Xocova - Incidence of Liver Abnormalities

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 indicated for post-exposure prophylaxis (PEP) 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]
- In the **XOCOVA Full Prescribing Information**, there is no information available on safety events involving liver function when using ensitrelvir[1]
- According to the **XOCOVA Full Prescribing Information**, no dosage adjustment of XOCOVA is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment; however, the impact of severe hepatic impairment on ensitrelvir pharmacokinetics is unknown[1]
- Decisions regarding the use of XOCOVA in patients with underlying hepatic conditions should be made by the treating healthcare professional based on the patient's medical history, concomitant medications, and individual patient factors

Clinical Studies

- The safety profile of ensitrelvir has been demonstrated at multiple doses in Phase 1, Phase 2, and Phase 3 studies in patients with COVID-19 and in healthy participants[2-10]
- **SCORPIO-PEP (Phase 3)**: the most common liver-associated TEAEs in the ensitrelvir group were AST increased (4/1190, 0.3%). No liver-associated TEAEs were considered related to ensitrelvir, and most were mild in severity[11]
- **SCORPIO-HR (Phase 3)**: the most common liver-associated TEAEs with ensitrelvir were AST increased (31/1037, 3.0%) and ALT increased (28/1037, 2.7%). Most events were mild-to-moderate, with no potentially life-threatening events or deaths due to liver abnormalities were reported with ensitrelvir[12]
- **SCORPIO-SR (Phase 3)**: the most common liver-associated TEAE with ensitrelvir was an asymptomatic, transient increase in blood bilirubin (125 mg: 36/604, 6.0%; 250 mg: 56/599, 9.3%; placebo: 6/605, 1.0%) that were resolved without additional treatment. There were no treatment discontinuations related to liver abnormalities and no deaths[4,13]
- **Phase 2/3 Study**:
  - **Phase 2a**: all liver-associated TEAEs were mild. A transient, asymptomatic increase in total bilirubin was observed with ensitrelvir and resolved without treatment. No serious TEAEs or discontinuations due to liver abnormalities occurred[2]
  - **Phase 2b**: liver-associated TEAEs were mostly mild, with 1 moderate hepatic-enzyme increase. A dose-dependent, transient, asymptomatic total-bilirubin change was observed on Day 6 and resolved by Day 14, without concurrent liver-enzyme elevation. No serious TEAEs or discontinuations due to liver abnormalities occurred[3,14]
  - **Phase 2b/3**: all liver-associated abnormalities were mild[6,15]

- **Phase 1**: no AEs related to liver abnormalities were reported across each study part (Parts 1-7)[2-5,10-13,15]

Real-World Evidence (RWE) and Post-Marketing Surveillance (PMS)

The real-world evidence studies by **Yamato et al (2024)** and **Tomita et al (2024)** and post-marketing surveillance study by **Hayashi et al (2025)** were conducted in Japan, where XOCOVA is approved by the Ministry of Health, Labour, and Welfare (MHLW) for both post-exposure prophylaxis and treatment of COVID-19.[16,17] In the US, XOCOVA is indicated only for post-exposure prophylaxis of COVID-19.[1] Real world evidence studies and a post-marketing surveillance study show ensitrelvir use in patients with hepatic comorbidities. These studies have not reported further AEs related to liver abnormalities.[18-20]

2. CLINICAL STUDIES

Phase 3 Clinical Studies

SCORPIO-PEP

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 household contacts (HHCs) of people who tested positive for COVID-19, conducted from June 2023 to September 2024.[10,21]

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 day 1 and 125 mg days 2-5) or placebo once daily for 5 days. Study participants began treatment within three days of when the household member with COVID-19 began showing symptoms (see **Appendix SCORPIO-PEP** for more information on study design and safety results).[10,22]

Relevant Inclusion/Exclusion Criteria

This study excluded patients with a known history of cirrhosis or liver decompensation, including ascites, variceal bleeding, or hepatic encephalopathy.[11]

Relevant Criteria for Study Intervention Discontinuation

The criteria for discontinuation of study intervention included if Day 1 chemistry showed an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 5 × upper limit of normal (ULN) range or ALT or AST ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN (> 35% direct bilirubin). Blood chemistry must have been repeated urgently.[11]

Relevant Assessments

Liver function tests (ALP, ALT, AST, total bilirubin, direct bilirubin, albumin, total protein) were performed in all HHCs as it was a protocol-specific requirement for inclusion or exclusion of participants. Laboratory assessments (including liver function tests) were conducted before taking the

first dose of study drug on Day 1 and on Days 6, 15, 28, and additionally at event-driven visits (new or worsening COVID-19 symptoms)[11]

Results

AEs Associated with Liver Abnormalities

Table 1 summarizes TEAEs associated to liver abnormalities in the safety population. None of these TEAEs were considered related to ensitrelvir.

Table 1. TEAEs Associated to Liver Abnormalities in Safety Population[11, a,b]

Preferred Term	**Ensitrelvir** (N=1190) n (%)	**Placebo** (N=1187) n (%)
AST increased	4 (0.3)[c,d]	2 (0.2)
ALT increased	2 (0.2)	3 (0.3)
Bilirubin conjugated	1 (<0.1)	0 (0)
Blood ALP increased	1 (<0.1)	0 (0)
Blood bilirubin increased	1 (<0.1)	1 (<0.1)
Hepatic enzyme increased	0 (0)	2 (0.2)
Autoimmune hepatitis	0 (0)	1 (<0.1)
Hepatic function abnormal	0 (0)	1 (<0.1)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse events.
[a]No TEAEs were related to ensitrelvir.
[b]Most AEs were mild in severity.
[c]AEs with moderate severity.
[d]AEs with severe severity.

A total of 7 liver events were reported in 7 participants; all events were associated with ALT or AST plasma levels ≥5 × upper limit of normal (ULN).[11]

SCORPIO-HR

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 and results).[5]

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 (see **Appendix SCORPIO-HR** for more information on study design and safety results).[5,23]

Relevant Inclusion/Exclusion Criteria

This study excluded patients with a known history of cirrhosis or liver decompensation, including ascites, variceal bleeding, or hepatic encephalopathy.[12]

Relevant Criteria for Study Intervention Discontinuation

The criteria for discontinuation of study intervention included if the Day 1 chemistry showed an ALT or AST ≥ 5 × ULN range or ALT or AST ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN (> 35% direct bilirubin); blood chemistry could be repeated urgently.[12]

Relevant Assessments

Blood chemistry tests (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, total protein) were performed in all participants as it was a protocol-specific requirement for inclusion or exclusion. Blood chemistry testing was done at study entry on Day 1, Days 4, 8, 16, 29, Week 12, event driven evaluation (worsening COVID-19 symptoms Days 6-29), premature study discontinuation before and after Day 29.[12]

Results

AEs Associated with Liver Abnormalities

The safety analysis population included participants who received ≥1 dose of ensitrelvir/placebo and was analyzed by study intervention received.[5]

Table 2 summarizes TEAEs associated to liver abnormalities in the safety population during the treatment period. The majority of the TEAEs were not associated with the study drug.

