Xocova - Use with Anticoagulants

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[1]
- 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.[1]
- 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**, **SCORPIO-HR**, and **SCORPIO-SR**) was not designed to evaluate DDIs and results based on the use of antiplatelet therapy with ensitrelvir were not assessed.[2-7] Details about the use of anticoagulants in the Phase 3 clinical trials can be found in **Phase 3 Studies** section of this letter.
- **Phase 1 Clinical Studies:**
  - A Phase 1 clinical study conducted in Japan (jRCT2031210202) evaluated the PK, tolerability, and safety of ensitrelvir in healthy adult male participants. This study consisted of multiple parts, including investigating the drug interaction potential of ensitrelvir (375/125 mg and 750/250 mg) with the CYP3A substrates midazolam, dexamethasone, and prednisolone. CYP3A inhibition by ensitrelvir ranged from mild to strong depending on the substrate.[8,9]
  - A Phase 1, single-center, single-arm, open-label study conducted in Japan (jRCT2031210595) evaluated the drug-drug interaction potential of ensitrelvir with drug transporters in healthy adult male participants using a cocktail approach with digoxin, rosuvastatin, and metformin. Ensitrelvir

increased exposure to digoxin, a P-gp substrate, and rosuvastatin, a BCRP, OATP1B1, and OATP1B3 substrate, but did not affect exposure to metformin, an OCT1 substrate.[10]

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. RELEVANT 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. Please see the XOCOVA FPI for additional important safety information for XOCOVA.

Section 1: Indications and Usage

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.[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 because they may significantly reduce ensitrelvir plasma concentrations, leading to 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 exposures 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, all medications taken by the patient should be assessed for potential drug-drug interactions to determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring (e.g., calcineurin inhibitors).[1] 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.[1] 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.[1] 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 from the XOCOVA Full Prescribing Information provides examples of drugs that are contraindicated with XOCOVA.[1]

- *Although anticoagulant medications are not specifically listed, the list is provided as a guide and is not a comprehensive list of all possible drugs that may interact with XOCOVA.*[1]
- *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.*[1]

Section 12.3 - Pharmacokinetics

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 1** summarizes key findings from Drug-Drug Interaction (DDI) studies described in Section 12.3 of the XOCOVA Prescribing Information

Table 1. 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 TRIALS

The Phase 3 clinical development program for ensitrelvir (**SCORPIO-PEP**, **SCORPIO-HR**, and **SCORPIO-SR**) was not designed to evaluate DDIs and results based on the concomitant use of ensitrelvir and anticoagulants were not assessed.[2-7] Relevant information from clinical trials, including concomitant use of anticoagulants, can be found in **Table 2**.

Table 2. Phase 3 Clinical Trial Overview

Study Name	Trial Status	Study Design	Description	Relevant Exclusion Criteria	Concomitant Use of Anticoagulants
SCORPIO-PEP[2,5,11] (NCT05897541)	Completed	Phase 3, randomized, double-blind, placebo-controlled, multicenter	Evaluating the safety and efficacy of ensitrelvir (oral once daily for 5 days) in the prevention of symptomatic COVID-19 from household contacts of people who tested positive for COVID-19, when compared to placebo (see Appendix-SCORPIO-PEP to see study design and results)	Participants who have used any of the following drugs within 14 days prior to randomization: • Strong CYP3A inducer • Products containing St. John's Wort Use of sensitive CYP3A substrates with narrow therapeutic index was prohibited from the time of informed consent through 28 days after the first dose of study intervention Use of other CYP3A substrates (except sensitive substrates with narrow therapeutic index), including rivaroxaban, were prohibited from the time of informed consent through 10 days after the last dose of study intervention (e.g., Ticagrelor). However, even if a prohibited concomitant therapy was used, the participant should have continued the study procedures according to the specified Schedule of Activities (SoA). Use of the following therapies was prohibited from the time of informed consent/assent to 10 days after the last study intervention administration or at the time of discontinuation. • Strong CYP3A inducers • Organic anion transporter 3 (OAT 3) substrates with a narrow therapeutic index • P-glycoprotein (P-gp) substrates with a narrow therapeutic index	This study was not designed to evaluate drug-drug interactions. Results based on concomitant use of anticoagulants were not assessed. 1/1190 (<0.1%) of the participants that received ensitrelvir in the safety analysis set concomitantly took apixaban during this trial.

