Xocova - Incidence of Hypersensitivity or Allergic Reactions

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

Key Prescribing Information

- XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any component of the product. Hypersensitivity reactions, including anaphylaxis, anaphylactic shock, and angioedema, have been reported with XOCOVA during post-marketing use outside of the United States.[1]
- As described in the XOCOVA **Full Prescribing Information**, these events were identified through voluntary post-marketing reports outside the United States from a population of uncertain size; therefore, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. XOCOVA should be immediately discontinued if signs or symptoms of a clinically significant hypersensitivity reaction occur.[1]
- Information regarding the specific number of reported cases, patients' prior exposure to similar medications, and detailed case assessments or adjudication processes is not available. Because these reports originate from spontaneous post-marketing pharmacovigilance activities, case-level information may be incomplete and is not routinely available in a form that allows for further characterization beyond the information reflected in the XOCOVA **Full Prescribing Information**.

Clinical Studies

- Across clinical studies, treatment-emergent adverse events (TEAEs) potentially related to hypersensitivity or allergic reactions primarily included rash, urticaria, pruritus, drug eruption, dermatitis contact, and hypersensitivity.[2-8] There were no reports of anaphylaxis, anaphylactic shock, or angioedema in the clinical trials.[2-11]
- Please see the **Clinical Studies** section of this letter for information on potential hypersensitivity reactions from Phase 3 studies (SCORPIO-PEP and SCORPIO-HR), Phase 2/3 studies (Phase 2a, Phase 2b, Phase 3 SCORPIO-SR, and Phase 2b/3), and Phase 1 study.

Post-marketing Surveillance (PMS) Study

- **Hayashi et al. 2025** reported results from a Japanese PMS study. Adverse drug reactions (ADRs) potentially related to hypersensitivity/allergic reactions occurring in ≥3 patients included rash (n=20), pruritus (n=9), urticaria (n=7), and erythema (n=3); all were non-serious.[12]

2. CLINICAL STUDIES

Phase 3 Clinical Studies

SCORPIO-PEP

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 conducted from June 2023 to September 2024 (see **Appendix-SCORPIO-PEP** for more information on study design and safety results).[13,14]

HHC participants with a negative screening test for SARS-CoV-2 infection and no symptoms, 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 72 hours of when the household member with COVID-19 began showing symptoms.[13]

Relevant Inclusion/Exclusion Criteria

Participants were excluded if they had any known allergy/sensitivity or any hypersensitivity to components of ensitrelvir or placebo for ensitrelvir.[2]

AEs Related to Hypersensitivity or Allergic Reactions

There were no patients in this study that reported anaphylaxis, anaphylactic shock, or angioedema.

TEAEs and TRAEs that could potentially be related to hypersensitivity/allergic reactions are presented in **Table 1.**

Table 1. SCORPIO-PEP Safety Cohort: Select TEAEs and TRAEs Potentially Related to Hypersensitivity or Allergic Reactions (Safety Analysis Set)[2]

Symptom	Ensitrelvir 125 mg (N=1190) n (%)	Placebo (N=1187) n (%)
Selected TEAEs potentially related to hypersensitivity/allergic reactions		
Urticaria	2 (0.2)	0
Drug eruption	1 (<0.1)	0
Dermatitis contact	0	1 (<0.1)
Rash	0	2 (0.2)
Hypersensitivity	1 (<0.1)	0
Selected TRAEs[a]		
Urticaria	1 (<0.1)	0
Drug eruption	1 (<0.1)	0
Rash	0	1 (<0.1)

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a]Selected TRAEs were treatment-related events reported among the hypersensitivity/allergic reaction preferred terms listed in the TEAE section. Only preferred terms with ≥1 TRAE in either treatment group are presented.