Table 2. TEAEs Associated to Liver Abnormalities in Safety Population (Day 1 to Day 29)[12, a,b]

Preferred Term	**Ensitrelvir** (N=1037) n (%)	**Placebo** (N=1048) n (%)
ALT increased	28 (2.7)	50 (4.8)
AST increased	31 (3.0)	33 (3.1)
Blood alkaline phosphatase increased	13 (1.3)	7 (0.7)
Hepatic enzyme increased	5 (0.5)	3 (0.3)
Transaminases increased	3 (0.3)	1 (0.1)
Blood bilirubin increased	2 (0.2)	5 (0.5)
Bilirubin conjugated increased	0 (0)	1 (0.1)
AST abnormal	0 (0)	1 (0.1)
Liver function test increased	0 (0)	1 (0.1)
Hyperbilirubinaemia	3 (0.3)	1 (0.1)
Hepatic steatosis	1 (0.1)	1 (0.1)
Hypertransaminasaemia	0 (0)	2 (0.2)
Hepatic function abnormal	0 (0)	1 (0.1)
Hepatitis	0 (0)	1 (0.1)
Hepatitis B	1 (0.1)	0 (0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse events.
[a] Most events were mild-to-moderate in severity. No potentially life-threatening events or deaths were reported with ensitrelvir due to liver abnormalities.
[b] Majority of the TEAEs were not associated to the study drug.

Table 3 provides a summary of potential liver function abnormalities in the safety population during the treatment period.

Table 3. Post-baseline ALT and AST Elevations in Safety Population (Day 1 to Day 29)[12]

Parameter	Post-baseline Category	Ensitrelvir (N=1037) n (%)	Placebo (N=1048) n (%)
ALT	<3× ULN	970 (93.5)	966 (92.2)
	≥3 to <5× ULN	8 (0.8)	15 (1.4)
	≥5 to <10× ULN	2 (0.2)	5 (0.5)
	≥10× ULN	1 (0.1)	1 (0.1)
	Missing	56 (5.4)	61 (5.8)
AST	<3× ULN	961 (92.7)	957 (91.3)
	≥3 to <5× ULN	10 (1.0)	8 (0.8)
	≥5 to <10× ULN	1 (0.1)	4 (0.4)
	≥10× ULN	1 (0.1)	1 (0.1)
	Missing	64 (6.2)	78 (7.4)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.
Baseline is defined as the last non-missing measurement prior to the first dose of study intervention.

Phase 2/3 Clinical Study

Study Design

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).[2-4,6,24]

Relevant Inclusion/Exclusion Criteria for parts 2a, 2b, 3, and 2b/3

Patients with a current or chronic history of moderate or severe liver disease and those with known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones) were excluded.[15]

Relevant Criteria for Study Intervention Discontinuation for parts 2a, 2b, 3, and 2b/3

The criteria for discontinuation of study intervention included ALT ≥3 x ULN and bilirubin ≥2 x ULN (direct bilirubin > 35%) or International Normalized Ratio (INR)> 1.5, if INR measured (INR value not applicable to subjects on anticoagulants); reported as serious adverse event in this case.[15]

Relevant Assessments for parts 2a, 2b, 3, and 2b/3

Blood chemistry tests (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, total protein) were performed in all participants as it was a protocol-specific requirement for inclusion or exclusion of participants. Blood chemistry testing was done on Day 1 of the intervention period, Days 6, 14, 28 of the follow-up period and at discontinuation.[15]

Phase 2a

Study Design

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.[2]

Results

AEs Associated with Liver Abnormalities

Patients were included in the safety cohort if they received ≥1 dose of the study drug.[2]

The incidence of TEAEs associated to liver abnormalities is summarized in **Table 4**.[2]

There were no serious TEAEs or TEAEs leading to treatment discontinuation reported that were due to liver abnormalities.[2]

Table 4. TEAEs and TRAEs in Phase 2a Safety Cohort: Liver Abnormalities[2,25, a,b]

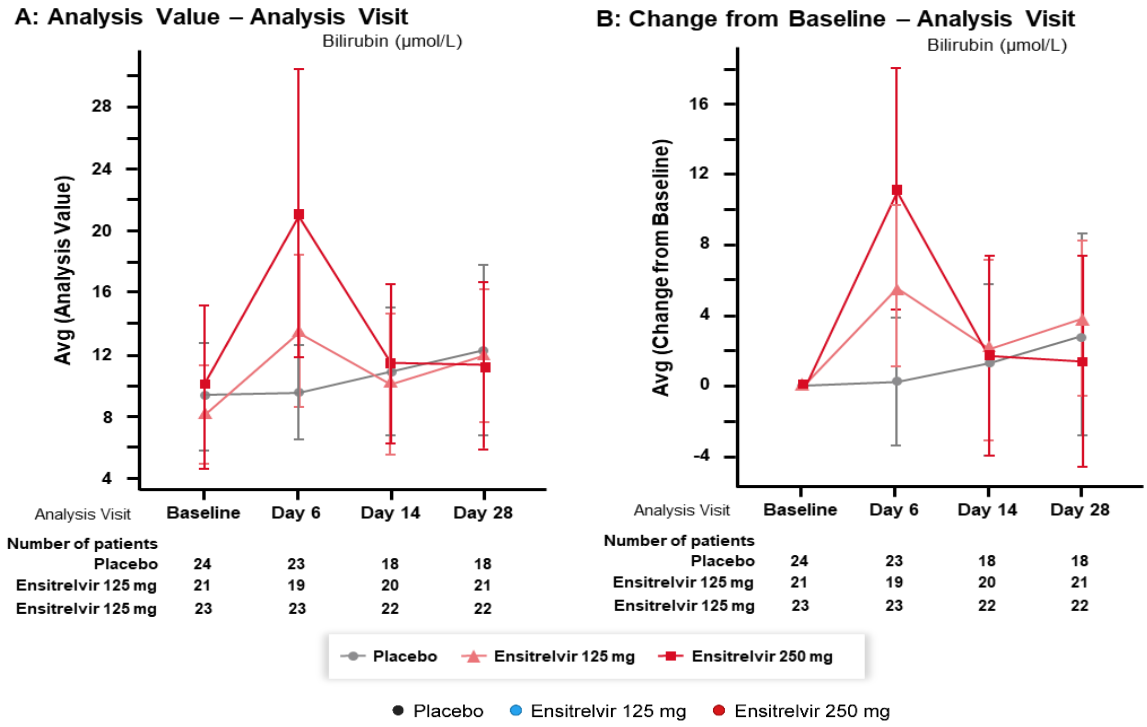
	Ensitrelvir 125 mg (N=21) n (%)	**Ensitrelvir 250 mg** (N=23) n (%)	**Placebo** (N=24) n (%)
TEAEs occurring in either group			
AST increased	1 (4.8)	1 (4.3)	2 (8.3)
Blood bilirubin increased	0 (0)	2 (8.7)	0 (0)
ALT increased	1 (4.8)	0 (0)	2 (8.3)
Hyperbilirubinaemia	0 (0)	1 (4.3)	0 (0)
GGT increased	1 (4.8)	0 (0)	1 (4.2)
TRAEs occurring in either group			
Blood bilirubin increased	0 (0)	1 (4.3)	0 (0)
Hyperbilirubinaemia	0 (0)	1 (4.3)	0 (0)

