Xocova – Drug-Drug Interactions

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

- Ensitrelvir is a strong inhibitor of CYP3A and an inhibitor of P-gp and BCRP. It is also a CYP3A substrate.[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]
- In addition, concomitant use of ensitrelvir with drugs transported by P-gp or BCRP may increase plasma concentrations of those drugs and may potentially lead to severe, life-threatening, or fatal events from increased exposure of concomitant medications.
- Prior to prescribing ensitrelvir, review all medications taken by the patient (including prescription and non-prescription medications, vitamins, and supplements) to assess potential drug-drug interactions (DDI) and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring. Consider the benefit of ensitrelvir and whether the risk of potential drug-drug interactions can be appropriately managed.[1]
- When evaluating concomitant use of ensitrelvir with other medications, healthcare professionals should consult the **XOCOVA Full Prescribing Information** and the labeling of concomitant therapies. If a drug or drug class is not listed in **Section 7 of the enclosed XOCOVA Full Prescribing Information**, this should not be interpreted as supporting coadministration with ensitrelvir. Healthcare providers should exercise clinical judgment, which may include consideration of factors beyond pharmacokinetic interactions, based on the individual patient and clinical context.
- In addition, re-initiation of contraindicated CYP3A substrates should be considered based on an assessment of the duration of CYP3A inhibition and patient-specific considerations.
- Please refer to **Section 7** of the **XOCOVA Full Prescribing** Information for additional information about drug interactions

Clinical Studies

- Across the **Phase 3 SCORPIO-PEP[2], Phase 3 SCORPIO-HR[3], Phase 3 SCORPIO-SR[4], Phase 2a[5], Phase 2b[6],** and **Phase 2b/3[7] studies**, participants were excluded if they had used the following drugs within 14 days prior to enrollment or randomization:
  - Products containing St. John's wort[2-7]
  - Strong cytochrome P450 3A (CYP3A) inducers[2-7]
  - Strong cytochrome CYP3A inhibitors[4-7]
- **STRIVE:** In the Phase 3 STRIVE trial that evaluated ensitrelvir plus local standard of care in adults hospitalized for COVID-19 with lower respiratory tract involvement, DDI risk was managed by prohibiting concomitant medications including strong CYP3A inhibitors, strong CYP3A inducers, and sensitive-to-moderate CYP3A substrates; nirmatrelvir/ritonavir and dexamethasone were particularly prohibited through Day 14, while alternative corticosteroids such as prednisone or prednisolone were permitted. In addition, an online web-portal was developed to provide guidance on DDI management for this study. This study was in collaboration with the NIAID as a part of the ACTIV public-private partnership program[8]

- Several Phase 1 clinical studies evaluating drug-drug interactions between ensitrelvir and several medications have been conducted, including **ethinyl estradiol/drospirenone**, **CYP3A substrates (dexamethasone, prednisolone, and midazolam)**, and **drug transporter substrates (digoxin, rosuvastatin, and metformin)**[9-12]. Information from these studies is summarized in the Clinical Studies Section of this letter.[9-12]

Additional Resource: Non-Shionogi

- The Liverpool COVID-19 Drug Interactions website is an online drug interaction resource based on publicly available data and may contain additional information regarding potential interactions involving ensitrelvir and select medications. This site is independently owned, and the content is not reviewed, controlled, or endorsed by Shionogi Inc. No clinical advice is provided or implied; healthcare providers should exercise clinical judgment, which may include consideration of factors beyond pharmacokinetic interactions, based on the individual patient and clinical context. The resource is accessible at: COVID-19 Drug Interactions Checker

2. KEY PRESCRIBING INFORMATION

Please refer to the **XOCOVA Full Prescribing Information** prior to and during treatment with ensitrelvir, as concomitant use with certain medications may result in potentially significant drug-drug interactions, including potentially severe, life-threatening, or fatal events.

The following sections of the Full Prescribing Information (FPI) provide details on drug-drug interactions with XOCOVA:

Section 1: Indications and Usage[1]

XOCOVA is indicated for post-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19.

Section 4: Contraindications:[1]

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

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

Section 5.2: Risk of Serious Adverse Reactions Due to Drug Interactions:[1]

XOCOVA is a strong CYP3A inhibitor and an inhibitor of P-gp and BCRP. In patients receiving or initiating medications metabolized by CYP3A or transported by P-gp or BCRP, XOCOVA may increase plasma concentrations of those medications and may potentially lead to severe, life-threatening, or fatal events from increased exposures of concomitant medications. In addition, medications that induce CYP3A may decrease concentrations of ensitrelvir, leading to loss of therapeutic effect of XOCOVA.

Prior to prescribing XOCOVA, review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring (e.g., calcineurin inhibitors). Consider the benefit

of XOCOVA and whether the risk of potential drug-drug interactions can be appropriately managed.

