Xocova® - SCORPIO-HR

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). 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

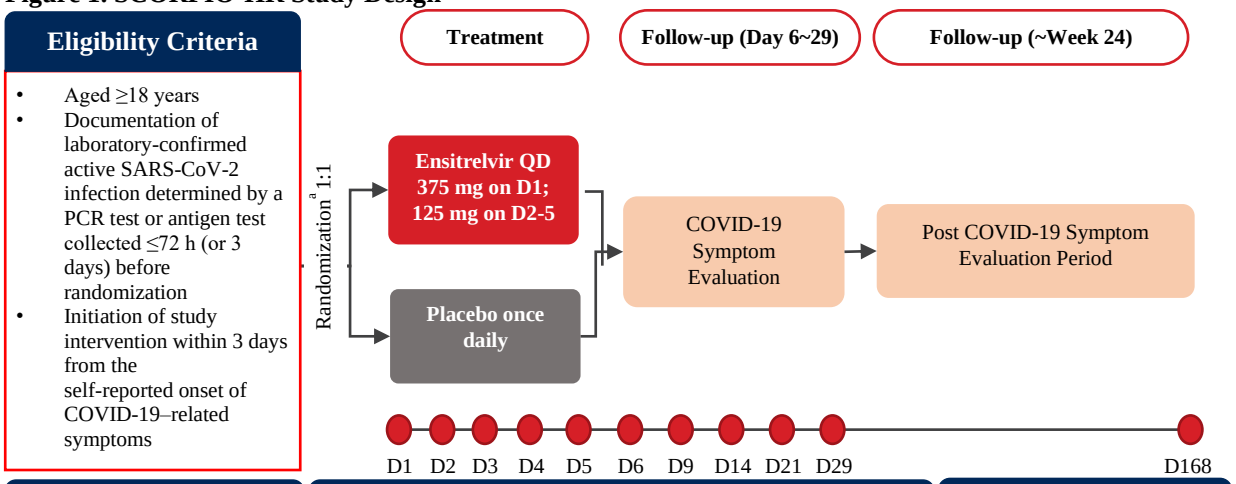
- The global, Phase 3 study, SCORPIO-HR (SCORPIO-HR, **S**topping **CO**VID-19 p**R**ogression with early **P**rotease **I**nhibit**O**r-**H**igh **R**isk), which assessed the clinical and antiviral effects of ensitrelvir vs placebo in nonhospitalized patients, has been completed.[1,2]
  - The primary endpoint for SCORPIO-HR, time to sustained resolution of 15 common COVID-19 related symptoms (completely absent for at least 2 days) through Day 29 demonstrated a numerical reduction for ensitrelvir compared to placebo, but was not statistically significant[2]
  - A pre-defined supportive analysis of time to resolution of 6 symptoms (completely absent for at least 1 day), yielded a numerical difference in time to resolution of symptoms, compared to placebo[2]
  - Ensitrelvir demonstrated an antiviral effect for both viral RNA and culture, compared to placebo[2]
  - Most treatment-emergent adverse events (TEAEs) were mild to moderate in severity, and no serious adverse events were considered treatment-related. There were no deaths observed in either group through Day 29[2]

2. SCORPIO-HR CLINICAL STUDY

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 (**Figure 1**). 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.[1-3]

Figure 1. SCORPIO-HR Study Design[1,2]



Primary Endpoints	Key Secondary Endpoints	Secondary Endpoints
• Time to sustained resolution (symptoms completely absent for ≥2 days) of 15 common COVID-19 related symptoms	• Change in quantitative nasopharyngeal SARS-CoV-2 RNA levels from Day 1 to 4 • Adjudicated COVID-19-related hospitalization or all-cause death through Day 29 • Persistent and/or late-onset symptoms of COVID-19	• Viral culture negativity at Day 4 • Viral rebound and symptomatic viral rebound • Safety outcomes

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

A fixed-sequence hierarchical approach was used to test the primary and key secondary endpoints. For tests higher in the hierarchy, a 2-sided significance level of 0.05 must be met to allow alpha to be passed to the next test down the chain. The remaining tests were not considered statistically significant and were not adjusted for multiplicity if the hierarchy was broken with a statistically nonsignificant result. These results should be interpreted like exploratory endpoints.[2]