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event; TRAEs, treatment-related adverse events.
[a]Data for all patients who received ≥1 ensitrelvir or placebo dose are shown.
[b]All the liver abnormalities were mild in severity.

Total Bilirubin Levels

Patients were evaluated for total bilirubin levels at baseline and Days 6, 14, and 28 (**Figure 1**). A transient and asymptomatic increase in total bilirubin was observed in patients receiving ensitrelvir, which resolved without additional treatment.[2]

Figure 1. Phase 2a Safety Cohort: Levels of Total Bilirubin as (A) Absolute Values and (B) Change from Baseline[2]



Adapted from Mukae et al. 2022.

Phase 2b

Study Design

The Phase 2b, dose-finding part of the study was conducted from 2 January to 9 February 2022 at 87 institutions in Japan and South Korea. Patients with mild-to-moderate COVID-19 were randomized (1:1:1) to orally receive 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) once daily without dose modification and followed up until Day 28.[3]

Results

AEs Associated with Liver Abnormalities

The safety cohort comprised all randomized patients who received ≥1 dose of ensitrelvir or placebo.[3] There were no serious TEAEs or treatment discontinuations associated to liver abnormalities.[3]

The incidence of TEAEs and TRAEs associated with liver abnormalities is summarized in **Table 5.**

Table 5. TEAEs and TRAEs in Phase 2b Safety Cohort: Liver Abnormalities.[14, a]

Preferred Term	Ensitrelvir 125 mg (N=140) n (%)	Ensitrelvir 250 mg (N=140) n (%)	Placebo (N=141) n (%)
TEAEs occurring in either group			
ALT increased	2 (1.4)	1 (0.7)	1 (0.7)
AST increased	2 (1.4)	0 (0)	0 (0)
Blood bilirubin increased	1 (0.7)	2 (1.4)	1 (0.7)
Bilirubin conjugated increased	0 (0)	1 (0.7)	0 (0)
Hepatic enzyme increased	0 (0)	1 (0.7)	0 (0)
TRAEs occurring in either group			
ALT increased	1 (0.7)	0 (0)	1 (0.7)
AST increased	1 (0.7)	0 (0)	0 (0)
Blood bilirubin increased	1 (0.7)	1 (0.7)	1 (0.7)
Hepatic enzyme increased	0 (0)	1 (0.7)	0 (0)

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TRAEs, treatment-related adverse events.

[a]Most of the liver abnormalities were mild in severity, except for the TEAE of increased hepatic enzyme, which was moderate in severity.

Liver Function Test Abnormalities

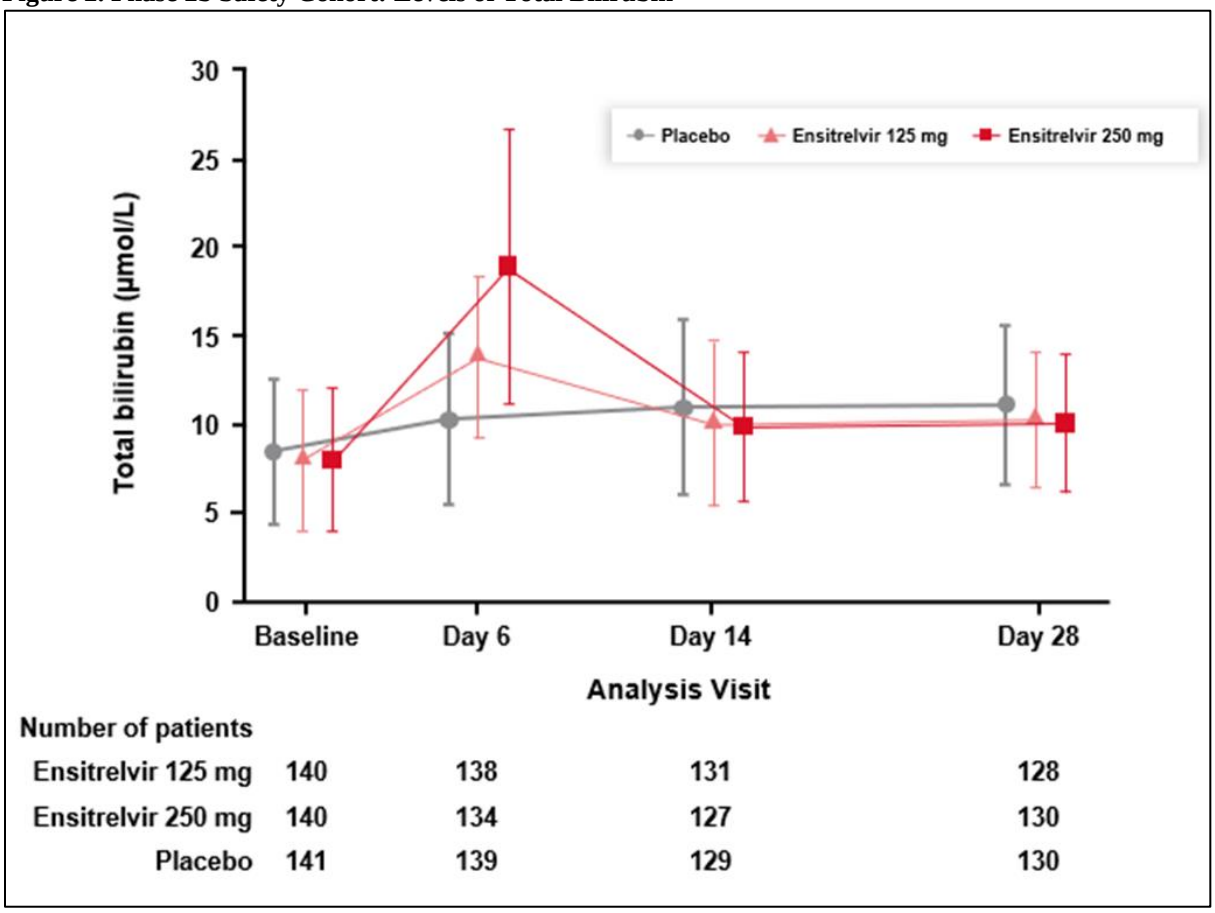
No participants met the criteria of ALT ≥3 × ULN and bilirubin ≥2 × ULN or international normalized ratio (INR) >1.5 (if INR was measured). Five participants had ALT values >5 × ULN, including 3 participants in the ensitrelvir 125 mg group and 2 participants in the ensitrelvir 250 mg group; no participants in the placebo group had ALT values >5 × ULN.[14]