Section 7: Drug Interactions:[1]

Section 7.1: Potential for XOCOVA to Affect Other Drugs:

Ensitrelvir is a strong inhibitor of CYP3A and an inhibitor of P-gp and BCRP. Co-administration of XOCOVA with drugs that are primarily metabolized by CYP3A or are transported by P-gp or BCRP may result in increased plasma concentrations of such drugs and increase the risk of adverse events. For drugs that are CYP3A substrates and contraindicated with XOCOVA, initiation of XOCOVA should be considered only after careful evaluation of relevant clinical and pharmacokinetic factors related to the concomitant medication. In addition, re-initiation of contraindicated CYP3A substrates should be considered based on an assessment of the duration of CYP3A inhibition and patient-specific considerations. Refer to individual drug prescribing information for additional information.

Section 7.2: Potential for Other Drugs to Affect XOCOVA

Ensitrelvir is a CYP3A substrate; therefore, drugs that induce CYP3A may decrease ensitrelvir plasma concentrations and reduce XOCOVA therapeutic effect. Therefore, use of XOCOVA with strong CYP3A4 inducers is contraindicated. No dose adjustment is recommended when XOCOVA is used concomitantly with moderate or weak CYP3A inducers. Refer to individual drug prescribing information for additional information.

Section 7.3: Established and Other Potentially Significant Drug Interactions

Section 7.3 (**Table 1**) from the XOCOVA FPI provides examples of drugs that are contraindicated with XOCOVA.

- *The table is provided as a guide and is not a comprehensive list of all possible drugs that may interact with XOCOVA.*
- *The healthcare provider should consult other appropriate resources, such as the prescribing information for the interacting drug, for comprehensive information on dosing and monitoring with concomitant use of a strong CYP3A inhibitor, like XOCOVA.*

Table 1. Examples of Drugs Contraindicated with XOCOVA due to Risk of Potentially Serious or Fatal Interaction.[1]

Drug Class	Example Drug(s) within Class	Effect on Drug Concentration	Clinical Comment
Antiarrhythmics	quinidine	↑ antiarrhythmic	Co-administration is contraindicated due to potential for cardiac arrhythmias.
Anticancer drugs	apalutamide, enzalutamide	↓ ensitrelvir	Co-administration is contraindicated due to potential loss of virologic response.
Anticonvulsants	carbamazepine*, phenytoin	↓ ensitrelvir	Co-administration is contraindicated due to potential loss of virologic response.
Antigout agents	colchicine	↑ colchicine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antimycobacterials	rifampin	↓ ensitrelvir	Co-administration is contraindicated due to potential loss of virologic response.

Drug Class	Example Drug(s) within Class	Effect on Drug Concentration	Clinical Comment
Antipsychotics	lurasidone, pimozide	↑ lurasidone, pimozide	Co-administration is contraindicated due to serious and/or life-threatening reactions, such as cardiac arrhythmias.
Cardiovascular drugs	eplerenone, ivabradine	↑ eplerenone, ivabradine	Co-administration is contraindicated.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ ensitrelvir	Co-administration is contraindicated due to potential loss of virologic response.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine, ergotamine, methylergonovine	Co-administration is contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues, including the central nervous system.
Herbal products (for depression)	St. John's wort	↓ ensitrelvir	Co-administration is contraindicated due to potential loss of virologic response.
HMG-CoA reductase inhibitors (statins)	simvastatin	↑ simvastatin	Co-administration is contraindicated. Discontinue use of simvastatin at least 12 hours prior to initiation of XOCOVA.
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration is contraindicated due to potential for acute and/or chronic nephrotoxicity.
Microsomal triglyceride transfer protein (MTTP) inhibitors	lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration is contraindicated due to potential for serious adverse reactions, including hyperkalemia, hypotension, and hyponatremia.
Sedatives	triazolam	↑ triazolam	Co-administration is contraindicated.
*For details, please refer to Section 12.3: Pharmacokinetics, Drug Interaction Studies of the Prescribing Information.			

Section 12.3: Pharmacokinetics:[1]

Drug Interaction Studies: Table 2 summarizes key findings from Drug-Drug Interaction (DDI) studies described in Section 12.3 of the XOCOVA Prescribing Information.