SCORPIO-HR

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).[15,16]

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.[15,16]

Relevant Inclusion/Exclusion Criteria

Patients were excluded if they had any known allergy, sensitivity, or hypersensitivity to any component of ensitrelvir or the ensitrelvir-matching placebo.[3]

AEs Related to Hypersensitivity or Allergic Reactions

No cases of anaphylaxis, anaphylactic shock, or angioedema were reported among patients treated with ensitrelvir in this study. One report of angioedema was reported in the placebo arm.[3]

TEAEs and TRAEs that could potentially be related to hypersensitivity/allergic reactions are presented in **Table 2.**

Table 2. SCORPIO-HR Safety Cohort: Select TEAEs and TRAEs Potentially Related to Hypersensitivity or Allergic Reactions Through Day 29 (Safety Analysis Set)[3]

Symptom	Ensitrelvir 125 mg (N=1037) n (%)	Placebo (N=1048) n (%)
Selected TEAEs potentially related to hypersensitivity/allergic reactions		
Rash	2 (0.2)	4 (0.4)
Pruritus	3 (0.3)	0
Dermatitis contact	2 (0.2)	0
Rash macular	1 (0.1)	1 (0.1)
Urticaria	1 (0.1)	1 (0.1)
Angioedema	0	1 (0.1)
Dermatitis	0	1 (0.1)
Dermatitis allergic	1 (0.1)	0
Urticaria papular	1(0.1)	0
Selected TRAEs[a]		
Rash	1 (0.1)	3 (0.3)
Pruritus	2 (0.2)	0
Rash macular	0	1 (0.1)
Urticaria	0	1 (0.1)

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a]Selected TRAEs were treatment-related events reported among the hypersensitivity/allergic reaction preferred terms listed in the TEAE section. Only preferred terms with ≥1 TRAE in either treatment group are presented.
The safety analysis population included participants who received ≥1 dose of ensitrelvir/placebo and were analyzed by the study intervention received.

Phase 2/3 Study

A Phase 2/3, multicenter, randomized, double-blind, placebo-controlled clinical study (RCT2031210350) was conducted in Asia to evaluate the efficacy, safety, and PK of ensitrelvir (125 and 250 mg) given orally, once daily for 5 days versus placebo in patients aged 12 to <70 years with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection. The Phase 2a part of the study was conducted in Japan, the Phase 2b part in both Japan and South Korea, and the Phase 3 part in Japan, South Korea, and Vietnam (see **Appendix-Phase 2/3 Study** for more information on study design and safety results).[17-23]

Relevant Inclusion/Exclusion Criteria

Participants were excluded from the study if they were considered ineligible for the study by the investigator/subinvestigator due to sensitivity to any of the study interventions or components thereof, drug allergy, or history of other allergy (except for seasonal allergies).[4-7]

Phase 2a

The Phase 2a, dose-finding part of the study was conducted from September 28, 2021 to January 1, 2022, at 56 sites across Japan. Patients with mild-to-moderate or asymptomatic COVID-19 were randomized (1:1:1) to orally receive ensitrelvir 125 mg (safety cohort n=21), ensitrelvir 250 mg (safety cohort n=23), or matching placebo (safety cohort n=24) once daily without dose modification and followed up until Day 28.[17]

AEs Related to Hypersensitivity or Allergic Reactions

No patients treated with ensitrelvir reported anaphylaxis, anaphylactic shock, or angioedema in the phase 2a part of the study.

The incidence of TEAEs that could be related to hypersensitivity/allergic reactions are summarized in **Table 3**. No TRAEs related to hypersensitivity/allergic reactions were observed in ≥5% of patients in either group.[17]

Table 3. Phase 2a Safety Cohort: Select TEAEs Potentially Related to Hypersensitivity or Allergic Reaction (Safety Analysis Set)[4]

	Ensitrelvir 125 mg (N=21) n (%)	**Ensitrelvir 250 mg** (N=23) n (%)	**Placebo** (N=24) n (%)
Selected TEAEs potentially related to hypersensitivity/allergic reactions			
Rash	0 (0)	1 (4.3)	0 (0)

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse events.
Patients were included in the safety cohort if they received ≥1 dose of the study drug.