STUDY RESULTS

Results

The modified intent-to-treat (mITT) analysis population for the primary endpoint included 1,888 patients total. Baseline characteristics were comparable between the ensitrelvir (N=945) and placebo arms (N=943). Overall, 32.7% of patients had ≥1 risk factors for progression to severe COVID-19 and 12.1% had ≥2 risk factors. Risk factors that were most commonly reported included obesity (15.2%), hypertension (13.2%), diabetes mellitus (7.5%), and age ≥65 years (6.0%).[2]

Efficacy

Primary Endpoint:

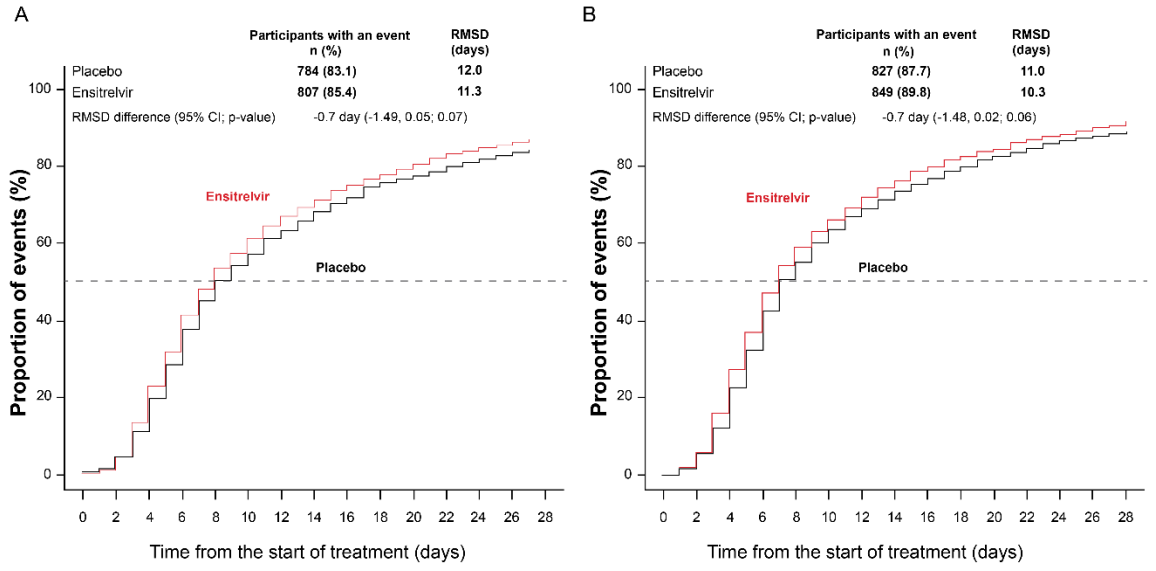
The primary endpoint of time to 2-day sustained resolution of 15 COVID-19 symptoms was not met (**Table 1**). The restricted mean time (days) to symptom resolution for 15 common COVID-19 related symptoms (symptoms completely absent for at least 2 days) for ensitrelvir vs placebo was 12.5 days vs

13.1 days respectively. Although a numerical reduction in the time to symptom resolution was demonstrated, the difference was not statistically significant (*P*=0.14 [Peto-Prentice's Wilcoxon test *P*=0.07]).[2]

Pre-defined Supportive Analysis:

Prespecified and post hoc supportive analyses similarly demonstrated numerically shorter time to symptom resolution with ensitrelvir than with placebo (**Table 1** and **Figure 2**).[2,4] An analysis of time to resolution of 6 symptoms (including cough, feeling feverish, fatigue, sore throat, and stuffy or runny nose) for at least 1 day in patients treated with ensitrelvir vs. placebo resulted in a restricted mean days to symptom resolution of 10.3 days vs 11 days, (unadjusted *P*=0.06 [Peto-Prentice's generalized Wilcox unadjusted *P*=0.02]), respectively. This analysis is similar to that used in SCORPIO-SR, but was not part of the statistical hierarchy, was not adjusted for multiplicity, and should be interpreted in an exploratory manner.[2]

Figure 2. SCORPIO-HR mITT population: Time to (A) ≥2 consecutive days and (B) ≥1 day of sustained resolution of 6 COVID-19 symptoms through Day 29



Adapted from Luetkemeyer et al. 2025
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; mITT, modified intention-to-treat; RMSD, restricted mean symptom duration.

