Xocova - Use with Immunosuppressants

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]
- *Information from Section 7 Specific to Immunosuppressants:* Ensitrelvir can increase the concentration of voclosporin when co-administered. Co-administration of voclosporin is contraindicated due to potential for acute and/or chronic nephrotoxicity.[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**) were not designed to evaluate drug-drug interactions (DDIs) and results based on the use of ensitrelvir with immunosuppressive treatments are not currently available.[2-4] Details about immunosuppressant use in Phase 3 clinical trials can be found in the **Clinical Trials** section of this document.
    - In the **SCORPIO-PEP** is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of ensitrelvir vs placebo in preventing symptomatic COVID-19 in household contacts (HHCs) who were exposed to a person with SARS-CoV-2 infection.[2]

        - Participants that had an underlying disease requiring systemic corticosteroids (excluding topicals) or immunosuppressive agents were excluded[5]
        - Participants using a strong CYP 3A inducer were also excluded[5]
    - The **SCORPIO-HR** global Phase 3 study 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.[3]
        - Participants were permitted to be in the study if they were taking immunosuppressive medications (for example, drugs to suppress rejection of transplanted organs or to treat rheumatologic and gastrointestinal conditions, such as anti-tumor necrosis factor agents, mycophenolate, and rituximab), but were excluded with use of certain corticosteroids, due to concern for possible DDIs with ensitrelvir[6]
        - Participants were also excluded if they were using a strong CYP 3A inducer within 14 days prior to randomization[7]
    - The **SCORPIO-SR (Phase 3)** clinical study conducted in Asia assessed efficacy and safety of ensitrelvir in a population of patients with mild-to-moderate COVID-19.[4,8]
        - The study included patients who were taking corticosteroids or other immunosuppressive medications Participants who had used a strong CYP 3A inhibitor and strong CYP 3A inducer were excluded[8]
    - **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.[9,10] CYP3A inhibition by ensitrelvir ranged from mild to strong depending on the substrate.[9,10]
        - 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.[11]

Retrospective Studies

- Retrospective studies have described outcomes of ensitrelvir for the treatment of COVID-19 in patients taking immunosuppressants but were not designed to evaluate DDIs. Information from these studies is summarized in the Retrospective Studies section of this letter.[12,13]

Case Presentations

- Several case reports of patients on immunosuppressants who were being treated for COVID-19 with ensitrelvir are summarized in the Case Presentations section of this letter.[14-16]

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 excerpted 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

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.
- 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.[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 FPI provides example(s) 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 immunosuppressants 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:

Table 1. Examples of Immunosuppressant(s) Contraindicated with XOCOVA Due to Risk of Potentially Serious or Fatal Interaction[1]

Drug Class	Examples of Drug within Class	Effect on Drug Concentration	Clinical Comment
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration is contraindicated due to potential for acute and/or chronic nephrotoxicity.

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 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.
Cytochrome P450 Enzymes	Ensitrelvir exhibits a time-dependent inhibitory effect on CYP3A. Ensitrelvir inhibits CYP2C8, but is not expected to cause clinically

Interaction Category	Findings
	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

SCORPIO-PEP (Global Phase 3 Study)

The SCORPIO-PEP study was not designed to evaluate drug-drug interactions and results based on concomitant use of immunosuppressive treatments were not assessed.[2]

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).[2,5]

Relevant Inclusion/Exclusion Criteria
Participants were excluded if any of the following exclusion criteria applied[5]:

- Have an underlying disease requiring systemic corticosteroids (excluding topical), antipyretics/analgesics, or immunosuppressive agents
- Have used any of the following drugs within 14 days prior to enrollment:
  - Strong CYP 3A inducer
  - Products containing St. John's wort

Use of certain CYP3A substrates concomitantly with ensitrelvir was prohibited from the time of informed consent through 10 days after the last dose of study intervention. 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).[17]

Use of sensitive CYP3A substrates with a narrow therapeutic index concomitantly with ensitrelvir was prohibited from the time of informed consent through 28 days after the first dose of study intervention.[17]

Prohibited sensitive CYP3A substrates with narrow therapeutic index included:

- cyclosporine
- sirolimus
- tacrolimus

For efficacy and safety results, please see the **Appendix-SCORPIO-PEP**.

SCORPIO-HR (Global Phase 3 Study)

SCORPIO-HR was not designed to evaluate drug-drug interactions and results based on concomitant use of immunosuppressive treatments were not assessed.[3]

Study Design

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).

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.[3,7,18]

Participants were defined as high risk if they were ≥65 years old or ≥18 years old with ≥1 of the immunocompromising conditions putting them at risk of developing severe COVID-19 based on risk factors determined early in the pandemic. High risk patients were enrolled from throughout the world, excluding the US which only enrolled standard-risk patients. Patients were included if they had 1 of the following immunocompromising conditions or immunosuppressive treatments:[3]

- Receiving chemotherapy or other therapies for cancer
- Hematologic malignancy (active or in remission)
- History of a hematopoietic stem cell or a solid organ transplant
- HIV infection: not on antiretroviral therapy or with CD4+ cell count <200 cells/mm^3
- Combined primary immunodeficiency disorder
- Taking immunosuppressive medications

Relevant Inclusion/Exclusion Criteria
Participants were permitted to be in the study if they were taking immunosuppressive medications (for example, drugs to suppress rejection of transplanted organs or to treat rheumatologic and gastrointestinal conditions, such as anti-tumor necrosis factor agents, mycophenolate, and rituximab). However, patients using specific corticosteroids were excluded due to concerns for possible DDIs with ensitrelvir.[7]