Among participants with ALT values >5 × ULN, AEs of increased ALT, and increased AST, which were considered unrelated to study intervention, were reported in 1 participant in the ensitrelvir 125 mg group. An AE of an increased hepatic enzyme, considered related to the study intervention due to temporal relationship, was reported in 1 participant in the ensitrelvir 250 mg group. All reported events were non-serious and resolved or were resolving during the study period. No AEs were reported in the remaining 3 participants because abnormal liver function values were present before initiation of study intervention.[14]

Total Bilirubin Levels

Patients were evaluated for total bilirubin levels at baseline and Days 6, 14, and 28 (**Figure 2**). A dose-dependent transient change in total bilirubin was observed on Day 6 in both ensitrelvir groups, the patients were asymptomatic and the abnormalities resolved without additional treatment by Day 14. None of the patients showed an increase in serum bilirubin occurring concurrently with liver enzyme elevation.[3]

Figure 2. Phase 2b Safety Cohort: Levels of Total Bilirubin[3]



Adapted from Mukae et al. 2023.

Phase 3 (SCORPIO-SR)

Study Design

The SCORPIO-SR Phase 3 study was conducted at 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.[4]

Results

AEs Associated with Liver Abnormalities

The safety cohort comprised all randomized patients who received ≥1 dose of ensitrelvir or placebo.[4]

The incidence of TEAE and TRAEs associated with liver abnormalities is summarized in **Table 6**.

There were no treatment discontinuations associated with liver abnormalities. There were no deaths reported in the study.[4]

Table 6. Phase 3 Safety Cohort: TEAEs and TRAEs of Liver Abnormalities[4,13, a,b]

	Ensitrelvir 125 mg (N=604) n (%)	**Ensitrelvir 250 mg** (N=599) n (%)	**Placebo** (N=605) n (%)
TEAEs occurring in either intervention group			
Blood bilirubin level increased	36 (6.0)	56 (9.3)	6 (1.0)
Bilirubin conjugated increased	15 (2.5)	20 (3.3)	3 (0.5)
Blood LDH level increased	6 (1.0)	15 (2.5)	6 (1.0)
AST level increased	4 (0.7)	9 (1.5)	12 (2.0)
ALT increased	6 (1.0)	11 (1.8)	11 (1.8)
Blood ALP increased	2 (0.3)	1 (0.2)	0 (0)
Blood bilirubin unconjugated increased	2 (0.3)	0 (0)	0 (0)
Blood LDH decreased	1 (0.2)	1 (0.2)	0 (0)
GGT increased	1 (0.2)	1 (0.2)	3 (0.5)
Hepatic function abnormal	1 (0.2)[c]	0 (0)	0 (0)
Cholecystitis acute	0 (0)	0 (0)	1 (0.2)[d]
Hypertransaminasaemia	0 (0)	0 (0)	1 (0.2)
TRAEs occurring in either intervention group			
Blood bilirubin level increased	17 (2.8)	35 (5.8)	3 (0.5)
Hypertransaminasaemia	0 (0)	0 (0)	1 (0.2)
Blood LDH increased	4 (0.7)	8 (1.3)	4 (0.7)
ALT increased	3 (0.5)	6 (1.0)	7 (1.2)
AST increased	1 (0.2)	5 (0.8)	7 (1.2)
Bilirubin conjugated increased	1 (0.2)	2 (0.3)	1 (0.2)
Blood bilirubin unconjugated increased	2 (0.3)	0 (0)	0 (0)
GGT increased	1 (0.2)	0 (0)	2 (0.3)
Blood ALP increased	0 (0)	1 (0.2)	0 (0)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a] Data for all patients who received ≥1 ensitrelvir or placebo dose are shown.
[b] Most AEs were mild in severity.
[c] AE with moderate severity.
[d] AE with severe severity