Table 2. Summary of Drug-Drug Interaction Findings with Ensitrelvir.[1]

Interaction Category	Findings
Clinical Drug Interaction Studies	
Effect of CYP3A4 Inducers on the PK of Ensitrelvir	
• Strong CYP3A4 Inducers (carbamazepine)	Coadministration with the strong CYP3A inducer carbamazepine (titrated from 100 mg twice daily to 300 mg twice daily over 1 week and then maintained at 300 mg twice daily dose for 11 days with some subjects requiring dose reduction) decreased the AUC of ensitrelvir by approximately 40-45%
• Moderate CYP3A4 Inducers (efcavirenz, bosentan)	Ensitrelvir AUC is predicted to decrease by approximately 28% following concomitant administration with efavirenz (moderate CYP3A4 inducer) and 10% with bosentan (moderate CYP3A4 inducer)
Effect of Ensitrelvir on PK of Other Drugs	
• CYP3A Substrate (Midazolam)[a]	Concomitant administration of midazolam (2-mg single oral dose) with ensitrelvir at the clinical dose (375 mg on Day 1 and 125 mg on Days 2-5) on Day 5 resulted in an approximately 2.80-fold increase in C_{max} and a 6.77-fold increase in $AUC_{0\text{-}inf}$ of midazolam compared to midazolam administered alone.
• Corticosteroid (Dexamethasone)[b]	Concomitant administration of dexamethasone (1-mg single dose) with ensitrelvir (750 mg on Day 1 and 250 mg on Days 2-5, two fold of the recommended dose) on Day 5 and administered alone on Day 9 (5 days after the last ensitrelvir dose) and Day 14 (10 days after the last ensitrelvir dose) resulted in an approximately 1.47-fold increase in C_{max} and a 3.47-fold increase in $AUC_{0\text{-}inf}$ of dexamethasone on Day 5, a 1.24-fold increase in C_{max} and 2.38-fold increase in $AUC_{0\text{-}inf}$ on Day 9, and a 1.17-fold increase in C_{max} and a 1.58-fold increase in $AUC_{0\text{-}inf}$ on Day 14, compared to dexamethasone administered alone.
• P-gp Substrate (Digoxin)[c]	Concomitant administration of ensitrelvir (500-mg single dose, not a recommended dosage of ensitrelvir) with a single oral dose of a transporter cocktail containing 0.25 mg digoxin resulted in a 2.17-fold increase in C_{max} and 1.31-fold increase in $AUC_{0\text{-}inf}$ of digoxin.
• BCRP Substrate (Rosuvastatin)[c]	Concomitant administration of ensitrelvir (500-mg single dose, not a recommended dosage of ensitrelvir) with a single oral dose of a transporter cocktail containing 2.5 mg rosuvastatin resulted in a 1.97-fold increase in C_{max} and 1.65-fold increase in $AUC_{0\text{-}inf}$ of rosuvastatin
• Other Drugs	No clinically significant differences in the pharmacokinetics of the following drugs were observed following concomitant use with ensitrelvir: prednisolone (CYP3A4 substrate), combined oral contraceptives containing ethinyl estradiol and drospirenone (CYP3A4 substrates), itraconazole (a strong CYP3A inhibitor and P-gp inhibitor), metformin (OCT1 and MATE1 substrate), and coproporphyrin I (an endogenous OATP1B substrate).
***In Vitro* Drug Interaction Studies**	
Transporter Systems	Ensitrelvir is a substrate of P-gp and BCRP, but not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2-K. Ensitrelvir inhibited P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, and MATE1, but no clinically significant interactions are expected between ensitrelvir and OCT2, OAT1, OAT3, and MATE1.

Interaction Category	Findings
Cytochrome P450 Enzymes	Ensitrelvir exhibits a time-dependent inhibitory effect on CYP3A. Ensitrelvir inhibits CYP2C8, but is not expected to cause clinically significant interactions. Ensitrelvir does not inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP2D6. Ensitrelvir induces CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4, but is not expected to cause clinically significant interactions.
Uridine diphosphate-glucuronosyl transferase (UGT) enzymes	Ensitrelvir does not inhibit UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15.

Abbreviations: AUC, area under the plasma concentration-time curve; $AUC_{0\text{-inf}}$, area under the plasma concentration-time curve from time 0 extrapolated to infinity; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; CYP, cytochrome P450; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; PK, pharmacokinetics; UGT, uridine diphosphate-glucuronosyl transferase.[a] Ensitrelvir was dosed at 375 mg on Day 1 and 125 mg on Days 2-5. [b] Ensitrelvir was dosed at 750 mg on Day 1 and 250 mg on Days 2-5, two-fold of the recommended dose. [c] Ensitrelvir was dosed at 500 mg single dose, not a recommended dosage of ensitrelvir.