Study Name	Trial Status	Study Design	Description	Relevant Exclusion Criteria	Concomitant Use of Anticoagulants
SCORPIO-HR[3,6,12] (NCT05305547)	Completed	Phase 3, randomized, double-blind, placebo-controlled, multicenter	A 24-week clinical study assessed the safety, clinical and antiviral effects of ensitrelvir (oral once daily for 5 days) vs placebo in nonhospitalized patients with confirmed symptomatic COVID-19 with or without high risk factors for severe COVID-19 (see Appendix-SCORPIO-HR to see study design and results)	Participants who have used any of the following drugs within 14 days prior to randomization: • Strong CYP3A inducer • Products containing St. John's Wort Prohibited: • Use of rivaroxaban from the time of consent through Day 28 • Use of strong CYP3A inducers during the study. • OAT-3 substrates with a narrow therapeutic index • P-gp substrates with a narrow therapeutic index, such as digoxin, and sensitive substrates Restart timeline for interacting drugs in the SCORPIO-HR trial is the following (Day 1 is the first day of ensitrelvir or placebo treatment): • CYP3A substrates: Study Day 28 • Sensitive substrate of P-gp or BCRP or OAT3: Study Day 6 • Strong or moderate CYP3A inducer; or strong CYP3A inhibitor: Day 6 o If the inducer or inhibitor is also a CYP3A substrate, then the most conservative timing was used	This study was not designed to evaluate drug-drug interactions. Results based on concomitant use of anticoagulants were not assessed. 12/945 (1.3%) of the participants that received ensitrelvir in the mITT population concomitantly took anticoagulants during this trial • Apixaban: 4/945 (0.4%) • Enoxaparin: 3/945 (0.3%) • Enoxaparin sodium: 1/945 (0.1%) • Rivaroxaban: 1/945 (0.1%) • Nadroparin: 1/945 (0.1%) • Sulodexide: 2/945 (0.2%) • Warfarin: 1/945 (0.1%) Concomitant medications are defined as any medication that started before the date of study Day 1 and ended on or after the date of study Day 1, or were ongoing at that time, or any medication that started on or after the date of study Day 1.

Study Name	Trial Status	Study Design	Description	Relevant Exclusion Criteria	Concomitant Use of Anticoagulants
SCORPIO-SR (Phase 3)[4,7,13,14] (jRCT2031210350)	Completed	Phase 3, multicenter, randomized, double-blind, placebo-controlled	Evaluated the efficacy and safety of oral, once daily 125 mg or 250 mg ensitrelvir vs placebo given for 5 days in participants with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection regardless of risk factors for progressing to severe disease (see Appendix-SR to see study design for the Phase 3 part of the study and results)	Participants who have used any of the following drugs within 14 days prior to randomization: • Strong CYP3A inhibitor • Strong CYP3A inducer • Products containing St. John's Wort Use of the following therapies was prohibited from the time of informed consent/assent to 10 days after the last study intervention administration or at the time of discontinuation. • Strong CYP3A inhibitors • Strong CYP3A inducers • Strong P-gp inhibitors • Strong BCRP inhibitors • The substrates of the following transporters (substrates susceptible to interaction and drugs with a narrow therapeutic range) ○ P-gp ○ BCRP ○ OATP 1B1 ○ OATP 1B3 ○ OCT 1 ○ OAT 3 ○ MATE 1 Use of CYP3A substrates was prohibited from the time of informed consent/assent to the completion of examinations on Day 28. However, even if a prohibited concomitant therapy is used, the participant should continue the study procedures according to the specified SoA as much as possible	This study was not designed to evaluate drug-drug interactions. Results based on concomitant use of anticoagulants were not assessed. 1/1203 (0.1%) of the participants that received ensitrelvir in the safety analysis population concomitantly took apixaban during this trial. Concomitant treatments (concomitant drugs/therapies) were defined as treatments (prescription drugs, over-the-counter drugs, and therapies other than drug therapy) the participants received after the first administration of study intervention.

