Xocova – Use with Cardiovascular Drugs

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]
- Additionally, 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.[1]
- Drug-drug interactions (DDIs) are frequently reported in patients receiving cardiovascular medications, with many clinically relevant interactions involving commonly used cardiovascular drug classes. Multimorbidity and polypharmacy are common in patients with cardiovascular disease, which increases the likelihood of DDIs. These interactions may require treatment modification, drug substitution, or drug monitoring to reduce the risk of adverse outcomes.[2]
- Prior to prescribing ensitrelvir, review all medications taken by the patient (including prescription and non- prescription medications, vitamins, and supplements) to assess potential DDIs 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 DDIs 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 labelling of concomitant therapies. If a drug or drug class is not listed in the enclosed in **Section 7** of the **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 Trials

- The Phase 3 clinical development program for ensitrelvir (**SCORPIO-PEP**[3] **SCORPIO-HR**[4] and **SCORPIO-SR**[5]) was not designed to evaluate DDIs and results based on the use of cardiovascular treatments are not currently available. Information from these studies is summarized in the **Clinical Trials** section of this letter.

- **Phase 1 Studies:**
  - **Phase 1 Pharmacokinetic Study:** Ensitrelvir inhibits CYP3A with a diverse drug-interaction profile ranging from mild to strong inhibition, as measured by the CYP3A substrates dexamethasone, prednisolone, and midazolam.[6,7]

- ***In Vitro* DDI Study:** *In vitro*, ensitrelvir was shown to be a substrate for P-gp, BCRP, organic anion transporter polypeptide 1B1 (OATP1B1), and organic anion transporter polypeptide 1B3 (OATP1B3).[8]
- **Clinical DDI Study:** In a clinical DDI study, ensitrelvir 500 mg increased the exposures of digoxin (a P-gp substrate) and rosuvastatin (a BCRP, OATP1B1, and OATP1B3 substrate), but did not have an effect on metformin (a substrate of OCT1).[8]

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** (FPI) 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 excerpted sections of the FPI provide details on drug-drug interactions with XOCOVA. Please see the XOCOVA FPI for additional important safety information for XOCOVA.

Section 1: Indications and Usage:

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

Section 4: 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, considered to significantly reduce ensitrelvir plasma concentrations and may be associated with the potential loss of virologic response.[1]

Section 5.2: Risk of Serious Adverse Reactions due to Drug Interactions:

> XOCOVA is a strong CYP3A inhibitor and an inhibitor of P-gp and BCRP.[1]
> - 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 exposure of concomitant medications.[1]
> - In addition, medications that induce CYP3A may decrease concentrations of ensitrelvir, leading to loss of therapeutic effect of XOCOVA.[1]

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. Consider the benefit of XOCOVA and whether the risk of potential drug-drug interactions can be appropriately managed.[1]

Section 7: Drug Interactions:

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.[1]

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.[1]

Section 7.3: Established and Other Potentially Significant Drug Interactions

Section 7.3 Table 1 from the **XOCOVA Full Prescribing Information** provides examples of drugs that are contraindicated with XOCOVA.[1]

- *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.*

Excerpted below is information from Table 1 listing examples of cardiovascular drugs contraindicated with XOCOVA. **See Table 1** in the XOCOVA FPI for the complete examples of drugs contraindicated with XOCOVA.

Excerpted Section of Table 1, XOCOVA FPI:

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

Drug Class	Drug(s) within Class	Effect on Drug Concentration	Clinical Comment
Antiarrhythmics	Quinidine	↑ antiarrhythmic	Co-administration is contraindicated due to potential for cardiac arrhythmias.
Cardiovascular drugs	eplerenone, ivabradine	↑ eplerenone, ivabradine	Co-administration is contraindicated.
HMG-CoA reductase inhibitors (statins)	Simvastatin	↑ simvastatin	Co-administration is contraindicated. Discontinue use of simvastatin at least 12 hours prior to initiation of XOCOVA, during the 5 days of XOCOVA administration, and for 14 days after completing XOCOVA.
Mineralocorticoid receptor antagonists	Finerenone	↑ finerenone	Co-administration is contraindicated due to potential for serious adverse reactions, including hyperkalemia, hypotension, and hyponatremia.
Microsomal triglyceride transfer protein (MTTP) inhibitors	Lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions.

