Xocova – Pharmacokinetics

This medical response contains information in addition to that provided in the Xocova® (ensitrelvir) tablets, for oral use Full Prescribing Information approved by the U.S. Food and Drug Administration (FDA). This document is being provided in response to an unsolicited request for medical information from a healthcare professional. Shionogi does not recommend the use of Xocova in any manner other than as described in the Full Prescribing Information. **Please read the attached Xocova Full Prescribing Information.**

1. SUMMARY

- XOCOVA (ensitrelvir) is indicated for the prevention of COVID-19 in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19. The recommended dosage is 375 mg on Day 1 followed by 125 mg once daily on Days 2-5.[1]
- **Please refer to the attached ensitrelvir enclosures for additional details on pharmacokinetics (PK) related to these topics: Drug-drug Interactions, Use in Renal Impairment, and Use in Hepatic Impairment.**

Key Prescribing Information

Ensitrelvir demonstrated consistent exposure following multiple dosing, with mean C_{max} and $AUC_{0-\tau}$ values of 18.1-18.2 mcg/mL and 345.9-380.8 mcg·hr/mL on Days 1 and 5, respectively. Exposure increased in an almost dose-proportional manner across the 20 to 2000 mg range in healthy adult individuals. Median T_{max} was 2.5 hours on Day 1 and 2.0 hours on Day 5, with no clinically meaningful effect of food (high-fat/ high-calorie) observed.[1]

Ensitrelvir demonstrated a high plasma protein binding (97.7% to 98.7%). Following single-dose administration of ensitrelvir 20 to 2000 mg in a Phase 1 study, the terminal half-life of ensitrelvir was reported to be 42.2 to 48.1 hours. Therefore, it would take approximately 9-10 days (average 9.4 days) for XOCOVA to be eliminated from the body[1,2] Ensitrelvir is primarily eliminated via the biliary route, with 64.8% and 25.8% of the doses recovered in feces and urine, respectively.[1]

Clinical Trials

- **Phase 1 PK Study**
  - Across Phase 1 studies, ensitrelvir exposure increased approximately dose-proportionally following single and multiple doses. Median time to maximum plasma concentration (T_{max}) was generally 1.5-4 hours in the fasted state, and the terminal half-life ($t_{1/2}$) ranged from approximately 42.2 to 58.9 hours across populations. Plasma concentration 24 hours postdose (C_{24}) exceeded the proposed target plasma concentration of 6.09 µg/mL across the evaluated multiple-dose regimens and populations.[2,3]
  - Food delayed T_{max} but had no clinically meaningful effect on maximum plasma concentration (C_{max}); area under the concentration-time curve (AUC) was comparable after a 250 mg suspension dose and increased by approximately 25% after a 375 mg tablet dose.[2,3]
  - Ensitrelvir was generally well tolerated, with decreased high-density lipoprotein cholesterol (HDL-C) the most frequently reported treatment-emergent adverse event (TEAE).[2,3]

- **Additional PK Analyses**
  - In the **SCORPIO-PEP** Phase 3 trial, which evaluated the safety and efficacy of ensitrelvir for preventing symptomatic SARS-CoV-2 infection in household contacts of people with COVID-19, participants received ensitrelvir or placebo for 5 days. The study met its primary endpoint, with comparable safety outcomes between groups. The population mean plasma concentration of ensitrelvir on Day 10 in participants that completed the 5-day course was 4.30 µg/mL, exceeding the proposed target threshold range of 2.99-3.70 µg/mL; the clinical implications have not been established.[4,5]

- **Avedissian et al. (2025)** evaluated the PK of oral ensitrelvir in nonhospitalized adults with COVID-19 from the Phase 3 SCORPIO-HR trial. In the final dataset of 166 participants, clearance was approximately 13% higher in males vs females, and body weight showed a linear relationship with apparent central volume of distribution (V_c/F; 6.8 vs 7.3 L when centered to 70 kg). The estimated $t_{1/2}$ was approximately 41 hours, and mean Day 4 predose and postdose concentrations were 17.5 and 20.5 µg/mL.[6]