Abbreviations: BCRP, breast cancer resistance protein; COVID-19, coronavirus disease 2019; CYP3A, cytochrome P450 3A; ITT, intention-to-treat; MATE, Multidrug and toxin extrusion; mg, milligram; mITT, modified intention-to-treat; OAT, Organic anion transporter; OATP, Organic anion transporter polypeptide; OCT, organic cation transporter; p-gp, P-glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoA, Schedule of Activities

4. PHASE 1 DDI STUDIES

Concomitant use of anticoagulants with ensitrelvir was not evaluated during the Phase 1 clinical trials.

Evaluations of DDI Potential of Ensitrelvir with CYP3A Substrates

Study Design

A Phase 1, multicenter, double-blind, randomized, placebo-controlled study conducted in Japan (jRCT2031210202) evaluated the PK, tolerability, and safety of ensitrelvir in healthy adult male participants. This 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.[8,9]

Results

- 42 healthy Japanese adults participated in the trial with mean ages range (SD) from 31.9 (5.1) – 36.0 (7.4) and a mean BMI range from 21.51 (2.24) – 23.20 (1.82) kg/m^2 across the cohorts[8]
- 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. Coadministration with ensitrelvir 750/250 mg had the following effects:[8,9]
  - For dexamethasone 1 mg, C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ increased 1.47-fold, 3.18-fold, and 3.47-fold, respectively, on Day 5[8]. The effect on C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ observed on Day 5 diminished over 10 days after the last ensitrelvir dose was given.[8]
  - For prednisolone 10 mg, C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ increased 1.11-fold, 1.24-fold, and 1.25-fold, respectively, on Day 5[8]
  - For midazolam 2 mg, C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were increased 2.78-fold, 7.23-fold, and 8.80-fold, respectively, on Day 6[9]
- The suggested therapeutic dose of ensitrelvir (375/125 mg) strongly inhibited midazolam 2 mg, as shown by increases in C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of 2.80-fold, 6.90-fold, and 6.77-fold, respectively, on Day 5[8]

Evaluations of DDIs of Ensitrelvir with Transporter Substrates

Study Design

A Phase 1 single-center, single-arm, open-label study was conducted in 14 healthy Japanese male participants aged 20-55 years (jRCT2031210595) to assess the drug-drug interaction 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).[10]

Results

- 14 healthy Japanese adults participated in the trial with a mean (SD) age of 31.7 (10.3) and a mean (SD) BMI of 22.61 (2.71) kg/m^2 [10]
- Ensitrelvir 500 mg increased the exposures of digoxin and rosuvastatin, but did not have an effect on metformin:[10]

- For digoxin 0.25 mg, C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ increased 2.17-fold, 1.30-fold, and 1.31-fold, respectively
- For rosuvastatin 2.5 mg, C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ increased 1.97-fold, 1.64-fold, and 1.65-fold, respectively
- For metformin 500 mg, C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ were unchanged at 1.03-fold, 1.02-fold, and 1.02-fold, respectively

5. LITERATURE SEARCH, ABBREVIATIONS, & REFERENCES

Literature Search

As of June 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) failed to identify any relevant references regarding use of ensitrelvir with anticoagulants. 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