Please read the attached XOCOVA FPI. 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

3. CLINICAL STUDIES

Effect On Combined Oral Contraceptives

Phase 1 DDI Study on the Effects of Combined Oral Contraceptives (Ethinyl Estradiol/Drospirenone)

Study Design

Shimizu et al. (2026) conducted a phase 1, single-arm, open-label study (NCT06775730) between September 11, 2024 to April 7, 2025, evaluating the effect of ensitrelvir on the PK of combined oral contraceptives (COCs; ethinyl estradiol [EE] 0.02 mg and drospirenone [DRSP] 3 mg) in 24 healthy premenopausal women aged 18-35 years.[9]

The study excluded women who were pregnant or breastfeeding. Women of childbearing potential required a negative pregnancy test within 24 hours prior to dosing, no oral contraceptive use for ≥28 days, and use of a highly effective contraceptive method during treatment and for ≥14 days after the last dose; prior use of injectable, implantable, or intrauterine hormonal contraceptives was excluded.[9]

Participants received COC once daily on Days 1–24 (fasted on Days 18–24). Ensitrelvir was coadministered at 375 mg on Day 20, followed by 125 mg once daily on Days 21–24. Plasma EE and DRSP concentrations were assessed on Days 19 (reference), 20, and 24, and ensitrelvir concentrations were measured on Days 20 and 24.[9]

The primary endpoint was evaluation of C_{max}, T_{max}, and $AUC_{0\text{-}\tau}$ over the 24-hour dosing interval.[9]

Results

As shown in **Table 3**, coadministration with ensitrelvir had no meaningful effect on EE exposure, with PK parameters remaining within the prespecified no-effect range (0.80–1.25). The median T_{max} for EE on days 19, 20, and 24 was 1.50 h, 1.52 h, and 1.45 h, respectively. Drospirenone exposure increased following multiple doses of ensitrelvir (Day 24) exceeding the prespecified no-effect range

(0.80–1.25); however, this increase was deemed not clinically meaningful. The median T_{max} for DRSP on Days 19, 20, and 24 was 1.51 h, 1.49 h, and 1.50 h, respectively. Ensitrelvir exposure was higher following multiple dosing (Day 24) compared with a single dose (geometric mean C_{max}: 22.1 vs 18.2 µg/mL; $AUC_{0-\tau}$: 418.6 vs 307.3 µg·h/mL).[9]

Table 3. Parameters and GMR for EE and DRSP (PK parameter set).[9]

	Parameter	Day 24[a] vs Day 19 GLS mean	Day 24 [a] vs Day 19 (Primary) GMR (90%CI)	Day 20 vs Day 19 GLS mean	Day 20 vs Day 19 (Exploratory) GMR (90% CI)	Interpretation[b]
EE (n=23)	$AUC_{0-\tau}$	662.1 pg·h/mL vs. 616.5 pg·h/mL	1.07 (0.98–1.18)	628.7 pg·h/mL vs. 616.5 pg·h/mL	1.02 (0.99–1.05)	Within no-effect range
EE (D 19 n=22/ D 24 n=23)	C_{max}	77.4 pg/mL vs. 68.9 pg/mL	1.12 (1.04–1.21)	74.3 pg/mL vs. 69.3 pg/mL	1.07 (1.01–1.14)	Within no-effect range
DRSP (n=23)	$AUC_{0-\tau}$	1062 ng·h/mL vs. 588.5 ng·h/mL	1.80 (1.69–1.93)	649.2 ng·h/mL vs. 588.5 ng·h/mL	1.10 (1.07–1.14)	Increased exposure on Day 24
DRSP	C_{max} (n=23/ 22)	77.6 ng/mL vs. 51.8 ng/mL	1.50 (1.38–1.63)	52.3 ng/mL vs. 51.8 ng/mL	1.01 (0.93–1.10)	Increased exposure on Day 24

Abbreviations: $AUC_{0-\tau}$, area under the plasma concentration-time curve over the dosing interval τ; CI, confidence interval; C_{max}, maximum plasma concentration; D, Day; DRSP, drospirenone; EE, ethinyl estradiol; GLS, geometric least squares; GMR, geometric mean ratio; PK, pharmacokinetic.
[a] Day 24 is ensitrelvir Day 5.
[b] When the 90% CI of the GMR was within the range of 0.80–1.25.

Safety
Treatment-emergent adverse events (TEAEs) were reported in 58.3% (14/24) of participants; most were mild in severity. No deaths, serious TEAEs, or TEAEs leading to treatment discontinuation were reported. The most common TEAEs reported in ≥2 participants were headache (16.7%), dizziness (12.5%), and constipation (12.5%). TEAEs related to COCs occurred in 16.7% (4/24) of participants, whereas TEAEs related to ensitrelvir occurred in 29.2% (7/24) of participants.[9]