- **Ishibashi et al. (2024)** developed a population PK model using 8,034 plasma concentration datasets from 2,060 participants across Phase 1 and Phase 2/3 studies. Body weight was the most significant covariate, affecting clearance and volume of distribution, while food and formulation affected the absorption rate. In SCORPIO-SR, mean Day 1 24-hour postdose concentrations were 16.6 µg/mL with the 375/125 mg regimen and 34.8 µg/mL with the 750/250 mg regimen, exceeding the proposed antiviral threshold of 6.09 µg/mL. Reductions in SARS-CoV-2 RNA by Day 4 were consistent across exposure quartiles and did not appear to differ by dose regimens or body weight.[7]

2. KEY PRESCRIBING INFORMATION

The following section of the Prescribing Information provides details on the PK of XOCOVA. Please refer to the **XOCOVA Full Prescribing Information** for PK information related to drug-drug interactions and PK in special populations.

Section 12.3: Pharmacokinetics

Table 1. Pharmacokinetic Properties of Ensitrelvir.[1]

Parameter	Ensitrelvir		
General Information			
Exposure[a]	Day 1	Day 5	Day 10[e]
C_{max} (mcg/mL)	18.1 (22.6)	18.2 (40.5)	N/A
C_{min} (mcg/mL)	13.2 (31.3)	13.0 (59.4)	N/A
$AUC_{0\text{-}tau}$ (mcg*hr/mL)	345.9 (28.4)	380.8 (47.0)	N/A
C_{day10} (mcg/mL)	N/A	N/A	1.48 (374.8)
Dose Proportionality	C_{max} and $AUC_{0\text{-}inf}$ exposures increase in an almost dose-proportional manner across the single dose range of 20 to 2000 mg in healthy adult individuals.		
Absorption			
Median T_{max} (hours) (range)[b]	Day 1: 2.50 (1.50, 8.00) hours Day 5: 2.00 (1.00, 8.00) hours		
Effect of Food[c]	No clinically significant differences in ensitrelvir pharmacokinetics were observed following administration of a high-fat, high-calorie meal.		
Distribution			
Apparent (Oral) Volume of Distribution in Central Compartment[d]	16.7 (22.9) L		
Human Serum Protein Binding	97.7% to 98.7% (in vitro)		
Blood to Plasma Ratio	0.538		
Elimination			

Parameter	Ensitrelvir
Major Route of Elimination	Primarily eliminated via the biliary route
Terminal Half-Life (hours)	42.2 to 48.1 hours[f]
Apparent (Oral) Clearance[d]	0.316 (52.6) L/hour
Metabolism	Unchanged ensitrelvir (≥ 90%) was the primary drug component detected in plasma.
Primary Responsible Metabolic Enzyme	CYP3A
Excretion	
Feces	64.8% of dose (50.7% unchanged)
Urine	25.8% of dose (19.0% unchanged)

N/A, not applicable.
[a]Represents data at the recommended clinical dose in Trial SCORPIO-PEP predicted by population PK analysis. Data represents geometric mean (coefficient of variation, CV%).
[b]Ensitrelvir 375 mg on Day 1 followed by 125 mg on Days 2 to 5; tau is dosing interval of 24 hours.
[c]High-fat, high-calorie meal. Total calories were 863 kcal (27.2% carbohydrates, 17.3% proteins, and 55.4% fat).
[d]Data from population pharmacokinetic analysis.
[e]The primary endpoint was assessed at Day 10.
[f]Following a single-dose administration of ensitrelvir 20 to 2000 mg.