Section 12.3: Pharmacokinetics:[1]

The majority of elimination of ensitrelvir is via the biliary route. The terminal elimination half-life ($t_{1/2}$) after a single oral dose of 20 mg to 2000 mg in healthy adult subjects ranged from 42.2 to 48.1 hours.[1]

Drug Interaction Studies: Table 2 summarizes key findings from 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.

Interaction Category	Findings
• 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.
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.

3. CLINICAL TRIALS

Phase 3 Studies

SCORPIO-PEP (Global Phase 3 Study)

The SCORPIO-PEP study was not designed to evaluate drug-drug interactions, and results based on concomitant use with cardiovascular treatments were not assessed.

Study Design

SCORPIO-PEP (NCT05897541) is a completed, global Phase 3 study that evaluated the safety and efficacy of ensitrelvir vs. placebo in the prevention of symptomatic SARS-CoV-2 infection in HHCs of people who tested positive for COVID-19. SCORPIO-PEP was conducted from June 2023 to September 2024 (see **Appendix – SCORPIO-PEP** for more information on study design, efficacy, and safety results).[9,10]

Concomitant cardiovascular medications were reported in study participants in both arms; however, the study did not assess drug-drug interactions or outcomes based on concomitant cardiovascular medication use.[3]

Relevant Exclusion Criteria

- Participants who had used a strong cytochrome P450 (CYP) 3A inducer within 14 days prior to enrollment were excluded from the study.[3]
- Sensitive CYP3A substrates with a narrow therapeutic index were prohibited from the time of informed consent through 28 days after the first dose of study intervention, such as quinidine.[3]
- Other CYP3A substrates were prohibited from the time of informed consent through 10 days after the last dose of study intervention; examples include: atorvastatin, azelnidipine, dronedarone, eplerenone, felodipine, finerenone, ivabradine, nisoldipine,riociguat, rivaroxaban, and ticagrelor.[3]
- The use of strong CYP3A inducers was prohibited from the time of informed consent through the day after the last study intervention.[3]
- Digoxin and dabigatran, P-gp substrates with a narrow therapeutic index, organic anion transporter 3 (OAT 3) substrates with a narrow therapeutic index, and high-dose rosuvastatin (20 to 40 mg) were prohibited from the time of informed consent through the day after the last dose of study intervention.[3]

SCORPIO-HR (Global Phase 3 Study)

Study Design

The SCORPIO-HR study was not designed to evaluate drug-drug interactions, and results based on concomitant use with cardiovascular treatments were not assessed.

SCORPIO-HR (NCT05305547) is a global Phase 3, multicenter, randomized, double-blind, parallel-group, 24-week clinical study that assessed the clinical and antiviral effects of ensitrelvir (oral once daily for 5 days) vs placebo in nonhospitalized patients with COVID-19 with or without high risk factors for severe COVID-19 (see **Appendix-SCORPIO-HR** for more information on study design, efficacy, and safety results).[11]

This study was conducted across North America, South America, Europe, Asia, and Africa. It is a part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-2 clinical trials portfolio, overseen by the AIDS Clinical Trials Group (ACTG) and supported by the National Institutes of Health (NIH). This study was conducted when Omicron variant infection was predominant and among a mostly vaccinated population.[11,12]

Concomitant cardiovascular medications were reported in study participants in both arms; however, the study did not assess drug-drug interactions or outcomes based on concomitant cardiovascular medication use.[4]

Relevant Exclusion Criteria

- Participants who had used a strong cytochrome P450 (CYP) 3A inducer within 14 days prior to enrollment were excluded from the study.[4]
- Participants who had used amiodarone or vorapaxar within the specified washout periods (180 and 24 days, respectively) before randomization were excluded.[4]
- Prohibited cardiovascular CYP3A substrates included atorvastatin, dronedarone, eplerenone, felodipine, lomitapide, lovastatin, nisoldipine, rivaroxaban, simvastatin, tadalafil, ticagrelor, and tolvaptan.[4]
- Strong CYP3A inducers were prohibited.[4]
- P-gp substrates with a narrow therapeutic index, such as digoxin, and sensitive P-gp substrates, such as aliskiren, were prohibited. High-dose rosuvastatin (20 to 40 mg) was also prohibited, whereas lower doses were permitted.[4]
- CYP3A substrates could be restarted on Study Day 28, whereas sensitive P-gp, BCRP, or OAT3 substrates and strong or moderate CYP3A inducers or strong CYP3A inhibitors could be restarted on Study Day 6.[4]