Effect On CYP3A Substrates

Phase 1 PK Study

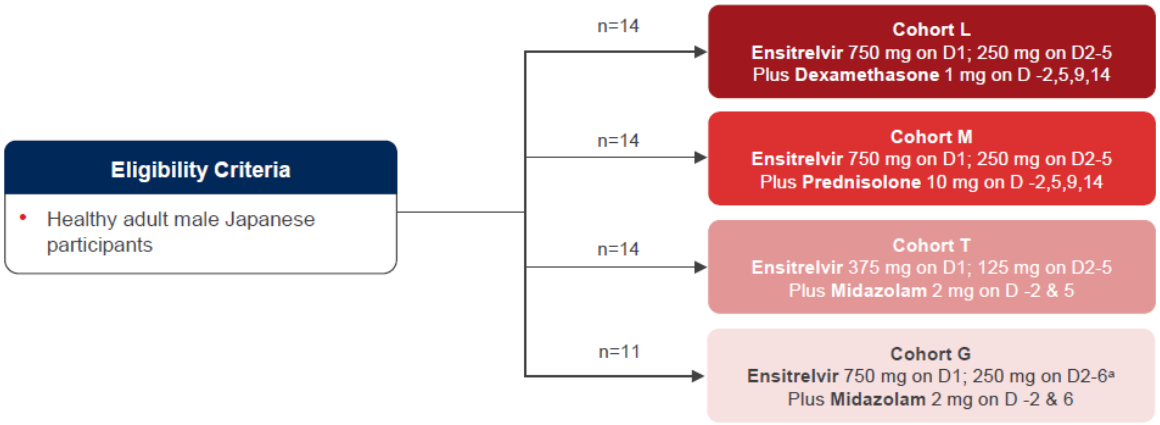
A Phase 1, multicenter, double-blind, randomized, placebo-controlled study conducted in Japan (jRCT2031210202) evaluated the PK, tolerability, and safety of single and multiple ascending oral doses of ensitrelvir in healthy adult male participants that were predominantly Japanese and some white. The phase 1 study consisted of multiple parts, several of which investigated the drug interaction potential of ensitrelvir (375/125 mg and 750/250 mg) with the CYP3A substrates midazolam, dexamethasone, and prednisolone (**Figure 1**).[10,11,13]

Study Design

A DDI analysis of the effects of ensitrelvir 750/250 mg on the PK of midazolam was published by **Shimizu et al. 2022** (**Figure 1**; cohort G).[10]

A separate DDI analysis of the effects of ensitrelvir on the PK of midazolam, dexamethasone, and prednisolone was subsequently published by **Shimizu et al. 2023** (**Figure 1**; cohorts T, L, and M).[11]

Figure 1. Study Designs of DDI Analyses in the Phase 1 Study.[10,11]



Abbreviations: D, day; DDI, drug-drug interaction.
[a]Corresponding placebo was administered.[10]

Results

Coadministration with Dexamethasone:[10,11]

- Coadministration of dexamethasone 1 mg with ensitrelvir 750/250 mg resulted in increased dexamethasone exposure. On Day 5, the geometric least squares (GLS) mean ratios (ensitrelvir + dexamethasone vs dexamethasone alone) were: C_{max}: 1.47-fold, $AUC_{0\text{-last}}$: 3.18-fold, and $AUC_{0\text{-inf}}$: 3.47-fold.
- The magnitude of this effect decreased over time. On Day 9, the corresponding GLS mean ratios were: C_{max}: 1.24-fold, $AUC_{0\text{-last}}$: 2.45-fold, and $AUC_{0\text{-inf}}$: 2.38-fold. By Day 14, the ratios further declined to 1.17-fold, 1.56-fold, and 1.58-fold, respectively (see **Table 4**).

Coadministration with Prednisolone:[10,11]

- Coadministration of prednisolone 10 mg with ensitrelvir 750/250 mg resulted in changes in prednisolone exposure. On Day 5, the GLS mean ratios (ensitrelvir + prednisolone vs prednisolone alone) were: C_{max}: 1.11-fold, $AUC_{0\text{-last}}$: 1.24-fold, and $AUC_{0\text{-inf}}$: 1.25-fold.[10]
- Based on these results, no clinically meaningful effect on prednisolone PK was observed (see **Table 4**).

Coadministration with Midazolam (CYP3A substrate):[10,11]

- Coadministration of midazolam 2 mg with ensitrelvir 750/250 mg (Day 6) increased midazolam exposure, with C_{max}: 2.78-fold, $AUC_{0\text{-last}}$: 7.23-fold, and $AUC_{0\text{-inf}}$: 8.80-fold.
- At the ensitrelvir 375/125 mg regimen (suggested therapeutic dose; Day 5), the increases were: C_{max}: 2.80-fold, $AUC_{0\text{-last}}$: 6.90-fold, and $AUC_{0\text{-inf}}$: 6.77-fold, respectively, compared to midazolam alone.
- These findings demonstrate strong CYP3A inhibition by ensitrelvir at both dosing regimens (see **Table 4**).