Phase 2b

The Phase 2b dose-finding part was conducted at 87 institutions in Japan and South Korea between January 2 and February 9, 2022. Participants with mild-to-moderate COVID-19 were randomized in a 1:1:1 ratio to receive once-daily oral ensitrelvir 375 mg on Day 1 followed by 125 mg on Days 2-5 (safety cohort, n=140), ensitrelvir 750 mg on Day 1 followed by 250 mg on Days 2-5 (safety cohort,

n=140), or matching placebo (safety cohort, n=141). No dose modifications were made, and participants were followed through Day 28.[18]

AEs Related to Hypersensitivity or Allergic Reactions

No patients treated with ensitrelvir reported anaphylaxis, anaphylactic shock, or angioedema in the phase 2b part of the study.

The incidence of TEAEs that could potentially be related to hypersensitivity or allergic reactions is summarized in **Table 4.**

Table 4. Phase 2b Safety Cohort: Select TEAEs Potentially Related to Hypersensitivity or Allergic Reaction (Safety Analysis Set)[5]

	Ensitrelvir 125 mg (N=140) n (%)	**Ensitrelvir 250 mg** (N=140) n (%)	**Placebo** (N=141) n (%)
Selected TEAEs potentially related to hypersensitivity/allergic reactions			
Rash	2 (1.4)	1 (0.7)	3 (2.1)
Pruritus	0 (0)	1 (0.7)	0 (0)
Urticaria	0 (0)	0 (0)	1 (0.7)
Selected TRAEs			
Rash	1 (0.7)	1 (0.7)	0
Pruritus	0	1 (0.7)	0

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
The safety cohort comprised all randomized patients who received ≥1 dose of ensitrelvir or placebo.

Phase 3 (SCORPIO-SR)

The SCORPIO-SR Phase 3 study was conducted within 92 institutions in Japan, Vietnam, and South Korea between February 10 to July 10, 2022. Eligible patients were aged 12 to <70 years, with mild-to-moderate COVID-19, and randomized within 120 hours of positive viral test at baseline. Patients were randomized 1:1:1 to receive ensitrelvir 375 mg on Day 1 followed by 125 mg on Days 2-5 (safety cohort n=604), ensitrelvir 750 mg on Day 1 followed by 250 mg on Days 2-5 (safety cohort n=599), or placebo (safety cohort n=605) for 5 days, with follow up to Day 28.[19]

AEs Related to Hypersensitivity or Allergic Reactions

No patients treated with ensitrelvir reported anaphylaxis, anaphylactic shock, or angioedema in the phase 3 part (SCORPIO-SR) of the study.

The incidence of TEAE and TRAEs potentially related to hypersensitivity/allergic reactions is summarized in **Table 5**.

Hypersensitivity or allergic reaction-related adverse events that led to a discontinuation of treatment and were determined to be treatment-related included mild rash and moderate rash in one patient each (ensitrelivr 250 mg).[19]

Table 5. Phase 3 Safety Cohort: Select TEAEs and TRAEs Potentially Related to Hypersensitivity or Allergic Reactions (Safety Analysis Set)[6]

	Ensitrelvir 125 mg (N=604) n (%)	**Ensitrelvir 250 mg** (N=599) n (%)	**Placebo** (N=605) n (%)
Selected TEAEs potentially related to hypersensitivity/allergic reactions			
Hypersensitivity	0	1 (0.2)	1 (0.2)
Rash	2 (0.3)	7 (1.2)	5 (0.8)
Urticaria	2 (0.3)	3 (0.5)	1 (0.2)
Dermatitis contact	0	1 (0.2)	0
Drug eruption	1 (0.2)	0	0
Pruritus	1 (0.2)	0	2 (0.3)
Urticaria contact	1 (0.2)	0	0
Mechanical urticaria	0	0	1 (0.2)
Selected TRAEs			
Rash	0	5 (0.8)	1 (0.2)
Urticaria	0	2 (0.3)	0
Dermatitis contact	0	1 (0.2)	0
Drug eruption	1 (0.2)	0	0
Mechanical urticaria	0	0	1 (0.2)

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
The safety cohort comprised all randomized patients who received ≥1 dose of ensitrelvir or placebo.