Liver Function Test Abnormalities

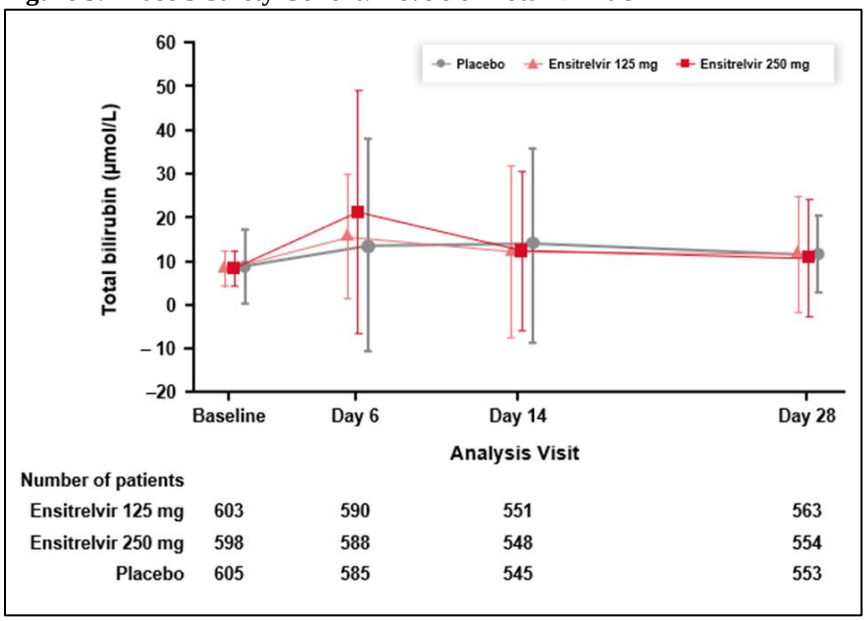
No participants met the criteria of ALT ≥3 × ULN with bilirubin ≥2 × ULN or INR >1.5 (if INR was measured). In the ensitrelvir 125 mg group, 3 participants had ALT values >5 × ULN and 1 participant had ALT values >3 × ULN for more than 4 weeks; no significant liver function test (LFT) abnormalities were reported in the ensitrelvir 250 mg group. In the placebo group, 3 participants had ALT values >5 × ULN.[13]

Among participants in the ensitrelvir 125 mg group, 1 participant with ALT >5 × ULN reported a non-serious AE of ALT increased that was considered related to the study intervention and was recovering at the end of follow-up. Another participant with ALT >5 × ULN reported a non-serious AE of abnormal hepatic function that was considered unrelated to the study intervention possibly due to progression of medical history. One participant with ALT >5 × ULN was considered to have hepatic dysfunction as a complication. The participant with ALT >3 × ULN for >4 weeks had abnormal liver function values prior to study intervention. No AEs related to LFTs were reported in the latter 2 participants.[13]

Total Bilirubin Levels

Patients from the safety cohort were evaluated for total bilirubin levels at baseline and Days 6, 14, and 28 (**Figure 3**). A transient change in total bilirubin was observed on Day 6 in both ensitrelvir groups, which resolved without additional treatment.[4]

Figure 3. Phase 3 Safety Cohort: Levels of Total Bilirubin[4]



Adapted from Yotsuyanagi et al. 2024.

Phase 2b/3

Study Design

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

Results

AEs Associated with Liver Abnormalities

The safety cohort comprised all randomized participants who received ≥1 dose of ensitrelvir or placebo.[6]

The incidence of TEAEs and TRAEs associated with liver abnormalities is summarized in **Table 7**.

There were no serious TEAEs associated with liver abnormalities.[6]

Table 7. Phase 2b/3 Safety Cohort: TEAEs and TRAEs of Liver Abnormalities[6,15, a,b]

	Ensitrelvir 125 mg (N=201) n (%)	**Ensitrelvir 250 mg** (N=202) n (%)	**Placebo** (N=201) n (%)
TEAEs occurring in either group			
Blood bilirubin increased	7 (3.5)	15 (7.4)	0 (0)
Bilirubin conjugated increased	3 (1.5)	7 (3.5)	0 (0)
Hepatic function abnormal	0 (0)	0 (0)	2 (1.0)
ALT increased	2 (1.0)	1 (0.5)	2 (1.0)
AST increased	2 (1.0)	0 (0)	2 (1.0)
Blood LDH increased	1 (0.5)	0 (0)	0 (0)
Hepatic enzyme increased	1 (0.5)	0 (0)	0 (0)
GGT increased	0 (0)	0 (0)	3 (1.5)
TRAEs occurring in either group			
Blood bilirubin increased	2 (1.0)	5 (2.5)	0 (0)
Hepatic function abnormal	0 (0)	0 (0)	2 (1.0)
ALT increased	1 (0.5)	0 (0)	1 (0.5)
AST increased	1 (0.5)	0 (0)	1 (0.5)
Blood LDH increased	1 (0.5)	0 (0)	0 (0)
GGT increased	0 (0)	0 (0)	2 (1.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a] Data for all patients who received ≥1 ensitrelvir or placebo dose are shown.
[b] All AEs associated with liver abnormalities were mild in severity.

Liver Function Test Abnormalities

No participants met the criteria of ALT ≥3 × ULN with bilirubin ≥2 × ULN or INR >1.5 (if INR was measured). One participant in the ensitrelvir 125 mg group had an ALT value >5 × ULN, which increased on Day 16 (11 days after the last administration of study intervention) and returned to within the normal range by Day 26. A non-serious TEAE of atypical pneumonia was reported, and no TEAEs associated with liver function tests were reported. The atypical pneumonia was considered unrelated to study intervention and resolved by Day 26. The investigator considered the ALT elevation to be associated with suspected atypical pneumonia, as ALT values on Day 10 were comparative to baseline

levels from before the study. No participants with significant LFT abnormalities were reported in the ensitrelvir 250 mg group or placebo group.[15]

Pooled Safety Analysis of Phase 2a, Phase 2b, Phase 3 (SCORPIO-SR), and Phase 2b/3 Parts

A pooled analysis combined the results of the safety population from the Phase 2a, Phase 2b, Phase 3, and Phase 2b/3 parts of the Phase 2/3 study.[15]

AEs Associated with Liver Abnormalities

The incidence of TEAEs and TRAEs associated with liver abnormalities is summarized in **Table 8**.