Participants who have used any of the following drugs within 14 days prior to randomization were excluded[7]:

- Strong CYP 3A inducer
- Products containing St. John's Wort

Use of the following drugs concomitantly with ensitrelvir were prohibited:[19]

- Corticosteroids
  - Prednisone and prednisolone were permitted
  - Dexamethasone could be readministered the day after the last dose (Day 6)
    - If dexamethasone was required earlier and during treatment with ensitrelvir for urgent treatment of deteriorating disease, investigators were to be aware of the continuing interaction and increased exposure to dexamethasone
- Some CYP3A substrates including sirolimus and tacrolimus
- Strong CYP3A inducers
- Organic anion transporter (OAT)-3 substrates with a narrow therapeutic index
- P-glycoprotein (P-gp) substrates with a narrow therapeutic index 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):[19]

- 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
  - If the inducer or inhibitor is also a CYP3A substrate, then the most conservative timing was used

Patients receiving concomitant immunosuppressants are summarized in **Table 3** below. However, results based on the use of immunosuppressive treatments were not assessed.[3,19]

Table 3. Patients Taking Concomitant[a] Corticosteroids or Other Immunosuppressive Medications in the mITT population[19]

Medication	Ensitrelvir (N=945) n (%)	Placebo (N=943) n (%)
Methotrexate	2 (0.2)	0
Azathioprine	0	1 (0.1)
Hydroxychloroquine	0	1 (0.1)
Mycophenolate mofetil	1 (0.1)	0
Prednisone	7 (0.7)	6 (0.6)
Prednisolone	2 (0.2)	2 (0.2)
Dexamethasone	1 (0.1)	1 (0.1)
Hydrocortisone	0	2 (0.2)

Abbreviations: mITT, modified intent-to-treat.
[a]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.

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.[19]

For efficacy and safety results of the overall study population, please see the **Appendix-SCORPIO-HR**.

SCORPIO-SR (Phase 3 part of the Phase 2/3 Study)

The SCORPIO-SR study was not designed to evaluate drug-drug interactions and results based on concomitant use of immunosuppressive treatments were not assessed.[4,20]

Study Design

The Phase 3 part of the Phase 2/3, multicenter, randomized, double-blind, placebo-controlled clinical study (SCORPIO-SR [**S**topping **CO**VID-19 p**R**ogression with early **P**rotease **I**nhibit**O**r-**S**tandard **R**isk]); (jRCT2031210350) was conducted in Japan, Vietnam, and South Korea to evaluate the efficacy and safety of ensitrelvir (125 mg and 250 mg) given orally, once daily for 5 days vs placebo in patients aged 12 to <70 years with mild-to-moderate COVID-19 (see **Appendix-SCORPIO-SR)** for more information on study design).[4,8]

Participants who had used any of the following drugs within 14 days prior to randomization were excluded:[21]

- Strong CYP 3A inhibitor
- Strong CYP 3A 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.[21]

- 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.[21]

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[21]

In the intention-to-treat (ITT) population of patients randomized <72 h after disease onset, patients taking corticosteroids or other immunosuppressive medications made up 1.2% (4/347) of the ensitrelvir 125 mg arm (primary analysis population), 0.9% (3/340) of the ensitrelvir 250 mg arm, and 0.9% (3/343) of the placebo arm. In the ITT population of patients randomized within 120 h after disease onset, patients taking corticosteroids or other immunosuppressive medications comprised 0.8% (5/603) of the ensitrelvir 125 mg arm, 0.5% (3/595) of the ensitrelvir 250 mg arm, and 0.7% (4/600) of the placebo arm.[4,20]

For efficacy and safety results of the overall patient population, please see the **Appendix-SCORPIO-SR**.

Phase 1 Studies

Phase 1 DDI Study 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.[9,10]

- Midazolam 2 mg was administered 2 days before starting ensitrelvir (375/125 mg) (Day -2) and co-administered with the last dose of ensitrelvir therapy (Day 5)[10]

Results

- 42 healthy Japanese adults participated in the trial with mean ages range 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[10]
- 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:[9,10]
  - 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[10]. 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 (**Table 4**).[10]
  - 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[10]
  - 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[10]

Table 4. Multiple-Dose Administration of Ensitrelvir on the PK of Dexamethasone[10]

Parameters	Dexamethasone alone (Day - 2)		Dexamethasone with ensitrelvir (Day 5)		5th day after the last ensitrelvir dose (Day 9)		10th day after the last ensitrelvir dose (Day 14)		Dexamethasone with ensitrelvir/dexamethasone alone (Day 5/Day -2)	5^{th} day after last ensitrelvir dose/dexamethasone alone (Day 9/Day -2)	10^{th} day after last ensitrelvir dose/dexamethasone alone (Day 14/Day -2)
	N	GLS mean	N	GLS mean	N	GLS mean	N	GLS mean	GLS mean ratio (90% CI)		
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)
$AUC_{0–last}$ (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)
$AUC_{0–inf}$ (ng·h/mL)	13	51.73	11	179.3	14	123.0	11	81.7	3.4666 (3.2318–3.7184)	2.3769 (2.2263–2.5377)	1.5792 (1.4704–1.6960)

Table adapted from Shimizu R, et al. JAMA Netw. Open. 2023.