Phase 2b/3

The Phase 2b/3 trial included individuals with asymptomatic SARS-CoV-2 infection and individuals with mild COVID-19 symptoms and was conducted at 57 medical institutions in Japan, South Korea, and Vietnam from January 6 to August 14, 2022. Eligible patients were randomized in a 1:1:1 ratio to receive ensitrelvir 125 mg (safety cohort n=201), ensitrelvir 250 mg (safety cohort n=202), or placebo (safety cohort n=201). Participants received the allocated intervention orally and were followed through Day 28.[20,21,22]

AEs Related to Hypersensitivity or Allergic Reactions

There were no reports of anaphylaxis, anaphylactic shock, or angioedema in the phase 2b/3 part of the study.

The incidence of TEAEs and TRAEs potentially related to hypersensitivity/allergic reactions is summarized in **Table 6**.

Table 6. Phase 2b/3 Safety Cohort: Select TEAEs and TRAEs Potentially Related to Hypersensitivity or Allergic Reaction (Safety Analysis Set)[7,22]

	Ensitrelvir 125 mg (N=201) n (%)	**Ensitrelvir 250 mg** (N=202) n (%)	**Placebo** (N=201) n (%)
Selected TEAEs potentially related to hypersensitivity/allergic reactions			
Rash	1 (0.5)	1 (0.5)	1 (0.5)
Dermatitis contact	0	1 (0.5)	0
Pruritus	0	1 (0.5)	1 (0.5)
Drug eruption	1 (0.5)	0	0
Rash pruritic	1 (0.5)	0	0
Urticaria	1 (0.5)	0	0
Selected TRAEs			
Drug eruption	1 (0.5)	0	0
Rash pruritic	1 (0.5)	0	0
Rash	0	0	1 (0.5)

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
The safety cohort comprised all randomized participants who received ≥1 dose of ensitrelvir or placebo.

Phase 1 Clinical Study

A Phase 1 study in Japan tested the safety, tolerability, and pharmacokinetics of ensitrelvir in healthy adult participants. TEAEs potentially related to hypersensitivity or allergic reactions were reported.[24]

Relevant Inclusion/Exclusion Criteria

The study included 7 parts. Across all parts, participants were excluded if they had hypersensitivity to any of the study interventions, or components thereof, or drug or other allergy (except for seasonal allergy) that, in the opinion of the investigator or subinvestigator, contraindicated participation in the study.[8]

AEs Related to Hypersensitivity or Allergic Reactions

Across the 7 parts, TEAEs potentially related to hypersensitivity/allergic reactions were limited to rash and erythema. Rash was reported in 1/8 participants (12.5%) receiving ensitrelvir 250 mg + midazolam in Part 2-Cohort G, and was considered treatment-related. Erythema was reported in 1/6 participants (16.7%) receiving placebo in Part 2-Cohorts N/O, and was not reported as treatment-related. No other selected hypersensitivity/allergic reaction TEAEs were identified across the remaining parts.[8]

Additionally, no reports of anaphylaxis, anaphylactic shock, or angioedema were identified in other Phase 1 studies, including the drug-drug interaction study of ensitrelvir with combined oral contraceptives[9], the study in participants with mild or moderate hepatic impairment[10], and the study in participants with mild, moderate, or severe renal impairment[11].