Table 4. Effect of Ensitrelvir on the Pharmacokinetics of CYP3A Substrates.[10,11]

Parameter	N	GLS mean (Day – 2)	N	GLS mean (Day 5)	N	GLS mean (Day 9)	N	GLS mean (Day 14)	GLS mean ratio (90% CI) (Day 5/Day – 2)	GLS mean ratio (90% CI) (Day 9/Day – 2)	GLS mean ratio (90% CI) (Day 14/Day – 2)
	Dexamethasone alone		Dexamethasone with ensitrelvir 750/250 mg[a]						Dexamethasone with ensitrelvir 750/250 mg[a]/ dexamethasone alone		
C_{max} (ng/mL)	14	11.4	14	16.9	14	14.2	14	13.4	1.4737 (1.3037-1.6660)	1.2376 (1.0948-1.3991)	1.1725 (1.0372-1.3255)
$AUC_{0\text{-last}}$ (ng • h/mL)	14	45.21	14	143.9	14	110.7	14	70.56	3.1840 (2.9607-3.4240)	2.4480 (2.2764-2.6326)	1.5608 (1.4514-1.6785)
$AUC_{0\text{-inf}}$ (ng • h/mL)	13	51.73	11	179.3	14	123.0	11	81.70	3.4666 (3.2318-3.7184)	2.3769 (2.2263-2.5377)	1.5792 (1.4704-1.6960)
	Prednisolone alone		Prednisolone with ensitrelvir 750/250 mg[a]						Prednisolone with ensitrelvir 750/250 mg[a]/ prednisolone alone		
C_{max} (ng/mL)	14	243	14	270	14	266	14	241	1.1141 (1.0035-1.2369)	1.0953 (0.9865-1.2160)	0.9927 (0.8941-1.1021)
$AUC_{0\text{-last}}$ (ng • h/mL)	14	1042	14	1293	14	1161	14	1070	1.2408 (1.2073-1.2752)	1.1142 (1.0842-1.1451)	1.0267 (0.9990-1.0552)
$AUC_{0\text{-inf}}$ (ng • h/mL)	14	1088	14	1358	14	1223	14	1131	1.2476 (1.2176-1.2784)	1.1243 (1.0973-1.1521)	1.0396 (1.0146-1.0653)
	Midazolam alone		Midazolam with ensitrelvir 375/125 mg[b]						Midazolam with ensitrelvir 375/125 mg[b]/ midazolam alone		
C_{max} (ng/mL)	14	12.6	14	35.2	NA	NA	NA	NA	2.8012 (2.3798-3.2971)	NA	NA
$AUC_{0\text{-last}}$ (ng • h/mL)	14	23.35	14	161.1	NA	NA	NA	NA	6.9011 (6.2722-7.5931)	NA	NA
$AUC_{0\text{-inf}}$ (ng • h/mL)	14	24.08	14	163.0	NA	NA	NA	NA	6.7685 (6.1572-7.4404)	NA	NA
	N	GLS mean (Day – 2)	N	GLS mean (Day 6)					GLS mean ratio (90% CI) (Day 6/Day – 2)		
	Midazolam alone		Midazolam with ensitrelvir 750/250 mg[c]						Midazolam with ensitrelvir 750/250 mg[c]/ midazolam alone		
C_{max} (ng/mL)	8	16.2	7	44.9					2.7763 (2.3341-3.3022)		
$AUC_{0\text{-last}}$ (ng • h/mL)	8	34.70	7	250.8					7.2293 (5.5817-9.3632)		
$AUC_{0\text{-inf}}$ (ng • h/mL)	8	35.69	5	314.1					8.8002 (6.7061-11.5484)		

Abbreviations: $AUC_{0\text{-inf}}$, area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing; CI, confidence interval; C_{max}, maximum plasma concentration; GLS, geometric least square.
[a]Multiple once-daily doses with 750 mg as the loading dose on Day 1 and 250 mg as the maintenance dose on Days 2-5.
[b]Multiple once-daily doses with 375 mg as the loading dose on Day 1 and 125 mg as the maintenance dose on Days 2-5.
[c]Multiple once-daily doses with 750 mg as the loading dose on Day 1 and 250 mg as the maintenance dose on Days 2-6.