3. CLINICAL TRIALS

PHASE 1 PHARMACOKINETIC STUDY

Study Overview

The PK, safety, and tolerability of ensitrelvir were evaluated in a Phase 1, multicenter, randomized, double-blind, placebo-controlled study conducted in Asia, in healthy adult participants, including Japanese and White populations. Studies assessed single-ascending doses, multiple-ascending doses, and food effects using both suspension and tablet formulations (see **Table 2**).[2,3]

Table 2. Phase 1 PK Study Program Structure.[2,3]

Formulation	Population	Design	Dosage	Cohorts	N (ensitrelvir + placebo)
Suspension	Healthy Japanese males	SAD	20-2000 mg	A, B, C, D, E, J	50
	Healthy Japanese males	Effect of food	250 mg	C	
	Healthy Japanese males	MAD	375/125 mg; 750/250 mg	F, G	33
	Healthy White males	MAD	375/125 mg	H	
Tablet	Healthy Japanese males	Effect of food	375 mg	P	14
	Healthy Japanese females	Multiple-dose	375/125 mg; 750/250 mg	N, O	22
	Healthy White adults	Multiple-dose	375/125 mg; 750/250 mg	Q, R	24
	Healthy Japanese elderly	Multiple-dose	375/125 mg	S	16

Abbreviations: MAD, multiple-ascending-dose; SAD, single-ascending-dose.

Single-Ascending-Dose and Effect of Food Study (Healthy Japanese Males) – Ensitrelvir Suspension

Study Design

A single-center, randomized, double-blind, placebo-controlled study evaluated single ascending oral doses of ensitrelvir suspension (20 to 2000 mg) in healthy Japanese adult males (N=50). The study consisted of 6 cohorts (A, B, C, D, E, and J) assessing PK under fasted conditions. Cohort C additionally evaluated the effect of food on a single ensitrelvir 250 mg dose using a two-group, two-period crossover design.[2]

Results

Pharmacokinetics

- Effect of Fasted State[2]

  Following single doses of 20 to 2000 mg in the fasted state (cohorts A, B, C, D, E, and J):
  - Median T_{max} ranged from 1.5 to 4 hours
  - Mean C_{max} ranged from 1.70 to 96.9 µg/mL, and mean $AUC_{0\text{-}inf}$ ranged from 91.44 to 6346 µg·h/mL; both increased in an almost dose-proportional manner
  - Geometric mean $t_{1/2,z}$ ranged from 42.2 to 48.1 hours
  - No clear relationship between dose and $t_{1/2,z}$, MRT, or V_z/F was observed

- Effect of Food[2]

  In Cohort C, the effect of food on PK parameters was evaluated following a single 250 mg dose of ensitrelvir.

  Following a single 250 mg dose of ensitrelvir:
  - Mean C_{max} was 15.2 µg/mL in the fasted state and 13.0 µg/mL in the fed state, representing an approximately 15% decrease under the fed state
  - Mean $AUC_{0\text{-}last}$ was 906.8 and 949.4 µg·h/mL, and mean $AUC_{0\text{-}inf}$ was 913.7 and 955.7 µg·h/mL, in the fasted and fed states, respectively; exposure was comparable between states.
  - Median T_{max} increased from 2.5 hours in the fasted state to 8 hours in the fed state

  These results suggest ensitrelvir can be taken without food restrictions.

Safety[2]
- Ensitrelvir suspension was well tolerated with no major safety concerns.
- TEAEs were reported in:
  - Cohort B: 2 events in 2/6 participants
  - Cohort E: 6 events in 6/6 participants
  - Cohort J: 11 events in 6/6 participants
- The most common TEAE was decreased high-density lipoprotein cholesterol (HDL-C) in 6/6 participants in each in Cohorts E and J)
- TEAEs were, for the most part, mild and resolved without treatment

Multiple-Ascending-Dose Study (Healthy Japanese and White Males) – Ensitrelvir Suspension

Study Design

A multicenter, randomized, double-blind, placebo-controlled study evaluated the safety, tolerability, and PK of multiple-ascending oral doses of ensitrelvir suspension in healthy Japanese and White adult males (N=33). The study consisted of 3 cohorts (F, G, and H) assessing repeated dosing and ethnic differences. Cohort G additionally evaluated the effect of ensitrelvir on the PK of midazolam (for drug interaction results with midazolam, please see Ensitrelvir – Drug-Drug Interaction Enclosure).[2]