SCORPIO-SR (Phase 3 Part of Phase 2/3 Study)

Study Design

The SCORPIO-SR study was not designed to evaluate drug-drug interactions, and results based on concomitant use with cardiovascular treatments were not assessed.

SCORPIO-SR (Phase 3) was a multicenter, randomized, double-blind, placebo-controlled clinical study that evaluated the efficacy and safety of oral, once daily 125 mg or 250 mg ensitrelvir vs placebo given for 5 days in patients with mild-to-moderate COVID-19 regardless of risk factors for progressing to severe disease. The trial was conducted in Japan, South Korea, and Vietnam between February to July 2022 during the Omicron BA.1-predominant period (see **Appendix-SCORPIO-SR** for more information on study design, efficacy, and safety results).[13]

Concomitant cardiovascular medications were reported in study participants in receiving ensitrelvir and placebo; however, the study did not assess drug-drug interactions or outcomes based on concomitant cardiovascular medication use.[5]

Relevant Exclusion Criteria

- In SCORPIO-SR participants who had used a strong CYP3A inhibitor or strong CYP3A inducer within 14 days before randomization were excluded.[5]
- CYP3A substrates were prohibited from the time of informed consent/assent through completion of the Day 28 examinations.[5]
- Strong CYP3A inhibitors, strong CYP3A inducers, strong P-gp inhibitors, strong BCRP inhibitors, and susceptible or narrow-therapeutic-range substrates of P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OAT3, and MATE1 were prohibited through 10 days after the last study intervention administration or until discontinuation.[5]

Phase 1 Studies

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 study consisted of multiple parts, several of which investigated the drug interaction potential of ensitrelvir with the CYP3A substrates midazolam, dexamethasone, and prednisolone.[6,7,14]

Study Design

A DDI analysis evaluating the effects of ensitrelvir 750/250 mg on the PK of midazolam 2mg was published by Shimizu et al (n=11).[6] A separate DDI analysis published by Shimizu et al evaluated the effects of ensitrelvir on the PK of midazolam 2 mg (n=14; ensitrelvir 375/125 mg), as well as dexamethasone 1 mg and prednisolone 10 mg (each n=14; ensitrelvir 750/250 mg).[7]

Results

Coadministration with CYP3A substrates demonstrated that ensitrelvir increased exposure of dexamethasone and midazolam. The magnitude of the interaction with dexamethasone decreased over time during continued ensitrelvir administration. In contrast, coadministration with prednisolone resulted in minimal changes in prednisolone pharmacokinetics and was not considered clinically meaningful.[6,7]

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.[8]

***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.[8]

Results

The *in vitro* findings indicated that ensitrelvir is a substrate of P-gp and BCRP and demonstrated inhibitory potential toward several transporters, including P-gp, BCRP, OATP1B1, and OATP1B3.[8] 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 drugs that are substrates of these transporters.[8]

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).[8,15]

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.[8]

Results

- Coadministration with Digoxin (P-gp substrate):[8]
  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 3**).

- Coadministration with Rosuvastatin (BCRP, OATP1B1, OATP1B3 substrate):[8]
  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 3**).

- Coadministration with Metformin (OCT1 substrate):[8]
  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 3**).

Table 3. Clinical DDI Study: Effect of Ensitrelvir on Drug Transporters.[8]

	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 August 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has identified additional relevant references regarding the use of ensitrelvir with cardiovascular drugs. For your review, these references are listed in the bibliography that follows:

Watari R, Tamura N, Yoshida S, Kido Y, Matsuzaki T. Minimal involvement of P-gp and BCRP in oral absorption of ensitrelvir, an oral SARS-CoV-2 3C-like protease inhibitor, in a non-clinical investigation. *J Pharm Sci*. 2024;113(9):2871-2878. doi: 10.1016/j.xphs.2024.06.009. [Web Link]

Horiuchi K, Koshimichi H, Matsuzaki T, et al. Prediction of drug-drug interaction of ensitrelvir as CYP3A substrate using Physiologically-based pharmacokinetic model. Poster presented at: ISSX 2023. September 10-13, 2023. Boston, MA.