AE	Adverse event	mITT	Modified intention-to-treat
AUC	Area under the plasma concentration-time curve	OAT	Organic anion transporter
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time 0 extrapolated to infinity	OATP	Organic anion transporting polypeptide
$AUC_{0\text{-}last}$	Area under the plasma concentration-time curve from time 0 to last quantifiable concentration	OATP1B1	Organic anion transporting polypeptide 1B1
BCRP	Breast cancer resistance protein	OATP1B3	Organic anion transporting polypeptide 1B3
CI	Confidence interval	OCT	Organic cation transporter
C_{max}	Maximum concentration	P-gp	P-glycoprotein
COVID-19	Coronavirus disease 2019	PK	Pharmacokinetics
CrCl	Creatinine clearance	RNA	Ribonucleic acid
CYP3A	Cytochrome P450 3A	RT-PCR	Reverse transcription polymerase chain reaction
D	Day	SAE	Serious adverse event
DDI	Drug-drug interaction	SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
FDA	U.S. Food and Drug Administration	SD	Standard deviation
FPI	Full Prescribing Information	SoA	Schedule of Activities
HDL	High-density lipoprotein	$t_{1/2}$	Terminal elimination of half-life
HHCs	Household contacts	TEAE	Treatment-emergent adverse event
ITT	Intention-to-treat	TRAE	Treatment-related adverse event
mAbs	Monoclonal antibodies	UGT	Uridine diphosphate-glucuronosyl transferase
MATE	Multidrug and toxin extrusion		