Study participants in a fasted state were administered placebo or ensitrelvir suspension once daily for 5-6 days at the following regimens:[2]
- Cohort F (Japanese males; n=11): 375 mg on Day 1 followed by 125 mg on Days 2-5
- Cohort G (Japanese males; n=11): 750 mg on Day 1 followed by 250 mg on Days 2-6 (with midazolam 2 mg coadministration on Day 6)
- Cohort H (White males; n=11): 375 mg on Day 1 followed by 125 mg on Days 2-5

Cohort G included an open-label, self-controlled crossover design to evaluate drug-drug interaction (DDI) with midazolam (2 mg syrup) administered alone 2 days prior to ensitrelvir initiation (Day –2) and coadministered on

Day 6 with placebo or ensitrelvir (for drug interaction results with midazolam, please see the Ensitrelvir Drug-Drug Interaction Enclosure).[2]

Results

Pharmacokinetics

Following multiple ascending doses of ensitrelvir in the fasted state:[2]

- Mean C_{max} ranged from 22.7 to 66.3 µg/mL, and mean $AUC_{0-\tau}$ ranged from 350.8 to 1337 µg·h/mL across dose regimens and study days; both increased in an almost dose-proportional manner.
  - For Cohort G (750/250 mg) versus Cohort F (375/125 mg), GLS mean ratios (90% CI) were 1.52 (1.27-1.81) for C_{max} and 1.69 (1.45-1.97) for AUC_{0-t} on Day 1, and 2.18 (1.95-2.44) and 2.24 (1.99-2.51), respectively, on Day 5.
- Median T_{max} ranged from 1.5 to 3 hours.
- Exposure was slightly lower in White participants than in Japanese participants.
  - GLS mean ratios (90% CI) for C_{max} ratios (White males/Japanese males) were 0.77 (0.67-0.88) on Day 1 and 0.87 (0.78-0.96) on Day 5; AUC_{0-t} ratios were 0.72 (0.65-0.80) and 0.86 (0.77-0.97) for White and Japanese males, respectively.

Safety[2]

- Ensitrelvir suspension was well tolerated with no major safety concerns
- TEAEs reported in ≥2 participants in the ensitrelvir group included:
  - Decreased HDL-C: 7/8 participants in each of Cohorts F, G, and H
  - Diarrhea: 4/8 participants in each of Cohorts F, G, and H
  - Headache: 4/8 participants in Cohort G; 2/8 in Cohort H
  - Drowsiness: 3/8 participants in Cohort G (observed after midazolam administration)
- Most TEAEs were mild and resolved without treatment

Single-Dose and Effect of Food Study (Healthy Japanese Males) – Ensitrelvir Tablet

Study Design

A single-center, randomized, open-label, two-group, two-period crossover study evaluated the effect of food on the PK of orally administered ensitrelvir tablets in healthy Japanese adult males (N=14).[3]

This was a one-cohort study (Cohort P) in which participants received a single oral dose of ensitrelvir 375 mg (three 125 mg tablets) under:[3]

- Fasted state (n=7)
- Fed state (high-fat, high-calorie meal; n=7)

Results

Pharmacokinetics

- Effect of Food[3]

  Following a single ensitrelvir 375 mg dose:
  - Mean C_{max} was 21.5 µg/mL in the fasted state and 20.0 µg/mL in the fed state.
  - Mean AUC_{0-last} was 1222 and 1519 µg·h/mL, and mean AUC_{0-inf} was 1235 and 1538 µg·h/mL, in the fasted and fed states, respectively.
  - Median T_{max} increased from 2.5 hours in the fasted state to 6 hours in the fed state.

- The 90% CIs for C_{max} were completely within the range of 0.80 to 1.25, indicating that there was no clinically meaningful difference in the exposure of ensitrelvir 375 mg between the fasted and fed states.
- Food intake increased both $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ of ensitrelvir by ~25%; upper limits of 90% CIs were slightly higher than 1.25.