Abbreviations: $AUC_{0\text{-}last}$, area under the concentration-time curve to the last measurable concentration; $AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GLS, geometric least square; h, hour; mL, milliliters; ng, nanograms; PK, pharmacokinetics

Phase 1 DDI Study with Drug Transporters

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).[11]

Results

- Ensitrelvir 500 mg increased the exposures of digoxin and rosuvastatin, but did not have an effect on metformin:[11]
  - 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

4. RETROSPECTIVE STUDIES

Yamato et al. 2025 (Retrospective Chart Review)

Study Design

- Single-center retrospective chart review (**Yamato et al. 2025**) evaluated patient characteristics, outcomes and treatment patterns in patients receiving ensitrelvir or remdesivir at Rinku General Medical Center in Japan between November 2022 and August 2024. Patients in the study received oral ensitrelvir 375 mg on Day 1 and 125 mg once a daily on Days 2-5 or IV remdesivir 200 mg on Day 1 and 100 mg once daily from Day 2 and up until Day 10.[12]
- All-cause mortality at Day 28, time to viral clearance up to Day 14 and time to discharge were endpoints assessed in this study. Subgroup analyses evaluated baseline COVID-19 severity, vaccination history and immunosuppressive conditions. Patients with immunosuppressive conditions were those patients with comorbidities including autoimmune disease and malignancies or patients taking concomitant drug therapy such as corticosteroids, methotrexate, rituximab and tacrolimus.[12]

Results

- *This study was not designed to evaluate DDIs.*
- There were 493 patients included in the analysis, 156 patients received ensitrelvir and 337 patients received remdesivir. Immunosuppressive conditions were present in 19.9% of the ensitrelvir group (31/156) and 16.0% of the remdesivir group (54/337). **Table 5** includes additional baseline characteristics pertaining to immunosuppression.[12]

Table 5. Baseline Immunosuppressive Characteristics[12]

Baseline Characteristic	Ensitrelvir n (%) (N=156)	Remdesivir n (%) (N=337)	Overall n (%) (N=493)
Chemotherapy	22 (14.1)	24 (7.1)	46 (9.3)
Immunosuppressive conditions	31 (19.9)	54 (16)	85 (17.2)

- All-cause mortality at Day 28 after IPTW modification was 3.8% and 5.7% for the ensitrelvir and remdesivir groups, respectively (HR: 0.66; 95% CI 0.19-2.29, E=2.4). In a subgroup analysis the non-adjusted all-cause mortality at Day 28 in immunosuppressive conditions was 3.2% (1/31) and 9.3% (3/54) in the ensitrelvir and remdesivir groups, respectively (HR: 0.34; 95% CI 0.04-2.91). The IPTW-adjusted all-cause mortality in immunosuppressive conditions was 5.3% (2.1/40) and 10.1% (4.5/44) in the ensitrelvir and remdesivir groups, respectively (HR: 0.52; 95% CI 0.06-4.51).[12] An analysis of patients taking chemotherapy was not provided.

Yamato et al. 2024 (Retrospective Chart Review)

Study Design

- A single-center, retrospective chart review (**Yamato et al. 2024**) assessed the outcomes of patients treated with ensitrelvir for SARS-CoV-2 infection in the Rinku General Medical Center (Izumisano, Japan) between November 2022 and April 2023. Patients received daily oral treatment with ensitrelvir over 5 days with a 375 mg loading dose on Day 1 and 125 mg maintenance dose on Days 2 to 5. Antiviral activity as indicated by PCR or antigen testing and investigator assessments of clinical improvement were used to assess effectiveness[13]

Results

- *This study was not designed to evaluate DDIs*
- A total of 32 patients were included in the analysis, of which 10 (31.3%) patients were receiving corticosteroids, 1 (3.1%) patient was receiving immunosuppressants, and 2 (6.25%) patients received rituximab prior to ensitrelvir[13]
- The study included 2 patients with ANCA-associated vasculitis, one patient with AML, and 2 patients with HSCT (See **Table 6**)[22]
- Although Patient 9 (ANCA-associated vasculitis) and Patient 20 (AML) experienced viral rebound after end of ensitrelvir treatment, they were discharged from hospital on Day 11 and Day 9, respectively[13,22]All patients, including those who were concomitantly taking immunosuppressants or corticosteroids with ensitrelvir, experienced clinical improvement as assessed by the investigator at the end of ensitrelvir treatment (Day 5)[13]
- No patients, including those who were concomitantly taking immunosuppressants or corticosteroids with ensitrelvir, discontinued treatment, there were no TRAEs, no patients progressed to severe disease, none were admitted to the intensive care unit, and no treatment-related deaths occurred[13]
- Ensitrelvir treatment outcomes reported for individual immunocompromised patients are summarized in **Table 6.**[13,22]
    - Information on patients' specific concomitant immunosuppressants is unavailable

Table 6. Virology Outcomes for Immunocompromised Patients in a Single-Center Chart Review[13,22]