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ENCLOSURE

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

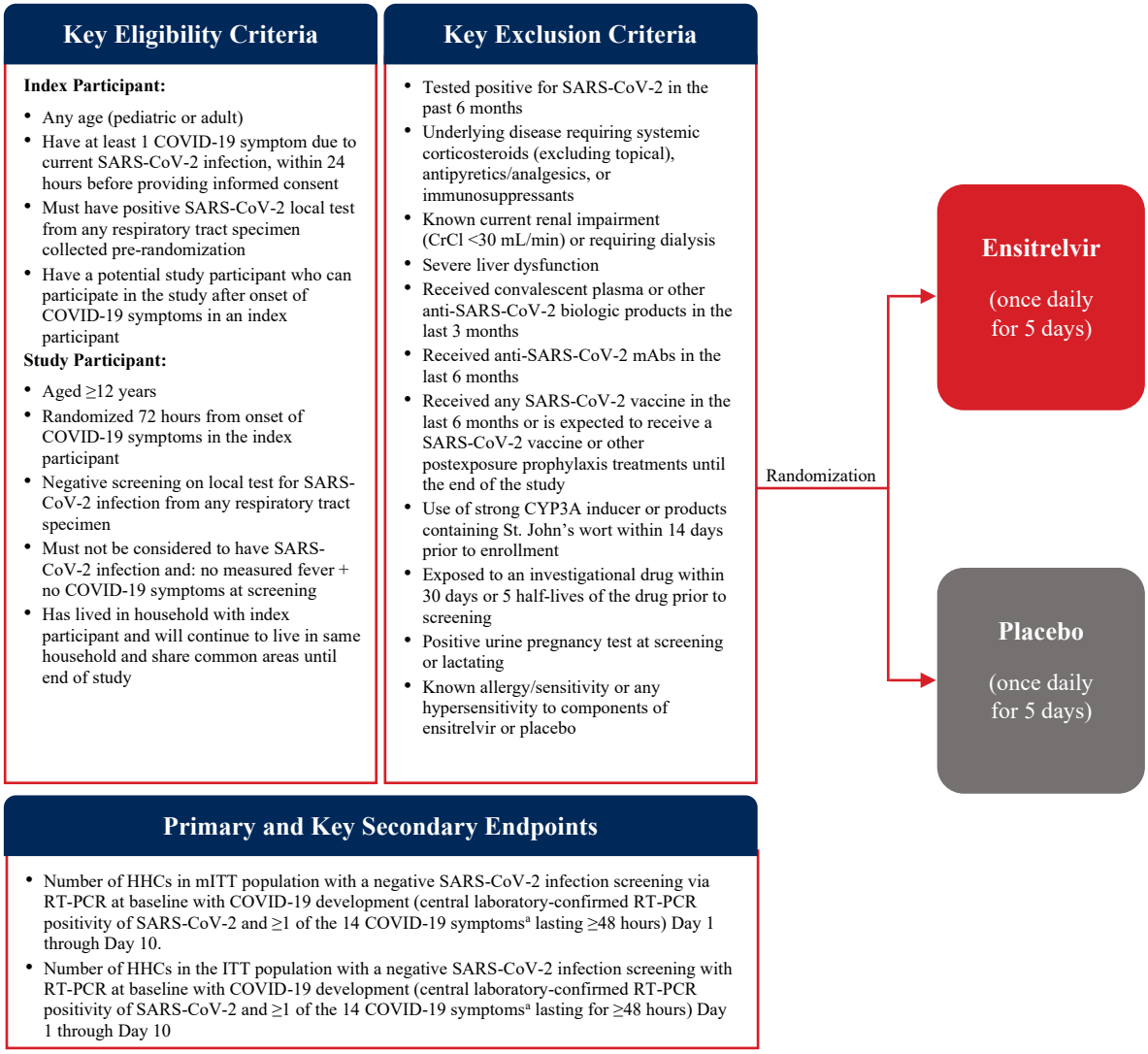
APPENDIX

SCORPIO-PEP (Global Phase 3 Study)

Study Design

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.[2]

Figure 1. SCORPIO-PEP Study Design[2,11]



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

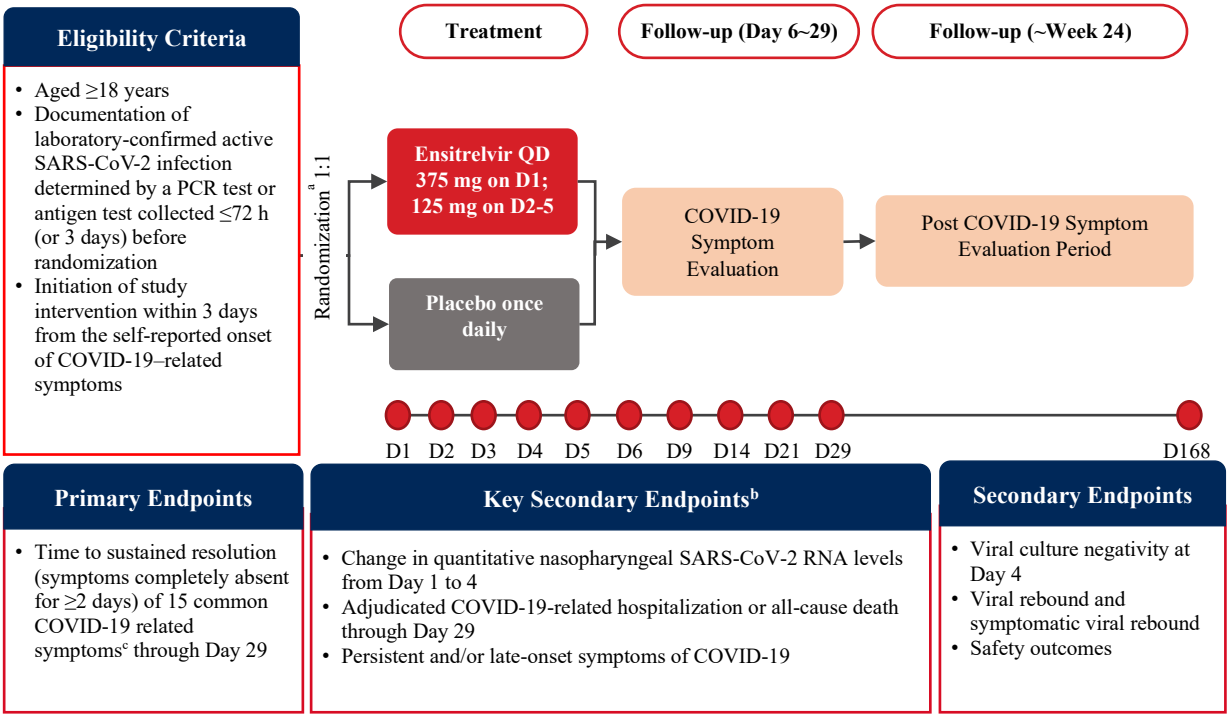
- **Primary Endpoint**: 2.9% (30/1030) of HHCs in the ensitrelvir group developed symptomatic COVID-19 compared to 9.0% (91/1011) of HHC participants on placebo through Day 10, a 67% reduction in the risk of developing COVID-19 (risk ratio: 0.33; 95% CI: 0.22-0.49; $P < 0.0001$) in uninfected individuals (mITT population) treated after exposure[2]