Safety[3]

- Ensitrelvir was well tolerated with no new safety signals observed.
- TEAEs more frequent in the ensitrelvir group versus placebo included:
  - Decreased HDL: 4/13 in fasted cohort and 7/14 in fed cohort
  - Headache: 1/13 in fasted cohort and 2/14 in fed cohort
  - COVID-19 and nausea: 1/14 in fed cohort
- All TEAEs, except COVID-19, were considered related to ensitrelvir

Multiple-Dose Study (Healthy Japanese Females) – Ensitrelvir Tablet

Study Design

The PK and safety of orally administered ensitrelvir tablets were evaluated in a phase 1, multicenter, randomized, double-blind, placebo-controlled study in healthy Japanese adult female participants (20-55 years; N=22).[3]

Two cohorts received multiple oral doses of ensitrelvir in the fasted state:[3]
- Cohort N: 375 mg on Day 1 followed by 125 mg once daily on Days 2-5 (n=11; ensitrelvir n=8, placebo n=3)
- Cohort O: 750 mg on Day 1 followed by 250 mg once daily on Days 2-5 (n=11; ensitrelvir n=8, placebo n=3)

Results

Pharmacokinetics

Following multiple-dose administration of ensitrelvir in healthy Japanese female participants:[3]
- Mean C_{max} ranged from 22.3 to 55.8 μg/mL, and mean $AUC_{0\text{-}\tau}$ ranged from 372.9 to 1019.0 μg·h/mL across dose regimens and study days; exposure increased in a dose-proportional manner.
- Mean C_{24} ranged from 14.0 to 36.1 μg/mL and exceeded the target plasma concentration of 6.09 μg/mL.
- Median T_{max} ranged from 2.0 to 3.5 hours; and the terminal half-life ranged from approximately 48.7 to 51.4 hours.

Safety[3]

- Ensitrelvir was well tolerated with no serious adverse events.
- All TEAEs were considered related to the study intervention. The most frequent TEAEs included:
  - Decreased HDL: 5/8 in the 375/125 mg cohort, 8/8 in the 750/250 mg cohort
  - Nausea and vomiting: 2/8 in the 375/125 mg cohort, 1/8 in the 750/250 mg cohort
  - Headache and constipation: 1/8 in the 375/125 mg cohort, 1/8 in the 750/250 mg cohort

Multiple-Dose Study (Healthy White Adults) – Ensitrelvir Tablet

Study Design

The PK and safety of orally administered ensitrelvir tablets were evaluated in a phase 1, multicenter, double-blind, randomized, placebo-controlled study in healthy White adult participants (female and male; 20-55 years; N=24).[3]

Two cohorts received multiple oral doses of ensitrelvir in the fasted state:[3]

- Cohort Q: 375 mg on Day 1 followed by 125 mg once daily on Days 2-5 (n=12; ensitrelvir n=8, placebo n=4)
- Cohort R: 750 mg on Day 1 followed by 250 mg once daily on Days 2-5 (n=12; ensitrelvir n=8, placebo n=4)

Results

Pharmacokinetics

Following multiple-dose administration of ensitrelvir in healthy White adults:[3]

- Mean C_{max} ranged from 19.7 to 42.1 µg/mL, and mean AUC0-τ ranged from 325.0 to 798.3 µg·h/mL across dose regimens and study days; exposure increased slightly less than dose-proportionally.
- Mean C_{24} ranged from 12.2 to 28.9 µg/mL and exceeded the target plasma concentration of 6.09 µg/mL.
- Median T_{max} ranged from 2.25 to 3.25 hours; the terminal half-life ranged from approximately 53.2 to 57.6 hours.