Patient	Underlying Diseases	Prior SARS-CoV-2 Treatment	Days From Start of Ensitrelvir Administration															Treatment Outcome by Day 6[a]	Treatment Outcome at Final Measurement[a]	Viral Rebound
			Day -1 and Day 0	Day 1	Day 2	Day 3	Day 4	Day 5 (EOT)	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14			
			Quantitative Viral Antigen (pg/mL)																	
9[b,c]	AAV, CKD, DM, HTN	Remdesivir[d] Molnupiravir Tixagevimab/ cilgavimab	5000	5000		2587.88		4.77	1210.73		5000	5000	5000							Viral Rebound (at Day 6)
10[e]	Recurrent FL, post-HSCT, CKD, HTN, hemodialysis	Molnupiravir		1227.48		182.59	200.71													
20	Kidney stone disease, acute myelogenous leukemia, post-HSCT, kidney injury, HTN	None		5000[f]			5000	97.79		344.12	5000				4664.69					
24[b]	AAV, UTI, dyslipidemia, HTN	Remdesivir[d] Casirivimab/ imdevimab	5000	5000			223.72		2.37	8.01	5.99	41.02		1.23	0.01			Viral Clearance	Viral Clearance	

This table is adapted under a Creative Commons CC BY 4.0 International License specific to the article published by Elsevier Ltd: Yamato M et al. *J Infect Chemother*. 2024:S1341-321X(24)00050-3
Shading indicates days the patient was hospitalized.
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; CKD, chronic kidney disease; DM, diabetes mellitus; EOT, end of treatment; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; HTN, hypertension; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UTI, urinary tract infection.
[a]Viral clearance defined as an antigen level of <89.73 pg/mL; viral rebound defined as an increase of antigen level of >89.73 pg/mL after viral clearance. [b]Patient was included in the subgroup analysis.
[c]Patient received rituximab at Day -48. [d]Patient received ≥3 days of remdesivi

5. CASE PRESENTATIONS

Miyata et al (2025) described a case report of an 81-year-old Japanese woman with rheumatoid arthritis-associated interstitial lung disease on tacrolimus 1.5 mg who was treated for COVID-19 with ensitrelvir.[14]

Past Medical History

- The patient had a history of diabetes, hypertension, dementia, and secondary Sjogren's syndrome and along with orally administered tacrolimus 1.5 mg, was being treated with prednisolone 3 mg orally once daily and abatacept 50 mg intravenous injection once monthly (no supplements or over the counter drugs). She was vaccinated for COVID-19 approximately 1 year prior.[14]

Hospital Course

- Day -30 (30 days before ensitrelvir course started): patient presented at a routine outpatient visit with sore throat, fatigue, and productive cough and tested positive for SARS-CoV-2 antigen. She was emergently admitted to the hospital due to a clinically and radiologically confirmed pneumonia with stable vital signs.[14]
- The initial treatment included a 5-day course of intravenous remdesivir, corticosteroids (either orally or intravenously administered), and a 6-day course of oral baricitinib. A second remdesivir course was administered around Day -15 due to persistent viral presence Ct value from SARS-CoV-2 PCR after treatment on Day 15 was 25.73), and she was also started on daily intravenous tocilizumab.[14]
- Day -7: the CT scan showed worsening of both respiratory status and pneumonia, viral load remained high, and the Ct value was 26.18.[14]
- Day -2: a third course of daily intravenous remdesivir was started (200 mg once, followed by 100 mg daily for 9 days).[14]
- Day 0: ensitrelvir was initiated (375 mg orally on Day 0, followed by 125 mg daily for 4 days) in combination with remdesivir.[14]
    - Around this time, the patient was taking tacrolimus 1.5 mg by mouth (level at Day -1 was 3.6 ng/mL), intravenous dexamethasone, oral sulfamethoxazole/trimethoprim, oral rosuvastatin, oral nicorandil, oral aspirin, oral esomeprazole, rivastigmine patch, and subcutaneous denosumab.[14]
    - Tacrolimus was discontinued on Day -1 (prior to starting ensitrelvir), rosuvastatin was discontinued on Day 0, and dexamethasone was switched to methylprednisolone on Day 1 due to possible drug interactions with ensitrelvir.[14]
- Tacrolimus blood levels were closely monitored using a Siemens Dimension EXL200 with Flex Cartridge Tacrolimus (ACMIA method, Siemens) and by Day 5, levels were reduced to 1.1 ng/mL (see **Table 7**). Tacrolimus levels began to fall below the target range so it was decided to restart oral tacrolimus 0.2 mg (on Day 5), 1 mg (from Day 7 to 14), and back to 1.5 mg (Day 15 onwards).[14]
- Throughout the treatment, the patient's serum creatinine and alanine aminotransferase remained within normal limits. No AEs were noted.[14]
- The SARS-CoV-2 PCR Ct values were 25.88 on Day 0, 30.03 on Day 5, 34.36 on Day 12, and 34.89 on Day 19, indicating a reduction in viral load. CT imaging on Day 18 showed improved inflammation in both lungs, although oxygen demand did not notably improve.[14]

Pharmacokinetic Parameters

- See **Table 7** for tacrolimus blood levels during ensitrelvir treatment and afterwards, when tacrolimus was re-started.[14]

- Under the assumption of a one-compartment model and a volume of distribution of 42 L (patient's body weight was 42 kg), blood tacrolimus levels were used to calculate the elimination rate constant, elimination half-life, and maximum plasma concentration.[14]
- Based on these calculations, tacrolimus half-life extended from 33.7 hours (Day -1 to 0) to 71.9 hours (Day 0 to 2) and to 114.6 hours (on Day 2 to 5; a 3.4-fold increase) during ensitrelvir treatment.[14]

Table 7. TAC Blood Levels during ESV Course (Days 0-4) and after Restarting TAC (Day 5 Onwards)[a][14]