INTERACTION WITH DRUG TRANSPORTERS

The DDI potential of ensitrelvir with the drug transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, multidrug and toxin extrusion (MATE) 1, and MATE2-K were evaluated in an *in vitro* study using the Caco-2 and human embryonic kidney (HEK) 293 cell systems. Based on the *in vitro* results, a clinical DDI study was conducted to evaluate the effect of ensitrelvir on the PK of P-gp, BCRP, OATP1B1, OATP1B3, and OCT1 substrates.[12]

In Vitro Study

Study Design

The *in vitro* study evaluated ensitrelvir as a substrate and inhibitor of multiple drug transporters using Caco-2 cells (P-gp and BCRP) and HEK293 cells expressing OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2-K. Transporter substrate and inhibition potential were assessed using radiolabeled ensitrelvir and established probe substrates in the presence and absence of selective transporter inhibitors.[12]

Results

The *in vitro* results demonstrated that:

- Ensitrelvir is a substrate of P-gp and BCRP, as indicated by reduced transport in the presence of selective inhibitors.[12]
- Ensitrelvir was not identified as a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K.[12]

- Inhibitory effect >50%d was observed for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE1 at the highest concentrations of ensitrelvir.[12]
- Less than 50% inhibitory effect was observed for MATE2-K at the highest concentrations of ensitrelvir (IC_{50} >250 μmol/L).[12]

According to the drug interaction guideline in Japan, the predicted values of the DDI potential of these drug transporters indicated that the therapeutic dose of ensitrelvir (375/125 mg) may affect the PK of substrates for P-gp, BCRP, OATP1B1, OATP1B3, and OCT1, with slight DDI potential for OAT3.[12]

Based on these findings, a clinical DDI study was conducted to evaluate whether transporter inhibition observed *in vitro* translated into clinically relevant effects.

Clinical DDI Study

Study Design

The clinical DDI study was a single-center, single-arm, open-label study conducted in 14 healthy Japanese male participants aged 20-55 years (jRCT2031210595) to assess the DDI potentials of ensitrelvir with drug transporters by using a cocktail approach with digoxin (P-gp substrate), rosuvastatin (BCRP, OATP1B1, and OATP1B3 substrate), and metformin (OCT1 substrate).[12,14]

Participants received a single oral dose of a substrate cocktail consisting of digoxin 0.25 mg, rosuvastatin 2.5 mg, and metformin 500 mg on Day 1. After a 10-day washout period, ensitrelvir 500 mg was coadministered with the same substrate cocktail on Day 11. Blood samples were collected before dosing and up to 96 hours after administration on Days 1 and 11 for determination of plasma drug concentrations.[12]

Results

Coadministration with Digoxin (P-gp substrate):[12]

- When a single 500 mg dose of ensitrelvir was coadministered with digoxin, the GLS mean ratios (ensitrelvir + digoxin vs digoxin alone) were: C_{max}: 2.17-fold, $AUC_{0\text{-last}}$: 1.30-fold, and $AUC_{0\text{-inf}}$: 1.31-fold. Mean plasma digoxin concentrations were higher following coadministration with ensitrelvir compared with digoxin alone (see **Table 5**).

Coadministration with Rosuvastatin (BCRP, OATP1B1, OATP1B3 substrate):[12]

- When ensitrelvir 500 mg was coadministered with rosuvastatin, the GLS mean ratios were: C_{max}: 1.97-fold, $AUC_{0\text{-last}}$: 1.64-fold, and $AUC_{0\text{-inf}}$: 1.65-fold. Mean plasma rosuvastatin concentrations were higher with ensitrelvir coadministration compared with rosuvastatin alone (see **Table 5**).

Coadministration with Metformin (OCT1 substrate):[12]

- When ensitrelvir 500 mg was coadministered with metformin, the GLS mean ratios were: C_{max}: 1.03-fold, $AUC_{0\text{-last}}$: 1.02-fold, and $AUC_{0\text{-inf}}$: 1.02-fold. These results indicate no meaningful effect of ensitrelvir on metformin PK (see **Table 5**).

Table 5. Clinical DDI Study: Effect of Ensitrelvir on Drug Transporters.[12]

	GLS Mean				GLS Mean Ratio (90% CI)[a]
Parameter	**N**	**Digoxin[b] (Without Ensitrelvir)**	**N**	**Digoxin[b] (With Ensitrelvir)**	**(Digoxin With Ensitrelvir/ Digoxin Without Ensitrelvir)**
C_{max} (ng/mL)	14	1.09	14	2.37	2.1682 (1.7212-2.7313)
$AUC_{0\text{-last}}$ (ng • h/mL)	14	14.23	14	18.56	1.3038 (1.1482-1.4804)
$AUC_{0\text{-Inf}}$ (ng • h/mL)	13	16.85	11	22.09	1.3110 (1.1314-1.5190)
Parameter	**N**	**Rosuvastatin[c] (Without Ensitrelvir)**	**N**	**Rosuvastatin[c] (With Ensitrelvir)**	**(Rosuvastatin With Ensitrelvir/ Rosuvastatin Without Ensitrelvir)**
C_{max} (ng/mL)	14	4.09	14	8.07	1.9729 (1.7269-2.2538)
$AUC_{0\text{-last}}$ (ng • h/mL)	14	37.28	14	61.3	1.6443 (1.4686-1.8411)
$AUC_{0\text{-Inf}}$ (ng • h/mL)	14	37.92	14	62.41	1.6460 (1.4709-1.8418)
Parameter	**N**	**Metformin[d] (Without Ensitrelvir)**	**N**	**Metformin[d] (With Ensitrelvir)**	**(Metformin With Ensitrelvir/ Metformin Without Ensitrelvir)**
C_{max} (ng/mL)	14	1040	14	1070	1.0291 (0.9143-1.1583)
$AUC_{0\text{-last}}$ (ng • h/mL)	14	6504	14	6660	1.0240 (0.9386-1.1171)
$AUC_{0\text{-Inf}}$ (ng • h/mL)	14	6672	14	6809	1.0206 (0.9363-1.1124)