Watari R, Sawada H, Hashimoto H, et al. Utility of coproporphyrin-I determination in first-in-human study for early evaluation of OATP1B inhibitory potential based on investigation of ensitrelvir, an oral SARS-CoV-2 3C-like protease inhibitor. *J Pharm Sci*. 2024;113(3):798-805. doi: 10.1016/j.xphs.2023.09.016. Epub 2023 Sep 23. [Web Link]

Yamato M, Kinoshita M, Miyazawa S, Seki M, Mizuno T, et al. Ensitrelvir in patients with SARS-CoV-2: a retrospective chart review. *J Infect Chemother.* 2024;30(9):946-950. doi:10.1016/j.jiac.2024.02.015. [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	3-chymotrypsin-like
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
BCRP	Breast Cancer Resistance Protein
COVID-19	Coronavirus Disease 2019
CYP	Cytochrome P450
CYP3A	Cytochrome P450 3A
DDI	Drug-Drug Interaction
FDA	Food and Drug Administration
GLS	Geometric Least Squares
HEK	Human Embryonic Kidney
IC50	Half-Maximal Inhibitory Concentration
MATE	Multidrug and Toxin Extrusion
MTTP	Microsomal Triglyceride Transfer Protein
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
UGT	Uridine Diphosphate-Glucuronosyltransferase