Safety[3]

- Ensitrelvir was well tolerated.
- Common TEAEs included:
  - Decreased HDL: 5/8 in the 375/125 mg cohort, 7/8 in the 750/250 mg cohort
  - Diarrhea: 2/8 in the 375/125 mg cohort, 1/8 in the 750/250 mg cohort
  - Constipation: 1/8 in the 375/125 mg cohort
  - Headache: 3/8 in the 750/250 mg cohort
  - Blood triglycerides: 1/8 in the 750/250 mg cohort
- Of these, all 12 events of decreased HDL, 3 events of headache, and 1 event of increased blood triglycerides were considered related to ensitrelvir.

Multiple-Dose Study (Healthy Japanese Elderly) – Ensitrelvir Tablet

Study Design

The PK and safety of orally administered ensitrelvir tablets were evaluated in a phase 1, multicenter, double-blind, randomized, placebo-controlled study in healthy Japanese elderly participants (≥65 years; N=16 (ensitrelvir n=11, placebo n=5).[3]

One cohort (Cohort S) received multiple oral doses of ensitrelvir 375 mg on Day 1, followed by 125 mg once daily on Days 2-5 in the fasted state.[3]

Results

Pharmacokinetics

Following multiple-dose administration of ensitrelvir 375/125 mg in Japanese elderly participants:[3]

- Mean C_{max} ranged from 19.7 to 23.8 µg/mL, mean $AUC_{0-\tau}$ ranged from 319.2 to 446.1 µg·h/mL.
- Mean C_{24} ranged from 11.5 to 17.1 µg/mL across Days 1 and 5 and exceeded the target plasma concentration of 6.09 µg/mL.
- Median T_{max} was 2 hours on Day 1 and 3 hours on Day 5 and the terminal half-life was approximately 58.9 hours.

Safety[3]

- Ensitrelvir was well tolerated with no serious adverse events.

- TEAEs included:
  - Decreased HDL: 5/11 in the ensitrelvir 375/125 mg cohort
  - Increased nausea, headache, and blood creatine phosphokinase
  - Increased C-reactive protein: 1/11 in the ensitrelvir 375/125 mg cohort
- Except for increased blood creatine phosphokinase, all TEAEs were considered related to ensitrelvir.

ADDITIONAL PK ANALYSES

SCORPIO-PEP (Phase 3)

Study Design

The SCORPIO-PEP phase 3 trial evaluated the safety and efficacy of XOCOVA in preventing symptomatic SARS-CoV-2 infection in household contacts (HHCs) of people who tested positive for COVID-19 through Day 10. Participants received a single 5-day course of ensitrelvir (375 mg was given orally once on Day 1 followed by 125 mg orally once daily on Days 2-5) or placebo.[4]

Results

The primary endpoint (proportion of participants in the mITT population with symptomatic COVID-19 through Day 10) was met. TEAEs were comparable between both arms.[4]

Pharmacokinetics

Based on a pharmacokinetic analysis from the SCORPIO-PEP study, the population mean plasma concentration of ensitrelvir on Day 10 was 4.30 µg/mL in participants that completed the full 5 day course of ensitrelvir, exceeding the proposed target threshold range of 2.99-3.70 µg/mL; however, the clinical implications of these findings have not been established.[5]

Population PK Analysis in Nonhospitalized Adults with COVID-19 from SCORPIO-HR Trial

Avedissian et al. (2025) evaluated the PK profile of oral ensitrelvir using population PK modeling in a subset of nonhospitalized adults with COVID-19 enrolled in the Phase 3, randomized, double-blind, placebo-controlled SCORPIO-HR trial (NCT05305547) that included participants with and without risk factors for severe disease. The overall aim was to develop a base model without incorporating patient-specific covariates, to explore covariant effects on PK, and develop a full covariate-adjusted model for ensitrelvir.[6]

Study Design

Participants were randomized 1:1 to receive either a 5-day regimen of once daily ensitrelvir (375 mg Day 1; 125 mg Days 2-5) or placebo. PK samples were collected on Days 1, 4, and 8, and analyzed using Pmetrics Nonparametric modeling.[6]

PK sampling was conducted in two groups:[6]

- Group 1 (n=150) had samples collected on Day 1 at 1 hour and 1.5 hours postdose, on Day 4 at predose and 1.5 hours postdose, and on Day 8 at any time postdose.
- Group 2 (n=250) had samples collected on Day 1 at 1 hour postdose and on Days 4 and 8 at any time postdose.