Day	TAC Blood Level (ng/mL)	Time Since Last TAC Dose (h)	TAC Dose (mg)	Notes
-1	3.6	21.5	Previously 1.5; discontinued	TAC discontinued before ESV course was initiated
0	2.7	35.5	0	ESV started
2	1.7	83.5	0	ESV continued
5	1.1	155.5	0	ESV course ended on Day 4. TAC restarted at 0.2 mg x 1 dose due to below-target TAC levels
7	1.0	36 (post-TAC restart)	0.2	TAC increased to 1.0 mg
8	3.9	12	1.0	TAC continued at 1.0 mg
12	6.5	12	1.0	TAC continued at 1.0 mg
14	3.7	20	1.0	TAC continued at 1.0 mg
15	-	-	1.5	TAC reset to original dose of 1.5 mg
19	5.1	11	1.5	-

Abbreviations: ESV, ensitrelvir; h, hour; mg, milligram; ng, nanogram;TAC, tacrolimus

[a]Tacrolimus blood levels monitored during the using a Siemens Dimension EXL200 with Flex Cartridge Tacrolimus (ACMIA method, Siemens).[14]

Naganawa et al (2024) reported a single-center case series of 3 kidney transplant patients with COVID-19, of which 1 Japanese male was treated with ensitrelvir (Patient 1).[15]

- Patient 1 was a Japanese male over 50 years old who had undergone a living donor kidney transplant for focal glomerulosclerosis over 25 years prior. He was taking tacrolimus 4 mg daily to prevent kidney transplant rejection, which was continued when ensitrelvir was administered. His tacrolimus blood trough levels were stable (between 3-5 ng/mL) at baseline.[15]
- Additional patient history included hypercholesterolemia and concomitant use of prednisolone 5 mg/day, azathioprine 50 mg/day, benzbromarone 12.5 mg/day, atorvastatin 5 mg/day, ambroxol 45 mg/day, and lactomin 2 g/day.[15]
- Day 1: When Patient 1 developed fever and was diagnosed with COVID-19, tacrolimus was continued and ensitrelvir was initiated (375 mg on Day 1 and 125 mg daily from Days 2 to 5).[15]
- Day 7 follow up: Patient 1 had an elevated tacrolimus blood trough level of 11.9 ng/mL (almost a 3-fold increase). No tacrolimus-related adverse effects were observed, such as renal dysfunction, high blood pressure, or headache, although the serum creatinine was slightly higher and eGFR slightly lower on Day 7 compared to baseline. Tacrolimus was stopped for 1 day and then resumed at a lower dose of 2 mg/day starting on Day 8.[15]
- Day 15 follow up: Patient 1's tacrolimus blood trough level decreased to 2.6 ng/mL and so the earlier tacrolimus dose of 4 mg/day was resumed. The serum creatinine and eGFR values returned to similar levels as seen at baseline. Changes in laboratory parameters from baseline to Day 7 and Day 15 are seen in **Table 8**.[15]
- Day 71 follow up: Patient 1's tacrolimus blood trough level was within normal range (3-5 ng/mL) and serum creatinine and eGFR values were similar to those seen at baseline.[15]
- No AE or organ rejection were observed, and Patient 1 recovered from COVID-19.[15]

Table 8. Laboratory Parameters before, at, and after Elevated Tacrolimus Blood Trough Levels in Patient 1[15]

Laboratory Parameters	Normal Range	Patient 1		
		Before (Day -48)	Onset (Day 7)	After (Day 15)
Hemoglobin (g/dL)	11.6-14.8	15.1	14.4	13.9
Hematocrit (%)	35.1-44.4	45.4	45.4	42.7
Aspartate aminotransferase (U/L)	13-40	21	24	18
Alanine aminotransferase (U/L)	10-42	14	20	15
Total bilirubin (mg/dL)	0.4-1.5	0.8	0.7	0.7
Urea nitrogen (mg/dL)	8-20	23	29	29
Sodium (mmol/L)	138-145	141	142	141
Potassium (mmol/L)	3.6-4.8	3.9	4.3	3.9
Chloride (mmol/L)	101-108	107	107	107
Magnesium (mg/dL)	1.8-2.4	—	—	—

Table adapted from Nagnawa et al. *Journal of Pharmaceutical Health Care and Sciences*. 2024.
Abbreviations: dL, deciliter; g, gram; L, liter; mg, milligram; mmol, millimole; U, unit.

Miyagawa et al. (2026) described a 74-year-old Japanese man with a prior kidney transplant who was hospitalized for severe COVID-19 pneumonia with acute hypoxemic respiratory failure.[16] The patients past medical history includes prior endoscopic surgery for early-stage gastric cancer, kidney transplantation for nephrosclerosis, and percutaneous coronary intervention.[16] His immunosuppressive regimen included tacrolimus 2.5 mg/day, prednisolone 5 mg/day, and mycophenolate mofetil 1,000 mg/day.[16]

Prior to Hospital Admission

- The patient's tacrolimus blood trough level was stable over the past year ranging from 4.34-6.61 ng/mL before admission[16]
- His drug therapy also included atorvastatin, nifedipine, olmesartan, and aspirin[16]
- The patient presented to a hospital with a cough and rhinorrhea and tested positive for COVID-19[16]
    - The patient received molnupiravir for 5 days, but his condition worsened over the following 14 days
- During his second hospital visit, he tested positive for COVID-19 again and pneumonia was identified on a chest x-ray. The patient was prescribed lascufloxacin 75 mg.[16]
    - The patient was prescribed lascufloxacin 75 mg, but after 4 days of treatment, he returned to the hospital again since his fever and cough did not improve
- Patient was then admitted to the hospital with a fever (38.5°C) and respiratory failure requiring high-flow oxygen supplementation[16]