Table 8. Phase 2/3 Pooled Safety Analysis: TEAEs and TRAEs of Liver Abnormalities (Mild/Moderate and Asymptomatic/Mild Symptoms of SARS-CoV-2 Infection).[15, a]

	Ensitrelvir 125 mg (N=966) n (%)	**Ensitrelvir 250 mg** (N=964) n (%)	**Placebo** (N=971) n (%)
TEAEs occurring in either group			
Hepatic function abnormal	1 (0.1)	0 (0)	2 (0.2)
Hyperbilirubinemia	0 (0)	1 (0.1)	0 (0)
Cholecystitis acute	0 (0)	0 (0)	1 (0.1)[c]
Hypertransaminasaemia	0 (0)	0 (0)	1 (0.1)
Blood bilirubin increased	44 (4.6)	75 (7.8)	7 (0.7)
Bilirubin conjugated increased	18 (1.9)	28 (2.9)	3 (0.3)
ALT increased	11 (1.1)	13 (1.3)	16 (1.6)
Blood LDH increased	8 (0.8)	15 (1.6)	6 (0.6)
AST increased	9 (0.9)	10 (1.0)	16 (1.6)
GGT increased	2 (0.2)	1 (0.1)	7 (0.7)
Blood ALP increased	2 (0.2)	1 (0.1)	0 (0)
Blood bilirubin unconjugated increased	2 (0.2)	0 (0)	0 (0)
Blood LDH decreased	1 (0.1)	1 (0.1)	0 (0)
Hepatic enzyme increased	1 (0.1)	1 (0.1)	0 (0)
TRAEs occurring in either group			
Hyperbilirubinaemia	0 (0)	1 (0.1)	0 (0)
Hepatic function abnormal	0 (0)	0 (0)	2 (0.2)
Hypertransaminasaemia	0 (0)	0 (0)	1 (0.1)
Blood bilirubin increased	20 (2.1)	42 (4.4)	4 (0.4)
Blood LDH increased	5 (0.5)	8 (0.8)	4 (0.4)
ALT increased	5 (0.5)	6 (0.6)	9 (0.9)
AST increased	3 (0.3)	5 (0.5)	8 (0.8)
Bilirubin conjugated increased	1 (0.1)	2 (0.2)	1 (0.1)

Blood bilirubin unconjugated increased	2 (0.2)	0 (0)	0 (0)
GGT increased	1 (0.1)	0 (0)	4 (0.4)
Blood ALP increased	0 (0)	1 (0.1)	0 (0)
Hepatic enzyme increased	0 (0)	1 (0.1)[b]	0 (0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a] Most AEs were mild in severity.
[b] AEs with moderate severity.
[c] AEs with severe severity.

Phase 1 Clinical Study

Study Design

A Phase 1 study in Japan tested the safety, tolerability, and pharmacokinetics of ensitrelvir in healthy adult participants. Liver-associated laboratory assessments were monitored.[7-9]

Relevant Inclusion/Exclusion Criteria

Patients with current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) were excluded in all parts of the study.[26]

Patients were also excluded for any of the following abnormal values at screening or on admission: total bilirubin > 1.5 × the upper limit of the institutional reference range, ALT > 1.5 × the upper limit of the institutional reference range, or AST > 1.5 × the upper limit of the institutional reference range[26]

Relevant Criteria for Study Intervention Discontinuation

The criteria for discontinuation of study intervention included ALT ≥3 x ULN. An SAE was reported if ALT ≥3 x ULN AND total bilirubin ≥ 2 x ULN (direct bilirubin > 35%) or ALT ≥3 x ULN and INR> 1.5, if INR measured (INR value not applicable to subjects on anticoagulants)[26]

Relevant Assessments

Blood chemistry tests (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, total protein, γ-GTP, LDH) were performed in all participants as it was a protocol-specific requirement for inclusion or exclusion of participants. Blood chemistry tests were performed in all parts of the study on specific days.[26]

Results

AEs Associated with Liver Abnormalities

Across each study part (Parts 1-7), no AEs associated with liver abnormalities were reported.[26]

Additionally, no AEs associated with liver abnormalities were reported in other Phase 1 studies, including the drug-drug interaction study of ensitrelvir with transporter substrates[27], the study in participants with mild or moderate hepatic impairment[28], and the study in participants with mild, moderate, or severe renal impairment[29]. In the drug-drug interaction study of ensitrelvir with combined

oral contraceptives, clinically significant increases in ALT, AST, and lactate dehydrogenase were reported in 1 participant on Day 32 in association with an adverse event of Epstein-Barr virus infection. This event was moderate in severity, considered not related to study intervention, and resolved.[30]

3. REAL-WORLD STUDIES

The following real-world evidence and post-marketing surveillance studies were conducted in Japan, where XOCOVA is approved by the Ministry of Health, Labour, and Welfare (MHLW) for both post-exposure prophylaxis and treatment of COVID-19.[16,17] In the US, XOCOVA is indicated only for post-exposure prophylaxis of COVID-19.[1]

There were two RWE studies with information regarding ensitrelvir incidence of liver abnormalities, summarized below:

Yamato et al. 2024[18]
A retrospective chart review conducted in a Japanese hospital reported treatment outcomes for patients who received ensitrelvir while hospitalized with COVID-19 (N=32). Liver failure, chronic hepatitis B, and liver metastasis from cancer of the sigmoid colon were reported as a comorbidity in one patient each. No TRAEs were observed; the incidence of liver-associated abnormalities is unknown.

Tomita et al. 2024[19]
A retrospective chart review from a Japanese hospital reported treatment outcomes for patients aged ≥80 years who received ensitrelvir while hospitalized with COVID-19 (N=9). Chronic hepatitis was reported as a comorbidity in one patient. There were no TRAEs reported during treatment to Day 14 of follow-up.

4. SURVEILLANCE STUDY

Hayashi et al. 2025[20]
In the final analysis of ensitrelvir post-marketing surveillance in Japan from November 2022 to December 2023, which included 3,760 patients in the safety population, hepatic dysfunction at baseline was reported in 10 patients (0.3%). The study reported the incidence of adverse drug reactions (ADRs), of which the majority were non-serious (n=374). No ADRs, including serious or non-serious ADRs, were reported in patients with hepatic dysfunction. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Furthermore, a causal relationship between ensitrelvir and liver abnormalities cannot be established from the study.

5. 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.

As stated in Section 6.1 of the XOCOVA Full Prescribing Information (FPI):

6.1 Clinical Trials Experience:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.[1]

The overall safety profile of XOCOVA is based on data from 2,831 adults and adolescents exposed to the recommended dosage and duration of XOCOVA in controlled clinical trials.[1]

Trial SCORPIO-PEP was a randomized, double-blind, placebo-controlled trial in which 1,190 subjects received oral XOCOVA (375 mg [Day 1]/125 mg [Days 2-5]) and 1,187 subjects received oral placebo (Days 1-5). The most common adverse events (regardless of causality) occurring in ≥1% of the XOCOVA group and at a greater frequency compared to placebo were headache (2.9% and 2.6%, respectively), diarrhea (1.7% and 1.3%, respectively), and cough (1.1% and 0.6%, respectively). The proportion of subjects who discontinued study intervention due to an adverse event was <0.1% in both the XOCOVA and placebo groups.[1]

Laboratory Abnormalities:

Asymptomatic hemoglobin declines from baseline of >2g/dL occurred in 3% of XOCOVA recipients versus 1% of placebo recipients.[1]

Use in Specific Populations

Hepatic Impairment
No dosage adjustment for XOCOVA is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The impact of severe hepatic impairment on the pharmacokinetics of ensitrelvir is unknown.[1]

As stated in Section 7.3 of the XOCOVA FPI:

Section 7.3 Table 1 from the XOCOVA FPI provides example(s) of drugs that are contraindicated with XOCOVA in patients with hepatic impairment.[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 medicines contraindicated with XOCOVA due to potential hepatic complications. **See Table 1** in the XOCOVA FPI for the complete examples of drugs contraindicated with XOCOVA.