3. POST-MARKETING SURVEILLANCE STUDY

Post-Marketing Surveillance (PMS)

Hayashi et al. 2025

In the final analysis of an ensitrelvir post-marketing surveillance study in Japan from November 2022 to December 2023 that included 3,760 patients in the safety population, the incidence of adverse drug reactions (ADRs) was listed for patients overall and within standard-risk and high-risk groups.[12]

A total of 379 ADRs occurred and those potentially related to hypersensitivity/allergic reactions occurring in ≥3 patients included rash (n=20), pruritus (n=9), urticaria (n=7), and erythema (n=3); all were deemed non-serious.[12]

4. RELEVANT PRESCRIBING INFORMATION

Indications and Usage

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

Contraindications

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

XOCOVA is contraindicated in patients taking drugs that are:[1]

- 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]

As stated in the XOCOVA Full Prescribing Information:

<u>Warnings and Precautions</u>

Section 5.3 – Hypersensitivity Reactions Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, anaphylactic shock, and angioedema, have been reported with XOCOVA. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue XOCOVA and initiate appropriate treatment.[1]

<u>Adverse Reactions</u>

The following clinically significant adverse reactions are described in the labeling:[1]

- Hypersensitivity reactions including anaphylaxis

Section 6.2 – Postmarketing Experience

The following adverse reactions have been identified during post approval use of XOCOVA outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.[1]

- Immune system disorders: Anaphylaxis (including anaphylactic shock), angioedema, hypersensitivity, urticaria

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

5. LITERATURE SEARCH, ABBREVIATIONS, REFERENCES

Literature Search

As of October 2026, a computerized search of the published medical literature internal and external databases (ie, Medline® and Embase®) has failed to identify any additional relevant references regarding the incidence of hypersensitivity/allergic reactions with ensitrelvir.

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 them should not be considered all-inclusive.

Abbreviations

ACTG	AIDS Clinical Trials Group
ACTIV-2	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ADR	adverse drug reaction
AE	adverse event
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CYP3A	Cytochrome P450 3A
HDL	high-density lipoprotein
HHC	household contact
ITT	intent-to-treat
mAbs	monoclonal antibodies
mITT	modified intent-to-treat
NIH	National Institutes of Health
PCR	polymerase chain reaction
PK	pharmacokinetic
PMS	post-marketing surveillance
QD	once daily
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event

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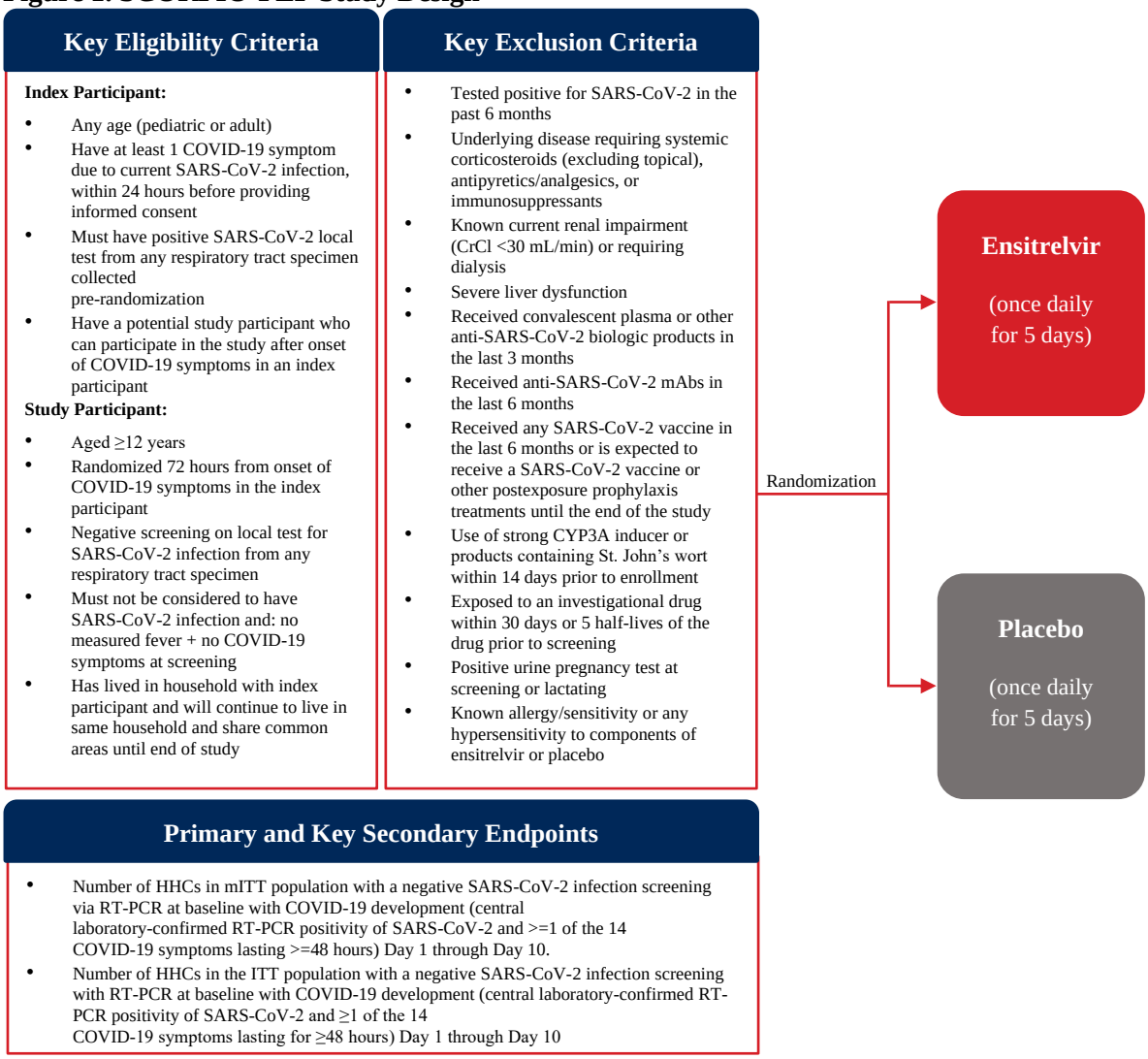
ENCLOSURE
XOCOVA® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.