Clinical Course

- The patient was brought to the ICU, where he was intubated and received mechanical ventilation[16]
- Imaging was consistent with COVID-19 pneumonia diagnosis and laboratory data showed elevated inflammatory markers and mildly impaired renal function[16]
- Treatment included ensitrelvir 375 mg on Day 1, followed by 125 mg once daily thereafter for

8 days, along with other supportive and anti-inflammatory therapies, including tocilizumab, 3 days of intravenous immunoglobulin, 9 days of dexamethasone, heparin, and empiric antibiotics[16]
    - Antibiotics were discontinued after evaluation did not identify another infectious pathogen.
- While receiving tacrolimus 2.5 mg/day, the trough level measured at the referring hospital was 4.89 ng/mL[16]
- At admission, the tacrolimus trough level was 6.70 ng/mL, and the tacrolimus dose was decreased to 2 mg/day[16]
- Tacrolimus trough levels increased to 19.7 ng/mL on Day 1 resulting in the tacrolimus dose being reduced to 1.5 mg/day on Day 2 and 1 mg/day from Day 3 onward[16]
- Tacrolimus trough levels were within target range (5.0-6.9 ng/mL) by Day 6 and no acute rejection or apparent tacrolimus-related toxicity was observed during ensitrelvir treatment[16]
- Serial SARS-CoV-2 PCR cycle threshold values increased over time, but remained detectable[16]
- The patient's respiratory status improved (he was extubated on Day 2 and then placed on nasal cannula, with noted improvement seen in pulmonary infiltrates on follow-up chest radiography), and on Day 9, he was transferred to the hospital where he had undergone kidney transplantation[16]

6. 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.

7. 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®) has identified additional relevant references regarding use of ensitrelvir with immunosuppressants. For your review, these references are listed in the bibliography that follows:

Furuya C, Yasuda H, Hiki M, et al. Case report: Ensitrelvir for treatment of persistent COVID-19 in lymphoma patients: a report of two cases. *Front Immunol*. 2024;15:1287300. doi:10.3389/fimmu.2024.1287300

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Shimazu H, Wada D, Maruyama S, et al. Clinical experience of treatment of immunocompromised individuals with persistent SARS-CoV-2 infection based on drug resistance mutations determined by genomic analysis: a descriptive study. *BMC infectious diseases*. 2023;23(1):780. doi:10.1186/s12879-023-08797-6

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	GA	genomic analysis
AAV	ANCA-associated vasculitis	h	hours
ACMIA	antibody-conjugated magnetic immunoassay	HDL	high-density lipoprotein
ACTG	AIDS Clinical Trials Group	HIV	human immunodeficiency virus
ACTIV-2	Accelerating COVID-19 Therapeutic Interventions and Vaccines-2	HHC	household contact
AE	adverse event	HSC	hematopoietic stem cell
AML	acute myeloid leukemia	mg	milligrams
ANCA	anti-neutrophil cytoplasmic antibody	MHLW	Ministry of Health, Labour and Welfare
$AUC_{0\text{-inf}}$	area under the concentration-time curve extrapolated to infinity	mITT	modified intention-to-treat
$AUC_{0\text{-last}}$	area under the concentration-time curve to the last measurable concentration	ng	nanograms
BCRP	Breast Cancer Resistance Protein	NIH	National Institutes of Health
BMI	Body Mass Index	OATP	organic anion transporting polypeptide
CI	confidence interval	OCT	organic cation transporters
CKD	chronic kidney disease	PCR	polymerase chain reaction
C_{max}	maximum concentration	PK	pharmacokinetic
COVID-19	Coronavirus disease 19	P-gp	P-glycoprotein
CT	Computed Tomography	RNA	ribonucleic acid
Ct	cycle threshold	RT-PCR	reverse transcription polymerase chain reaction
CYP	cytochrome P450	RT-qPCR	real-time quantitative polymerase chain reaction
DDI	drug–drug interaction	SAE	serious adverse event
DM	diabetes mellitus	TEAE	treatment-emergent adverse event
eGFR	estimated glomerular filtration rate	TRAE	treatment-related adverse event
EOT	end of treatment	UTI	urinary tract infection
F	female	y	years
FL	follicular lymphoma		

References

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3. Luetkemeyer AF, Chew KW, Lacey S, et al. Ensitrelvir for the treatment of nonhospitalized adults with COVID-19: results from the SCORPIO-HR, phase 3, randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. Feb 17 2025;80(6):1235-1244. doi:10.1093/cid/ciaf029