Results

The final data set included 166 participants of the initially 222 randomized participants, from which there were 579 detectable ensitrelvir levels.[6]

- Sex influenced clearance in the final base model, with males showing ~13% higher CL/F than females.[6]
- Body weight showed a linear relationship with V_c/F; lower weight was associated with lower V_c/F and higher drug concentrations (centered to a 70 kg person, 6.8 L vs 7.3 L).[6]
- The final covariate-adjusted model estimated CL/F at 0.313 L/h, V_d/F at 18.66 L, and a terminal half-life of approximately 41 hours.[6]
- Day 4 mean concentrations were 17.5 (±5.8) µg/mL predose and 20.5 (±6.7) µg/mL postdose.[6]

Ensitrelvir PK in COVID-19 patients were consistent with healthy subjects, as seen in **Table 3** below.

Table 3. Final base model comparison with literature parameters.[2,3,6]

Cohort	CL/F (L/h)	V/F (L)	Half-life (hours)
SCORPIO-HR (Present Analysis)[6]	0.224	16.4	51.3
Healthy Japanese Adults[2] (250 mg single-dose, fasted)	0.274	17.0	43.1
Healthy Japanese Adults[3] (375 mg single-dose, fasted/fed)	0.304 / 0.247	20.9 / 17.1	47.7 / 48.5

Table adapted from Avedissian et al. IDWeek 2025; October 19-22, 2025; Atlanta, Georgia.
Abbreviations: CL/F, apparent clearance; V/F, apparent volume.

Safety

No safety outcomes were reported.[6]

Population PK Modeling and Analysis of Ensitrelvir from Phase 1 and Phase 2/3 Studies

Ishibashi et al. (2024) conducted a population PK analysis using data from two Phase 1 studies in healthy adults and the Phase 2/3 study in participants with SARS-CoV-2 infection. The study aimed to characterize ensitrelvir PK and explore exposure-response relationships with the dosing regimen.[7]

Study Design

In the two Phase 1 studies, ensitrelvir was administered as single doses of 20 – 2000 mg or as regimens of 375 mg on Day 1 followed by 125 mg on Days 2-5, or 750 mg on Day 1 followed by 250 mg on Days 2-5. The analysis also evaluated the effect of food in the fasted and fed states and concomitant administration with transporter substrates. In the Phase 2/3 study, participants received the 375/125 mg or 750/250 mg regimen.[7]

A population PK model was developed using nonlinear mixed-effect modeling software, selecting a two-compartment structure with first-order absorption. The model was validated through goodness-of-fit plots, visual predictive checks, and bootstrap analysis.[7]

Results

The analysis included 8,034 plasma concentration datasets from 2,060 participants (175 healthy adults and 1,885 infected participants). Body weight was identified as the key covariate influencing clearance and volume, while food and formulation affected absorption.[7]

The PK parameters for the final model are presented in **Table 4** below.

Table 4. Population PK parameter estimates for the final model (model no. 511) and bootstrap estimations.[7]

PK parameter (unit)	Estimate (95% CI)	Bootstrap Estimate Median (95% CI)	%RSE
K_a (1/h)	1.50 (1.25-1.75)	1.50 (1.23-1.80)	8.6
CL/F (L/h)	0.211 (0.208-0.214)	0.211 (0.207-0.214)	0.8
V_c/F (L)	14.7 (13.9-15.5)	14.8 (13.9-15.5)	2.7
Q/F (L/h)	0.539 (0.321-0.757)	0.534 (0.331-0.823)	20.6
V_p/F (L)	2.50 (1.80-3.20)	2.49 (1.74-3.26)	14.3
Effect of food on K_a	0.594 (0.398-0.790)	0.599 (0.447-1.00)	16.8
Effect of formulation on K_a	0.362 (0.262-0.462)	0.367 (0.280-0.469)	14.1
Effect of body weight on CL/F	0.521 (0.456-0.586)	0.527 (0.459-0.585)	6.4
Effect of body weight on Vc/F	1.04 (0.960-1.12)	1.04 (0.959-1.11)	3.9

Table adapted from Ishibashi et al. *Clinical Pharmacokinetics.* 2024.