Excerpted Section of Table 1, XOCOVA FPI: Relevant Examples of Drugs 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
Antigout agents	colchicine	↑ colchicine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment
Microsomal triglyceride transfer protein (MTTP) inhibitors	lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions

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

6. LITERATURE SEARCH, ABBREVIATIONS, REFERENCES

LITERATURE SEARCH

As of August 2026, a computerized search of the published medical literature using PubMed has failed to identify any additional relevant references regarding ensitrelvir incidence of liver abnormalities. 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

3CL	3-chymotrypsin-like
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
LDH	lactate dehydrogenase
MHLW	Ministry of Health, Labour, and Welfare
PK	pharmacokinetic
PMS	post-marketing surveillance
RWE	real-world evidence
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event

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ENCLOSURE

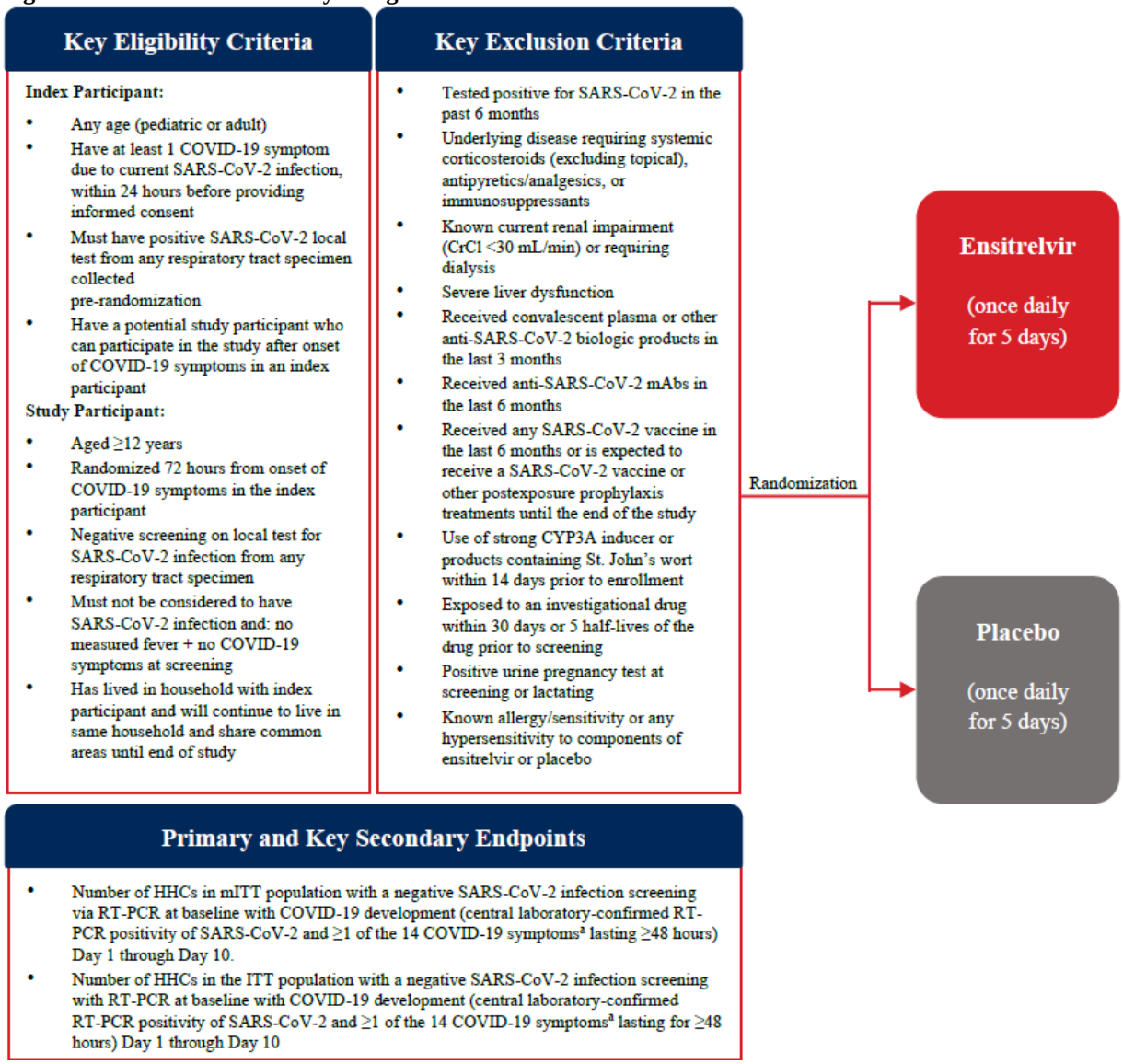
XOCOVA® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.