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ENCLOSURE

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

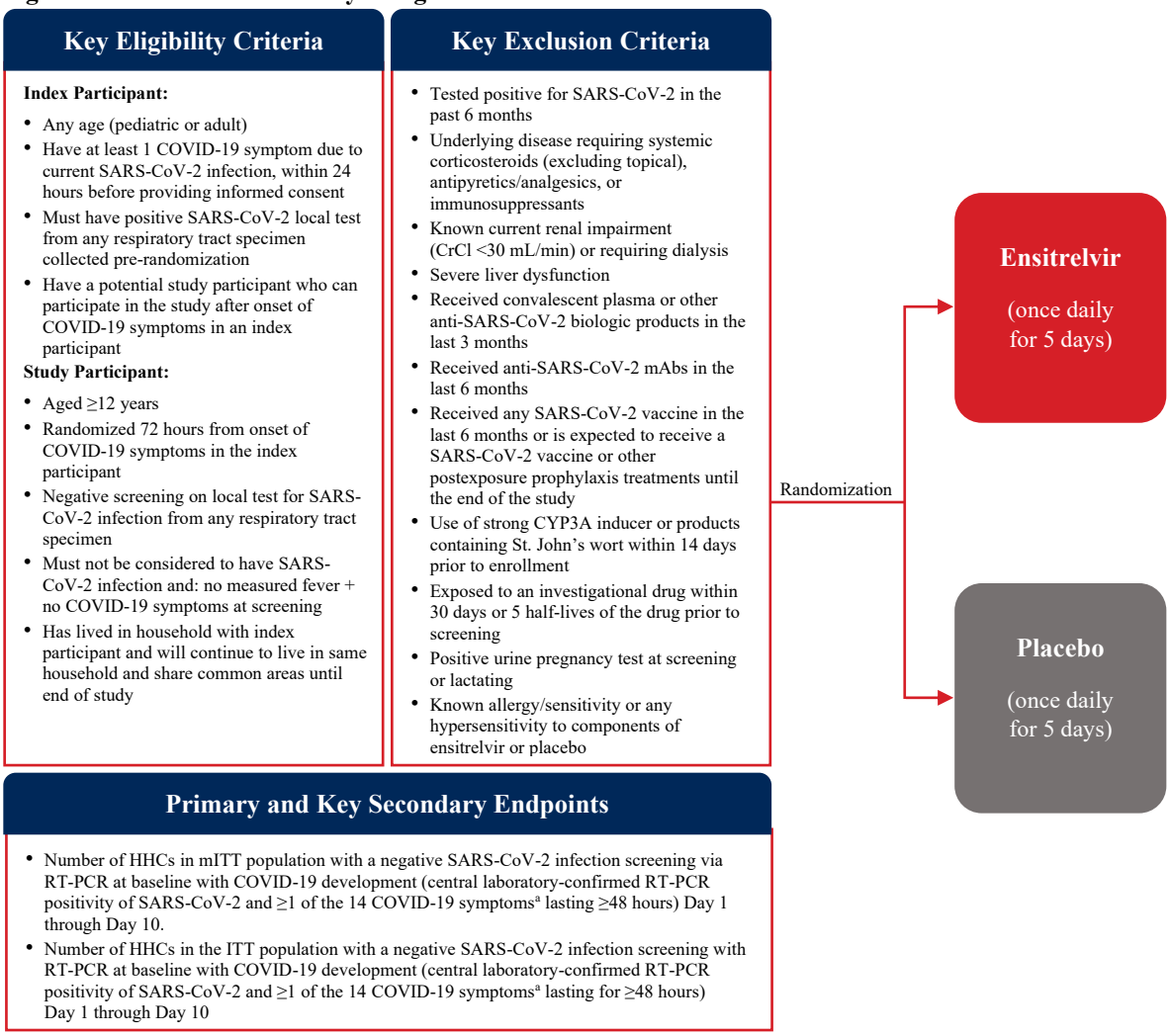
APPENDIX

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.[2]

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.[2,5]

Figure 1. SCORPIO-PEP Study Design[2,5]



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

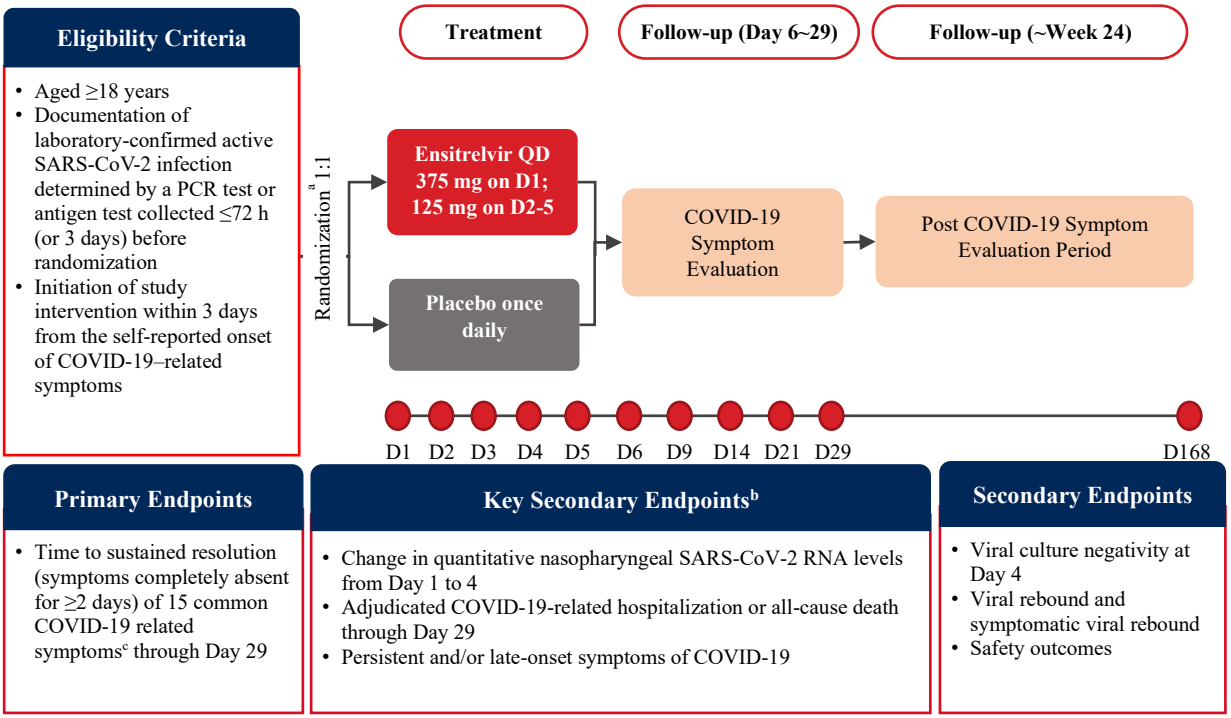
- **Primary Endpoint**: 2.9% (30/1030) of HHCs in the ensitrelvir group developed symptomatic COVID-19 compared to 9.0% (91/1011) of HHC participants on placebo through Day 10, a 67% reduction in the risk of developing COVID-19 (risk ratio: 0.33; 95% CI: 0.22-0.49; $P < 0.0001$) in uninfected individuals (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[7,18]