Abbreviations: CI, confidence interval; CL/F, apparent total clearance; K_a, first-order rate of absorption; Q/F, apparent intercompartmental clearance; Vc/F apparent volume of distribution in central compartments, Vp/F apparent volume of distribution in peripheral compartments, %RSE relative standard error in percent.

Exposure-Response Analyses:[7]

- In the Phase 2/3 study, mean ensitrelvir plasma concentrations 24 hours after the Day 1 dose were 16.6 µg/mL with 37/5125 mg regimen and 34.8 µg/mL with the 750/250 mg regimen, exceeding the proposed antiviral threshold of 6.09 µg/mL required for a two-log reduction in viral titer**.**
- Analysis of the Phase 3 part (SCORPIO-SR) of the Phase 2/3 study showed that reductions in SARS-CoV-2 RNA by Day 4 were consistent across exposure quartiles of ensitrelvir and did not appear to differ by dose regimen or body weight.

Safety

No safety outcomes were reported.[7]

4. RELEVANT PRESCRIBING INFORMATION

Indications and Usage

XOCOVA is indicated for post-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19.[1]

Contraindications

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[1]

XOCOVA is contraindicated in patients taking drugs that are:

- Primarily metabolized by CYP3A for which elevated concentrations may be associated with serious and/or life-threatening reactions and
- Strong CYP3A inducers because they may significantly reduce ensitrelvir plasma concentrations, leading to the potential loss of virologic response.[1]

Please read the attached XOCOVA **Full Prescribing Information**. The use of XOCOVA in any manner other than as described in the Full Prescribing Information approved by the U.S. Food and Drug Administration (FDA) is not recommended.

5. LITERATURE SEARCH, ABBREVIATIONS, & REFERENCES

LITERATURE SEARCH

As of August 2026, a computerized search of the published medical literature using internal and external databases (eg, PubMed®) has identified additional relevant references regarding the pharmacokinetics of ensitrelvir. For your review, these references are listed in the bibliography that follows:

- Fukao K, Nobori H, Kuroda T, et al. Pharmacokinetic and Pharmacodynamic Analysis of the 3CL Protease Inhibitor Ensitrelvir in a SARS-CoV-2 Infection Mouse Model. *Viruses*. 2023;15(10):2052. Published 2023 Oct 5. doi:10.3390/v15102052 [Web Link]

Please keep in mind that medical literature databases, while considered a major source of biomedical information, are selective in their sources, and the information derived from it should not be considered all-inclusive.

ABBREVIATIONS

3CL	3C-like
CL/F	Apparent clearance
COVID-19	Coronavirus disease 2019
CYP3A	Cytochrome P450 3A
DDI	Drug-drug interaction
HDL-C	High-density lipoprotein cholesterol
MAD	Multiple-ascending-dose
MATE1	Multidrug and toxin extrusion protein 1
MHLW	Ministry of Health, Labour and Welfare
NONMEM	Nonlinear mixed-effect modeling
OATP1B1/1B3	Organic anion transporting polypeptide 1B1/1B3
OCT1	Organic cation transporter 1
P-GP	P-glycoprotein
PK	Pharmacokinetics
SAD	Single-ascending-dose
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TEAE	Treatment-emergent adverse event
Vc/F	Apparent volume of distribution in the central compartment
Vd/F	Apparent volume of distribution

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ENCLOSURES

1. XOCOVA® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.
2. XOCOVA – Drug-Drug Interactions
3. XOCOVA – Use in Renal Impairment
4. XOCOVA – Use in Hepatic Impairment