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ENCLOSURE

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

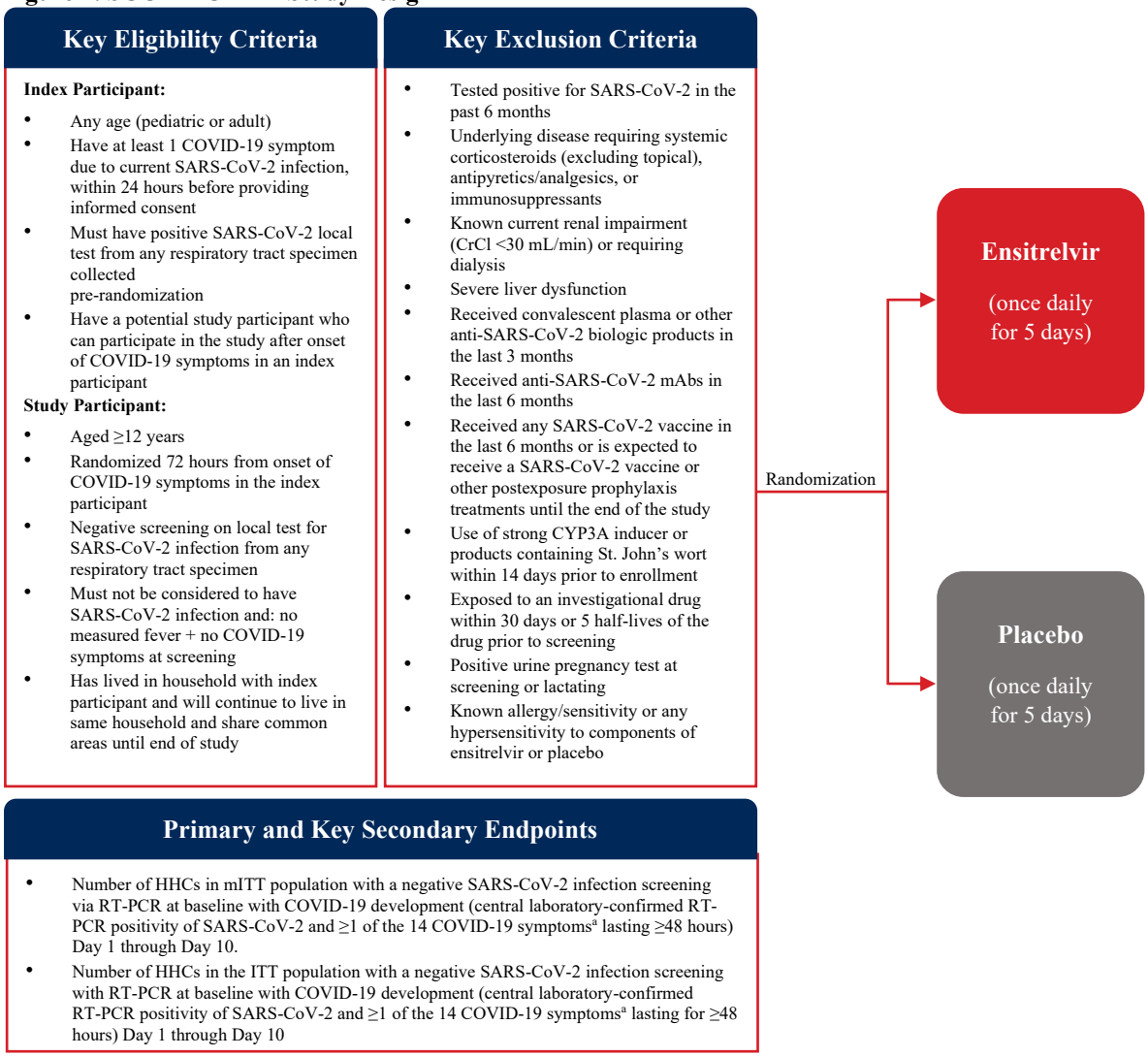
APPENDIX

SCORPIO-PEP (Global Phase 3 Study)

HHC participants with a negative screening test for SARS-CoV-2 infection and no symptoms (mITT population), who were exposed to a person living in their household with symptomatic COVID-19, were randomly assigned in a 1:1 ratio to receive ensitrelvir 125 mg (375 mg on Day 1 and 125 mg on Days 2-5) or placebo once daily for 5 days. Study participants began treatment within 3 days of when the household member with COVID-19 began showing symptoms.[9,10]

The primary endpoint was the proportion of HHCs with COVID-19 development (central laboratory–confirmed RT-PCR positivity of SARS-CoV-2 and ≥1 of the 14 COVID-19 symptoms lasting ≥48 hours) through Day 10 in the mITT population.[9,10]

Figure 1. SCORPIO-PEP Study Design[9,10]



Abbreviations: COVID-19, coronavirus disease 19; CYP3A, cytochrome P450 enzyme 3A4; mITT, modified Intention-to-Treat; RT-PCR, Reverse transcriptase polymerase chain reaction SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Note: mITT population included all randomized HHCs with a central laboratory-confirmed SARS-CoV-2 negative result by RT-PCR at baseline. Patients with local (-) and central (+) were excluded from mITT population.
[a]14 COVID-19 symptoms: Stuffy nose, runny nose, cough, sore throat, low energy or tiredness, feeling hot or feverish, shortness of breath or difficulty breathing, chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, loss of taste and loss of smell