APPENDIX

SCORPIO-PEP (Phase 3)

Study Design

Figure 1. SCORPIO-PEP Study Design[13,14]



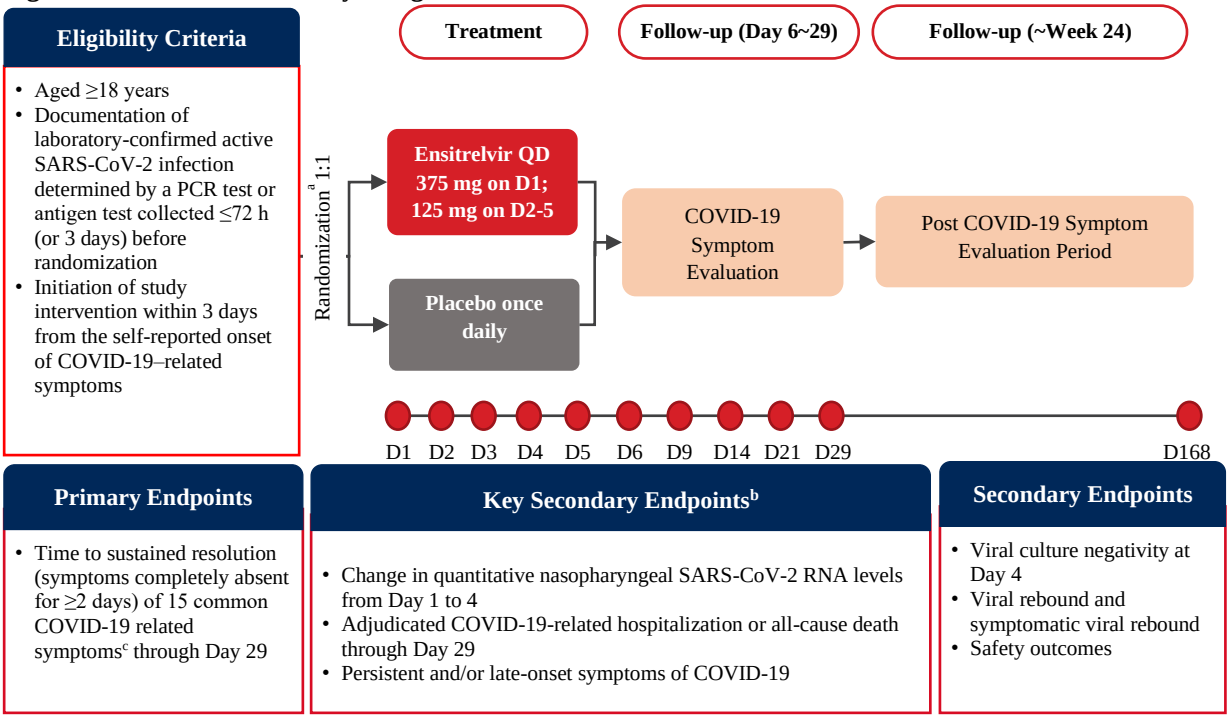
Safety Results

- 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.[13]
- 2 serious TEAEs occurred in each group and they were considered to be unrelated to the study drug.[13]
- There were no AEs that led to hospitalization and no deaths were observed in either group.[13]

SCORPIO-HR (Phase 3)

Study Design

Figure 2. SCORPIO-HR Study Design[15,16]



Abbreviations: COVID-19, coronavirus disease 19; D, day; h, hours; n; 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.