Abbreviations: $AUC_{0\text{-Inf}}$, area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing; CI, confidence interval; C_{max}, maximum plasma concentration; DDI, drug-drug interaction; GLS, geometric least square.
[a]Analysis is based on the analysis of variance model.
[b]Substrate of P-gp.
[c]Substrate of BCRP, OATP1B1, and OATP1B3.
[d]Substrate of OCT1.

4. ADDITIONAL RESOURCE: NON-SHIONOGI

The Liverpool COVID-19 Drug Interactions website is an online drug interaction resource based on publicly available data and may contain additional information regarding potential interactions involving ensitrelvir and select medications. This site is independently owned, and the content is not reviewed, controlled, or endorsed by Shionogi Inc. No clinical advice is provided or implied; healthcare providers should exercise clinical judgment, which may include consideration of factors beyond pharmacokinetic interactions, based on the individual patient and clinical context. The resource is accessible at: COVID-19 Drug Interactions Checker

5. LITERATURE SEARCH, ABBREVIATIONS, & REFERENCES

LITERATURE SEARCH

As of May 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has identified additional relevant references regarding information on drug-drug interactions with ensitrelvir. The references below reflect the authors' independent evaluations and conclusions and may include information that is inconsistent with the XOCOVA Full Prescribing Information or describes off-label use. Shionogi does not recommend the use of XOCOVA in any manner other than as described in the XOCOVA Full Prescribing Information. For your review, these references are listed in the bibliography that follows:

- Havens JP, Kang N, Chung L, et al. Implementation of an Online Drug-Drug Interaction Screener for the STRIVE Ensitrelvir Trial for COVID-19. *Open Forum Infect Dis*. 2025;12(7):ofaf327. Published 2025 Jun 11. doi:10.1093/ofid/ofaf327. [Web Link]
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- Naganawa H, Katada Y, Nakagawa S, et al. Influence of ensitrelvir or nirmatrelvir/ritonavir on tacrolimus clearance in kidney transplant recipients: a single-center case series. *J Pharm Health Care Sci*. 2024;10(1):37. doi: 10.1186/s40780-024-00361-x. [Web Link]
- Horiuchi K, Koshimichi H, Matsuzaki T, et al. No change of pharmacokinetics of metformin by concomitant use of ensitrelvir. Poster presented at: ID Week 2022. October 19-23, 2022. Washington, DC.
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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.

This letter may include off-label information. Shionogi does not recommend the use of XOCOVA in any manner other than as described in the XOCOVA Full Prescribing Information

ABBREVIATIONS

3CL	3-chymotrypsin-like
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AUC	Area Under the Curve
$AUC_{0\text{-inf}}$	Area Under the Plasma Concentration–Time Curve from Time Zero to Infinity
$AUC_{0\text{-last}}$	Area Under the Plasma Concentration–Time Curve from Time Zero to Last Measurable Concentration
$AUC_{0-\tau}$	Area Under the Plasma Concentration–Time Curve over the Dosing Interval
BCRP	Breast Cancer Resistance Protein
C_{max}	Maximum Plasma Concentration
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CYP	Cytochrome P450
CYP3A	Cytochrome P450 3A
DRSP	Drospirenone
DDI	Drug-Drug Interaction
EE	Ethinyl Estradiol
FDA	Food and Drug Administration
FPI	Full Prescribing Information
GLS	Geometric Least Squares
GMR	Geometric Mean Ratio
HEK	Human Embryonic Kidney
IC50	Half-Maximal Inhibitory Concentration
MATE	Multidrug and Toxin Extrusion
MTTP	Microsomal Triglyceride Transfer Protein
NIAID	National Institute of Allergy and Infectious Diseases
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
P-gp	P-glycoprotein
PK	Pharmacokinetics
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
STRIVE	**S**trategies and **T**reatments of **R**espiratory **I**nfections and **V**iral **E**mergencies
UGT	Uridine Diphosphate-Glucuronosyltransferase

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ENCLOSURE

XOCOVA® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.