Results

Efficacy

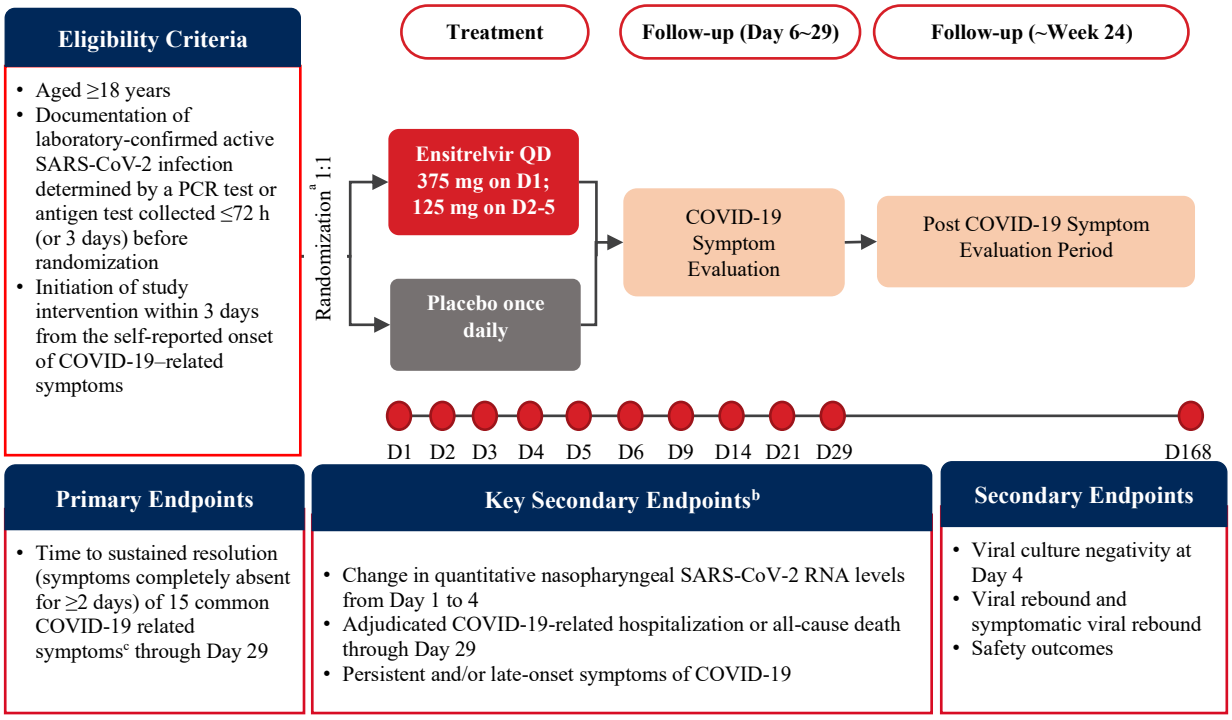
- **Primary Endpoint**: 2.9% (30/1030) of HHCs in the ensitrelvir group developed symptomatic COVID-19 compared to 9.0% (91/1011) of HHC participants on placebo through Day 10, a 67% reduction in the risk of developing COVID-19 (risk ratio: 0.33; 95% CI: 0.22-0.49; $P <$ 0.0001) in uninfected individuals (mITT population) treated after exposure[9]

Safety

- TEAEs occurred in 15.1% (180/1190) of patients in the ensitrelvir group and 15.5% (184/1187) of patients in the placebo group, with 1 event in each group leading to discontinuation of treatment[9]
- 2 serious TEAEs occurred in each group and they were considered to be unrelated to the study drug[9]
- There were no AEs that led to hospitalization and no deaths were observed in either group[9]

SCORPIO-HR (Global Phase 3 Study)

Figure 2. SCORPIO-HR Study Design[11,12]



Abbreviations: COVID-19, coronavirus disease; D, day; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]N=~2000; ~1000 patients in each treatment arm
[b]Primary and key secondary endpoints were tested using a fixed-sequence hierarchical approach at two-sided significance level of 0.05.
[c]15 COVID-19 symptoms: stuffy nose, runny nose, cough, sore throat, low energy or tiredness, feeling hot or feverish, shortness of breath or difficulty breathing, chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, loss of taste and loss of smell.