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[2]
- 2 serious TEAEs occurred in each group and they were considered to be unrelated to the study drug[2] There were no AEs that led to hospitalization and no deaths were observed in either group[2]

SCORPIO-HR (Global Phase 3 Study)

Figure 2. SCORPIO-HR Study Design[3,15]



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

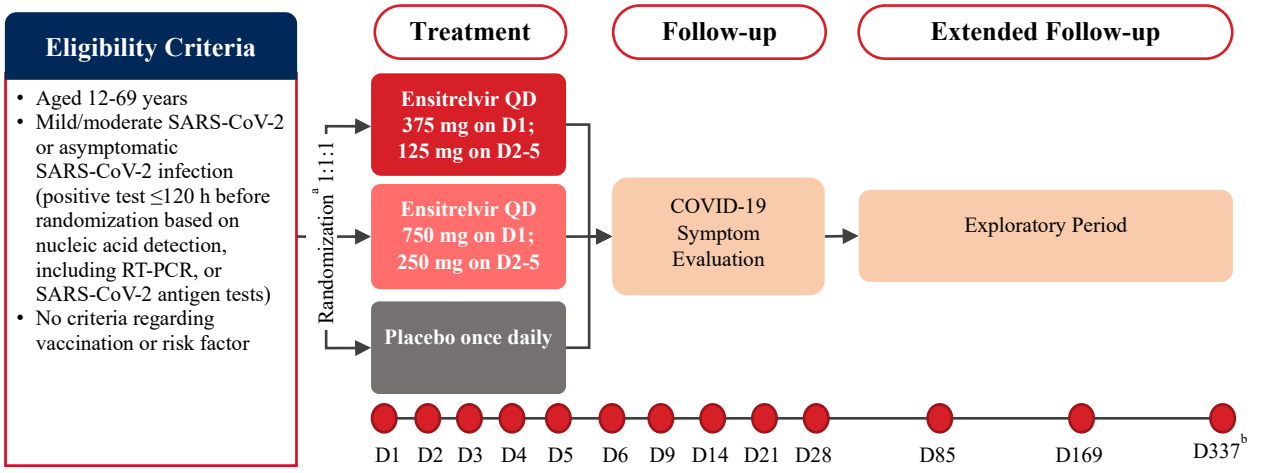
- **Primary Endpoint:** In the modified intent-to-treat (mITT) population, the restricted mean time to sustained symptom resolution was not significantly different between the ensitrelvir (12.5 days) and placebo (13.1 days) groups (difference, -0.6 days; 95% CI: -1.38, 0.19; *P*=0.14).[3]

Safety

- AEs occurred in 638 patients treated with ensitrelvir (61.5%; n=1037), and 635 patients treated with placebo (60.6%; n=1048).[3]
- TRAEs occurred in 86/1037 (8.3%) of patients treated with ensitrelvir and 74/1048 (7.1%) of patients that were given placebo.[3]
- Serious TEAE occurred in 5/1037 (0.5%) of the ensitrelvir-treated participants and 6/1048 (0.6%) of the patients given placebo.[3]
- 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.[3]

SCORPIO-SR (Phase 3 Study)

Figure 3. Phase 2/3 Study, Phase 3 Part[4,14]



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

Efficacy

- **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).[4]

Safety

- Most adverse events (AEs) were mild in severity, and a decrease in high-density lipoprotein (HDL) was the most commonly reported AE and treatment-related adverse event (TRAE). There were 2 serious adverse events (SAE) 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.[4]