APPENDIX

SCORPIO-PEP (Phase 3)

Study Design

Figure 1. SCORPIO-PEP Study Design[10,21]



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

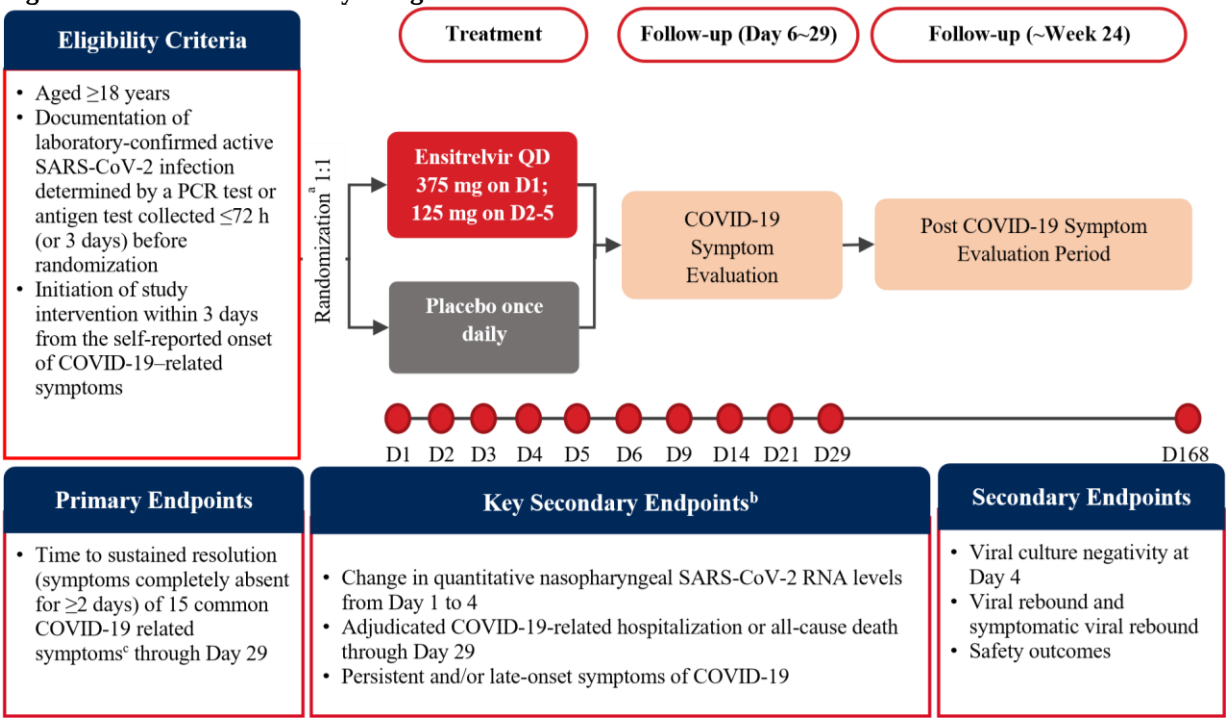
Safety

- 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[10]
- 2 serious TEAEs occurred in each group and they were considered to be unrelated to the study drug[10]
- There were no AEs that led to hospitalization and no deaths were observed in either group[10]

SCORPIO-HR (Phase 3)

Study Design

Figure 2. SCORPIO-HR Study Design[5,23]



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.

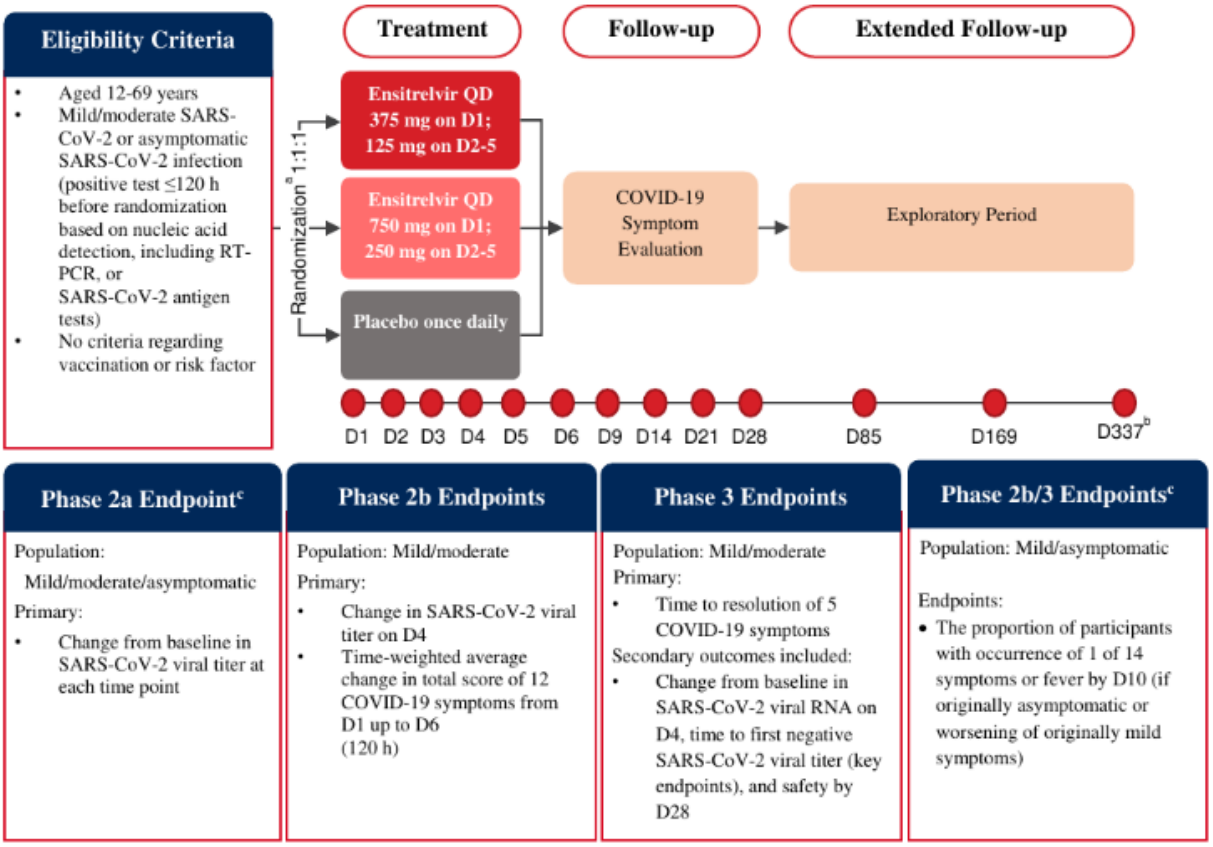
Safety

- 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 ensitrelvirtreated participants and 6/1048 (0.6%) of the patients given placebo. No serious treatment-related adverse events occurred in either group[5]

Phase 2/3 Study

Study Design

Figure 3. Phase 2/3 Study Design[2-4,6]



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

- Ensitrelvir therapy was well-tolerated, and no deaths were reported in the Phase 2/3 study; in the Phase 3 part, two serious TEAEs were reported (one in the ensitrelvir 125 mg and one in the placebo arm)[13,15]