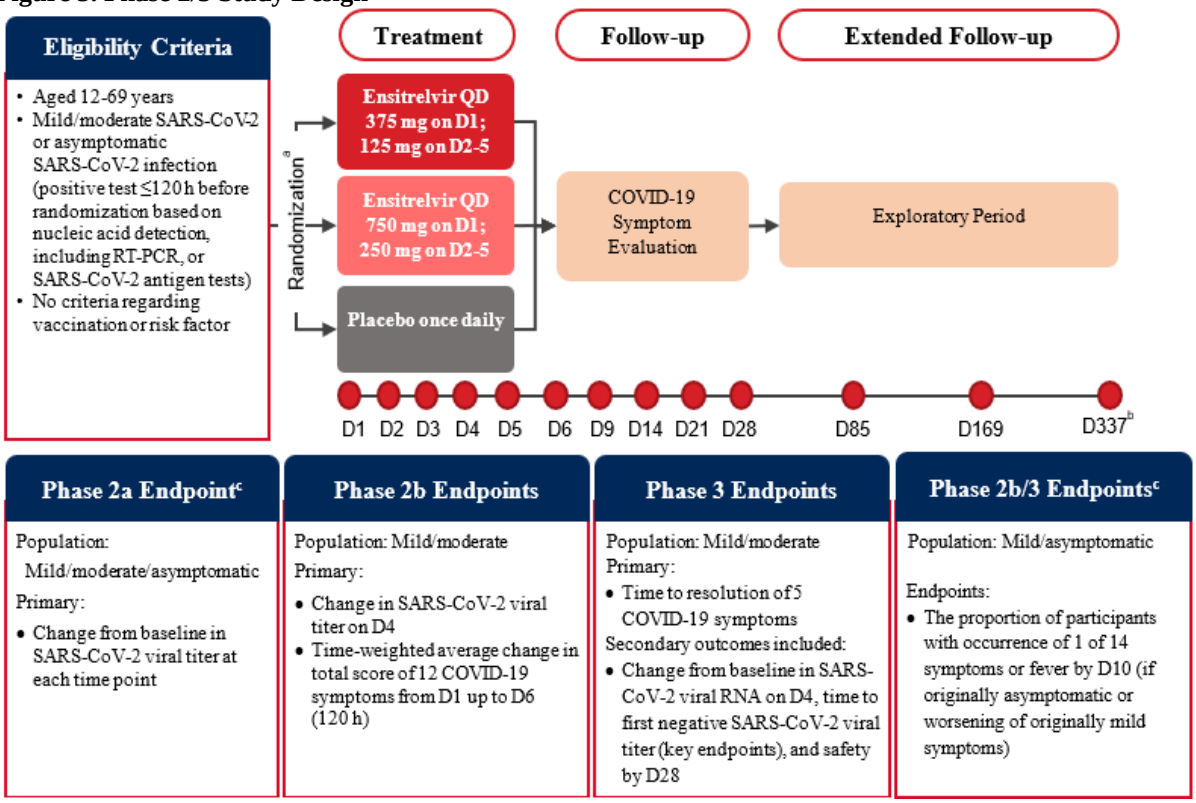
Safety Results

- Adverse events occurred in 638 patients treated with ensitrelvir (61.5%; n=1037), and 635 patients treated with placebo (60.6%; n=1048). Treatment-related adverse events occurred in 86/1037 (8.3%) of patients treated with ensitrelvir and 74/1048 (7.1%) of patients that were given placebo. Serious treatment emergent adverse events (TEAE) occurred in 5/1037 (0.5%) of the ensitrelvir-treated participants and 6/1048 (0.6%) of the patients given placebo. No serious treatment-related adverse events occurred in either group.[16]
- 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.[16]

Phase 2/3 Study

Study Design

Figure 3. Phase 2/3 Study Design[17-19,21]



Abbreviations: COVID-19, coronavirus disease 19; D, day; h, hours; PASC, post-acute sequelae of SARS-CoV-2; RNA, ribonucleic acid; QD, once a day; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. [a]Asymptomatic patients were included in the 2a part. [b]Patients were stratified based on their vaccination status and time from onset to allocation (< 72 h, ≥ 72 h).[c]Exploratory analysis.

Safety Results

<u>Phase 2a Part</u>

- TEAEs were mild to moderate in severity (ensitrelvir 125 mg, 11/21 [52.4%] patients; ensitrelvir 250 mg, 16/23 [69.6%] patients; placebo, 9/24 [37.5%] patients)[17]
  - The most common TEAE was reduction in HDL (ensitrelvir 125 mg, 3/21 [14.3%]; ensitrelvir 250 mg, 12/23 [52.2%]; placebo, 2/24 [8.3%])
  - Treatment-related transient decreases in HDL cholesterol and increases in triglycerides (TGs) occurred after treatment initiation and resolved without additional treatment