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

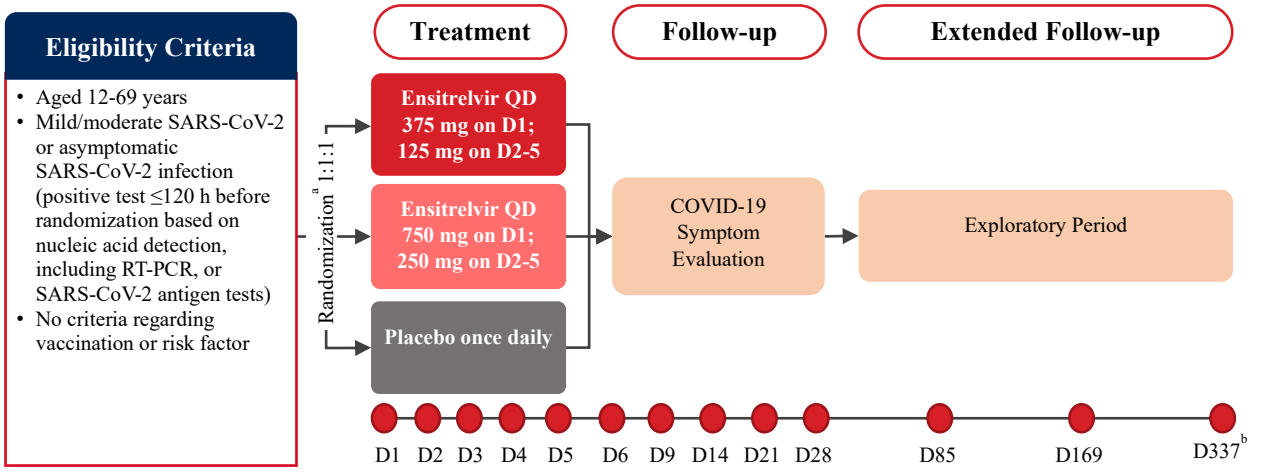
- **Primary Endpoint:** In the modified intent-to-treat (mITT) population, the restricted mean time to sustained symptom resolution was not significantly different between the ensitrelvir (12.5 days) and placebo (13.1 days) groups (difference, -0.6 days; 95% CI: -1.38, 0.19; *P*=0.14).[18]

Safety

- AEs occurred in 638 patients treated with ensitrelvir (61.5%; n=1037), and 635 patients treated with placebo (60.6%; n=1048).[18]
- TRAEs occurred in 86/1037 (8.3%) of patients treated with ensitrelvir and 74/1048 (7.1%) of patients that were given placebo.[18]
- Serious TEAE occurred in 5/1037 (0.5%) of the ensitrelvir-treated participants and 6/1048 (0.6%) of the patients given placebo.[18]
- 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.[18]

SCORPIO-SR (Phase 3 Study)

Figure 3. Phase 2/3 Study, Phase 3 Part[4,20]



Phase 3 Endpoints

Population: Mild/moderate
Primary:
- Time to resolution of 5 COVID-19 symptoms[a]

Secondary outcomes included:
- Change from baseline in SARS-CoV-2 viral RNA on D4, time to first negative SARS-CoV-2 viral titer (key endpoints), and safety by D28

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). See **Table 9**.[4]
- 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]

Table 9. Phase 3 Part: Time to Resolution of 5 COVID-19 Symptoms[4,a]

	COVID-19 Onset to Randomization: <72 h (Primary Analysis)[b]		
	Ensitrelvir 125 mg (n=347)	Ensitrelvir 250 mg (n=340)	Placebo (n=343)
Kaplan-Meier estimator (h)			
Median (95% CI)	167.9 (145.0, 197.6)	171.2 (150.8, 190.3)	192.2 (174.5, 238.3)
Difference from placebo (95% CI)	−24.3 (−78.7, 11.7)	−21.0 (−73.8, 7.2)	-
Stratified Peto-Prentice's generalized Wilcoxon test[c]			
P-value (two-tailed)	0.04	0.0203	-

The efficacy analysis group comprised of the ensitrelvir 125 mg treatment arm and placebo arm.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 19; h, hours; ITT, intention-to-treat; RNA, ribonucleic acid; 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). [b]Analysis in the ITT population (all cases confirmed positive for SARS-CoV-2 viral RNA at baseline) with any of the 5 symptoms at baseline. [c]Adjusted for SARS-CoV-2 vaccination status.