	1 (12.5)
BMI [kg/m^2], mean (SD)	27.98 (2.88)	28.76 (5.76)	28.49 (4.56)

Results: Safety

- The incidence of treatment-emergent adverse events (TEAEs) by system organ class and preferred term are shown in Table 2.
- Of the TEAEs, treatment-related TEAEs were reported for 2 participants overall, 1 participant in normal function (diarrhea) and 1 participant in mild hepatic impairment (glomerular filtration rate decreased). The 2 treatment-related TEAEs were mild (diarrhea) and moderate (glomerular filtration rate decreased). No TEAEs led to withdrawal of study treatment. No serious adverse events were reported.

Table 2 Incidence of Treatment-emergent Adverse Events

System Organ Class - Preferred Term	Normal (N = 8) n (%)	Mild (N = 9) n (%)	Moderate (N = 8) n (%)
Any TEAEs	1 (12.5)	2 (22.2)	1 (12.5)
Gastrointestinal disorders	1 (12.5)	0 (0)	0 (0)
Diarrhea	1 (12.5)	0 (0)	0 (0)
Investigations	0 (0)	1 (11.1)	0 (0)
Glomerular filtration rate decreased	0 (0)	1 (11.1)	0 (0)
Musculoskeletal and connective tissue disorders	0	1 (11.1)	1 (12.5)
Back pain	0	1 (11.1)	0
Myalgia	0	0	1 (12.5)
Nervous system disorders	0	0	1 (12.5)
Headache	0	0	1 (12.5)
Renal and urinary disorders	0	1 (11.1)	0
Dysuria	0	1 (11.1)	0

Treatment-Emergent Adverse Events are defined as AEs occurring after the initial administration of study drug.

Results: Pharmacokinetics

- The plasma concentrations were similar among participants with mild or moderate hepatic impairment and healthy control participants (Figure 1).
- The summary of PK parameters is shown in Table 3.
- Geometric mean ratios (90% confidence interval) in participants with mild and moderate hepatic impairment compared to healthy control participants were 0.886 (0.772-1.015) and 0.743 (0.604-0.913), respectively, for C_{max} and 1.026 (0.815-1.293) and 0.872 (0.705-1.079), respectively, for $AUC_{0\text{-}inf}$ (Table 4). Elimination half-life was slightly higher in participants with mild and moderate hepatic impairment.
- Plasma unbound fraction was similar across the groups (1.1% to 1.6%).

Figure 1 Mean Plasma Concentrations of Ensitrelvir After Single Dose

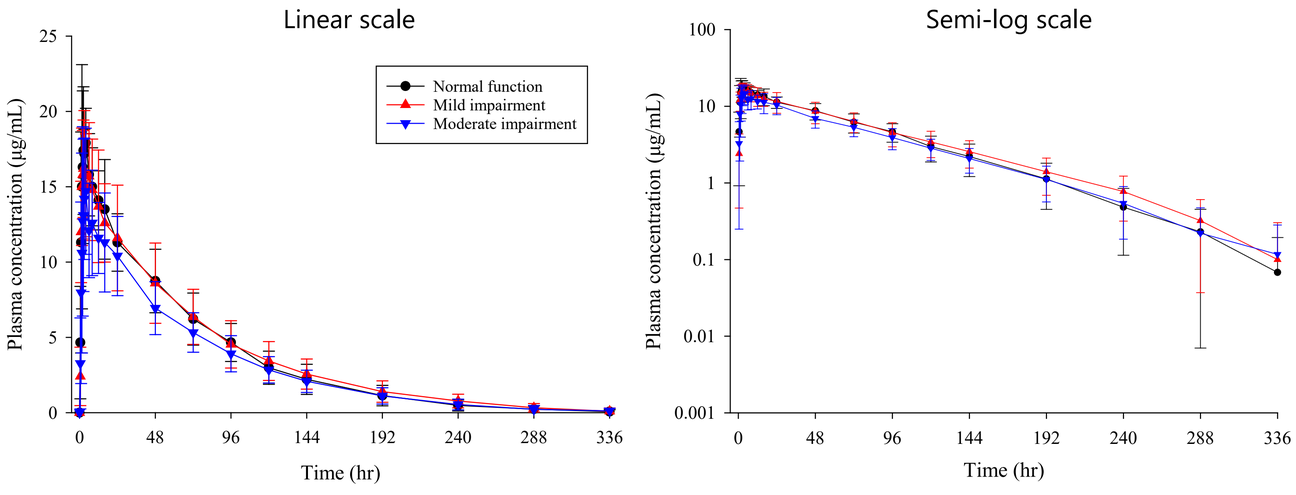

Table 3 Summary of Ensitrelvir PK Parameters

	Normal (N = 8)	Mild (N = 9)	Moderate (N = 8)
T_{max} (h)[a]	2.0 (1.0-8.0)	2.0 (1.5-6.0)	3.0 (2.0-6.0)
C_{max} (μg/mL)	20.5 (15.1)	18.2 (17.0)	15.3 (30.4)
$AUC_{0\text{-}inf}$ (μg·h/mL)	1150 (24.4)	1180 (30.1)	1003 (24.6)
$t_{1/2,z}$ (h)	43.9 (16.9)	47.6 (19.6)	47.5 (23.0)
V_z/F (L)	20.7 (12.8)	21.8 (32.7)	25.6 (29.6)
MRT (h)	67.4 (20.9)	75.1 (32.7)	74.3 (22.2)
CL/F (L/h)	0.326 (24.4)	0.318 (30.1)	0.374 (24.6)
CL_R (L/h)	0.0525 (24.0)	0.0518 (30.1)	0.0623 (49.6)
Feu (%)	15.8 (38.4)	16.2 (35.9)	16.3 (50.8)

Geometric Mean (CV% Geometric Mean). [a] Median (range).
$AUC_{0\text{-}inf}$ = area under concentration-time curve extrapolated from time zero to infinity, CL/F = apparent total clearance, CL_R = renal clearance, C_{max} = maximum plasma concentration, Feu = fraction of dose excreted in urine, MRT = mean residence time, $t_{1/2,z}$ = terminal elimination half life, T_{max} = time to maximum plasma concentration, V_z/F = apparent volume of distribution in the terminal elimination phase

Table 4 Statistical Analysis of Ensitrelvir PK Parameters

	Mild vs Control	Moderate vs Control
C_{max}	0.886 (0.772-1.015)	0.743 (0.604-0.913)
$AUC_{0\text{-}inf}$	1.026 (0.815-1.293)	0.872 (0.705-1.079)
$t_{1/2,z}$	1.083 (0.927-1.266)	1.081 (0.907-1.289)

Geometric least squares mean ratio (90% confidence interval)

Conclusion

- There were no clinically meaningful differences in the PK of ensitrelvir after a single 375-mg dose in participants with mild or moderate hepatic impairment, compared with healthy control participants.
- A single 375-mg dose of ensitrelvir was well tolerated in participants with mild to moderate hepatic impairment and in healthy control participants.
- The results from this study suggest that no dose adjustment would be required due to mild or moderate hepatic impairment.

Reference

[1] Xocova® (Ensitrelvir Fumaric Acid) tablets 125 mg approved in Japan for the treatment of SARS-CoV-2 infection [press release, 22 Nov 2022 and 5 Mar 2024].

[2] Shimizu R, et al. Antimicrob Agents Chemother. 2022;66:e00632-e722.

Conflict of Interest

T. Katsube, R. Shimizu, and R. Kubota are employees of Shionogi & Co., Ltd.
S. Kezbor is an employee of Shionogi Inc.