  - No deaths, serious TEAEs or TEAEs leading to treatment discontinuation occurred
- TRAEs were observed in 5/21 (23.8%) and 10/23 (43.5%) patients in the ensitrelvir 125- and 250-mg groups, respectively[17]

<u>Phase 2b Part</u>

- TEAEs were generally mild in patients taking ensitrelvir 125 mg, n=48/140 [(34.3%) or ensitrelvir 250 mg, n=60/140 (42.9%) compared with the placebo group (n=44/141 [31.2%])[18]
  - The most frequent TEAEs occurring in >5% of patients in the ensitrelvir groups were decrease in HDL and increase in blood TGs; no serous adverse events (AEs) or deaths occurred

- TRAEs were reported in 19 (13.6%), 31 (22.1%), and 7 (5.0%) patients in the ensitrelvir 125-mg, ensitrelvir 250-mg, and placebo groups, respectively[18]
    - The most frequent TRAE in the ensitrelvir groups (occurring in ≥5% of patients) was decrease in HDL
    - Transient and asymptomatic changes in HDL and TGs were observed on Day 6 in both ensitrelvir groups which resolved without additional treatment

Phase 3 Part

- 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 two serious adverse events (AEs) reported in the study (one in the ensitrelvir 125 mg arm and one in the placebo arm), both of which were judged as not treatment related.[19]

Phase 2b/3 Part

- Ensitrelvir was well tolerated, with two serious TEAEs reported in the ensitrelvir 250-mg group and no deaths in any group[21]
    - Three patients in the ensitrelvir arm discontinued due to TEAEs (one patient in 125-mg and two patients in 250-mg group)
    - Among the most common TEAEs were temporary decreases in HDL, increased blood TGs, and increased bilirubin, as observed in previous studies