Results

Efficacy

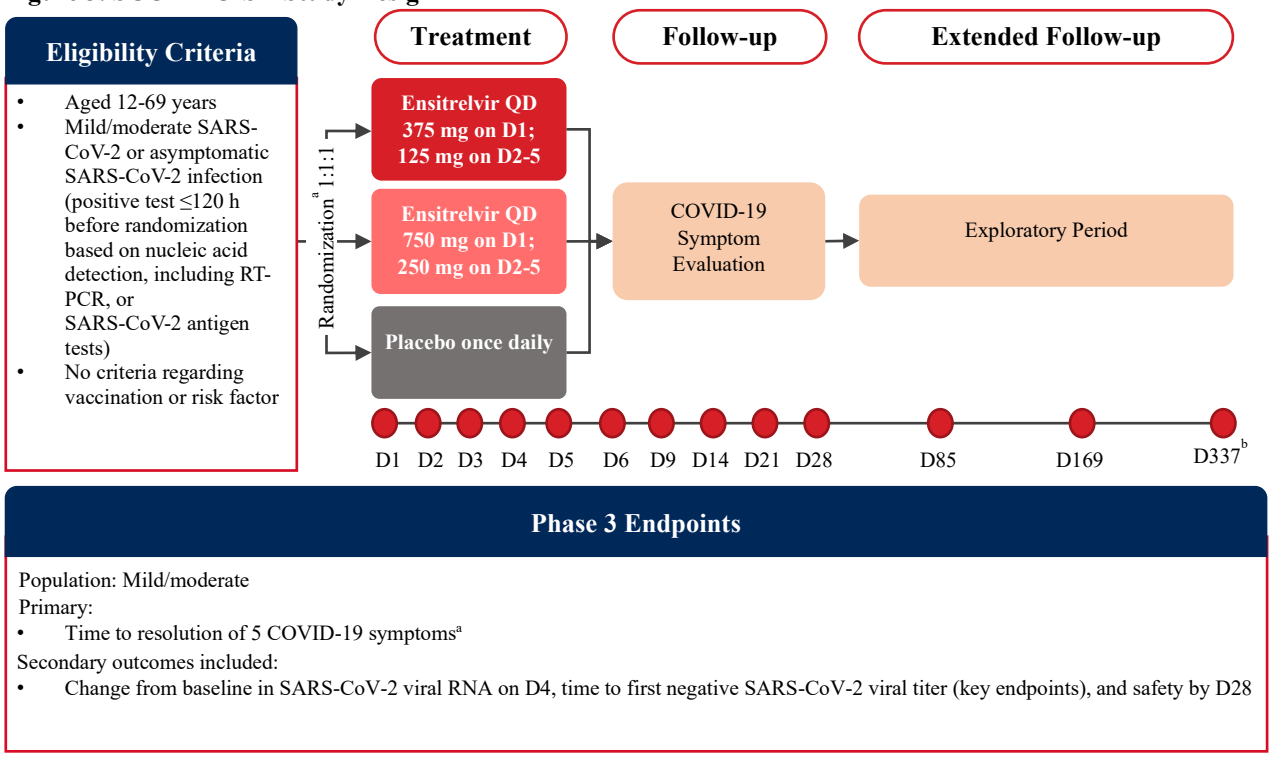
- **Primary Endpoint:** In the modified intent-to-treat (mITT) population, the restricted mean time to sustained symptom resolution was not significantly different between the ensitrelvir (12.5 days) and placebo (13.1 days) groups (difference, -0.6 days; 95% CI: -1.38, 0.19; *P*=0.14).[11]

Safety

- AEs occurred in 638 patients treated with ensitrelvir (61.5%; n=1037), and 635 patients treated with placebo (60.6%; n=1048).[11]
- TRAEs occurred in 86/1037 (8.3%) of patients treated with ensitrelvir and 74/1048 (7.1%) of patients that were given placebo.[11]
- Serious TEAE occurred in 5/1037 (0.5%) of the ensitrelvir-treated participants and 6/1048 (0.6%) of the patients given placebo.[11]
- No serious TRAEs occurred in either group. COVID-19–related hospitalization was observed in 3/1037 (0.3%) ensitrelvir-treated patients and 1/1048 (0.1%) placebo treated participant. No deaths were observed in either group.[11]

SCORPIO-SR (Phase 3 Part of Phase 2/3 Study)

Figure 3. SCORPIO-SR Study Design[13,16]



Abbreviations: COVID-19, coronavirus disease 19; D, Day; RNA, ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]5 COVID-19 symptoms were runny or stuffy nose, sore throat, cough, feeling hot or feverish, and malaise (fatigue).

Results

- **Primary Endpoint:** The time to resolution of 5 COVID-19 symptoms was significantly reduced with ensitrelvir 125 mg vs placebo in the primary analysis population (*P*=0.04 with a Peto-Prentice generalized Wilcoxon test).[13]
- Most treatment-related adverse events (TRAEs) were mild in severity, and a decrease in high-density lipoprotein (HDL) was the most commonly reported TRAE. There were 2 serious adverse events (AEs) reported in the study (1 in the ensitrelvir 125 mg arm and 1 in the placebo arm), both of which were judged as not treatment related.[13]