Post-hoc supportive analysis:
An additional analysis of time to resolution of 15 symptoms for at least 1 day was shorter in patients treated with ensitrelvir vs. placebo (*P*=0.02 [Peto-Prentice's generalized Wilcox test]; **Table 1**). This analysis was not part of the statistical hierarchy, was not adjusted for multiplicity, and should be interpreted in an exploratory manner.[2]

Table 1. Time to Resolution of COVID-19 Symptoms Through Day 29[2]

Analysis	Number of COVID-19 symptoms evaluated[a]	Analysis population	Symptom resolution definition	Restricted mean days to symptom resolution				Median (IQR) from KM Estimate		Peto-Prentice's generalized Wilcoxon test (*P* value)
				Ensitrelvir	Placebo	Difference (95% CI)	*P* value	Ensitrelvir	Placebo	
Primary analysis	**15**	**mITT (N=1888)**	**≥ 2 consecutive days**	**12.5**	**13.1**	**-0.6 (-1.38, 0.19)**	**0.14**	**9.0 (5.0, 20.0)**	**10.0 (6.0, 22.0)**	**0.07**
Prespecified supportive analyses[b]	**15**	**mITT2[c] (N=1535)**	**≥ 2 consecutive days**	**12.3**	**13.0**	**-0.7 (-1.56, 0.16)**	**0.11**	-	-	-
	15	**mITT (N=1888)**	**≥ 1 day**	**11.4**	**12.2**	**-0.8 (-1.54, 0.01)**	**0.05**	-	-	-
	6	**mITT (N=1888)**	**≥ 1 day**	**10.3**	**11.0**	**-0.7 (-1.48, 0.02)**	**0.06**	**7.0 (4.0, 14.0)**	**7.0 (5.0, 15.0)**	**0.02**
Post hoc supportive analyses[b]	**15**	**mITT (N=1888)**	**≥ 1 day**	-	-	-	-	**8.0 (5.0, 16.0)**	**9.0 (5.0, 18.0)**	**0.02**
	15	**mITT2[c] (N=1535)**	**≥ 2 consecutive days**	-	-	-	-	**9.0 (6.0, 19.0)**	**10.0 (6, 21.0)**	**0.08**

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 19; IQR, interquartile range; KM, Kaplan-Meier; LoD, limit of detection; mITT, modified intention-to-treat; PCR, polymerase chain reaction.

Peto-Prentice's generalized Wilcoxon test is employed to compare the entire KM curve of time to symptom resolution between treatment groups. This test is often selected to increase the sensitivity of detecting a group difference in survival distributions in situations where the group difference in the KM curve is large during the early time points but decreases toward the end of a period.

[a]15 COVID-19 symptoms: stuffy nose, runny nose, sore throat, cough, 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. The 6 targeted COVID-19 symptoms for the prespecified supportive analysis were stuffy nose, runny nose, sore throat, cough, low energy or tiredness, and feeling hot or feverish.

[b]Supportive analyses were not part of the statistical hierarchy, were not adjusted for multiplicity, and should be interpreted in an exploratory manner.

[c]The mITT2 population included all randomized participants who took ≥1 dose of ensitrelvir or placebo and who started intervention within 3 d of symptom onset with positive PCR results (above limit of detection) on Day 1.

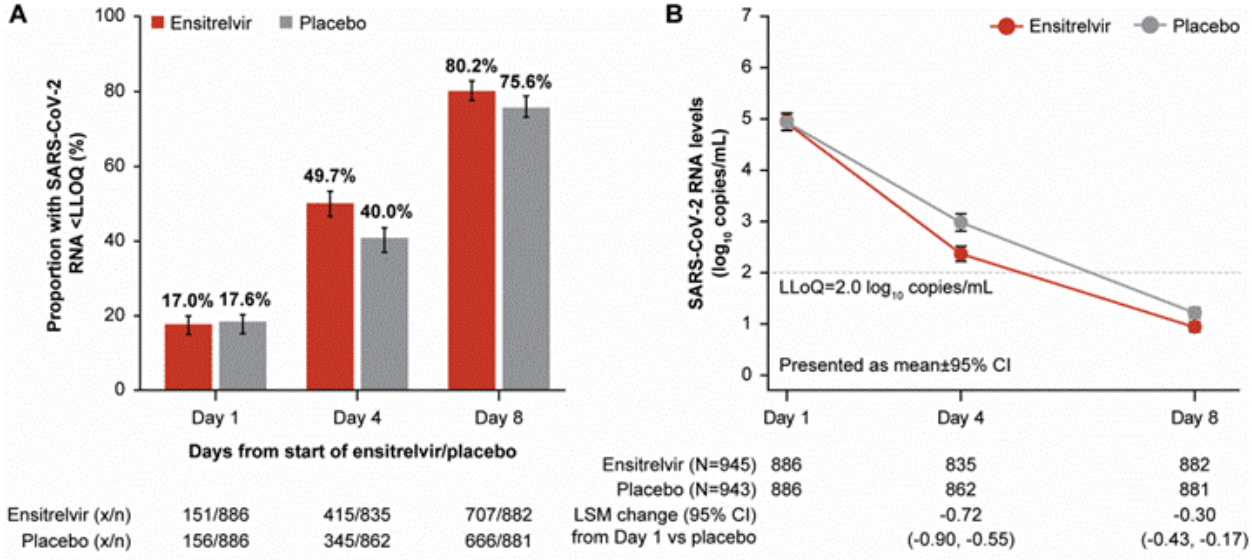
Key Secondary and Secondary Endpoints:

For SCORPIO-HR, the primary efficacy endpoint was not statistically significant, therefore secondary endpoint results are descriptive in nature; as such, secondary endpoints should be interpreted in an exploratory manner.[2]

Key Secondary Endpoint: The change in quantitative SARS-CoV-2 RNA level at Day 4 showed a 0.72 log_{10} copies/mL greater reduction in least squares mean RNA with ensitrelvir vs placebo (**Figure 3**).[2]

At Day 4, the proportion of patients (mITT population) in the ensitrelvir arm vs placebo arm with a SARS-CoV-2 RNA less than the lower limit of quantification (LLoQ) is 50% (415/835) vs 40% (345/862), respectively, copies/ml greater reduction in least squares mean RNA with ensitrelvir vs placebo (**Figure 3**).[2]

Figure 3. Antiviral Efficacy as Assessed by (A) Proportion of Participants with SARS-CoV-2 RNA level <LLoQ (mITT population), and (B) Change in Quantitative SARS-CoV-2 RNA Level on D4 and D8 (mITT population)[2]



Adapted from Luetkemeyer et al. 2025

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LLoQ, lower limit of quantification; LSM, least-squares mean; mITT, modified intention-to-treat; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ULoQ, upper limit of quantification.

A, The proportion of participants with SARS-CoV-2 RNA levels below the LLoQ in the mITT population. Data are presented as percentage (%) ± 95% CI.

B, The adjusted mean change in SARS-CoV-2 viral RNA from D 1 in the mITT population.

ANCOVA was used to obtain the estimate of difference in mean and associated 95% CI adjusted for D1. Participants who were alive and not hospitalized on D4 or D8 but who had missing RNA values (including due to loss to follow-up, samples not obtained, lost samples, and laboratory issues) on D4 or D8, respectively, were excluded. As the primary efficacy endpoint was not statistically significant, secondary endpoint results are descriptive. For quantitative analyses of log_{10} SARS-CoV-2 RNA, D1, D4, and D8 values were imputed. D1, D4, and D8 values that were detected and were <LLoQ were imputed as 1.7 log_{10} SARS-CoV-2 RNA; undetected values were imputed as 0.0; and values above ULoQ = 8.0 were imputed as 8.3 log_{10} SARS-CoV-2 RNA.

Secondary endpoint: Among participants with positive viral culture (>LLoQ) at enrollment, negative viral culture was seen in 95.5% (274/287) of patients treated with ensitrelvir and 75% (210/280) patients treated with placebo at Day 4.[2]

Secondary endpoint: Viral rebound occurred in 0.6% of ensitrelvir-treated and 1.4% of placebo-treated participants by Day 29. Viral rebound was defined as an increase in quantitative viral RNA by at least 1.0

log_{10} from the previous quantifiable value or increase to at least 1.0 log_{10} above LoD or LLoQ if the previous value was <LoD or <LLoQ.[2]

Secondary endpoint: No symptomatic viral rebound (defined as viral rebound in the setting of new or worsening clinical symptoms) was observed.[2]

Key Secondary endpoint: Ensitrelvir did not demonstrate a statistically significant reduction in the proportion of participants with post COVID-19 symptoms (long COVID-19) at 3 months. There was a tendency for a higher proportion of participants to report "having returned to pre-COVID health" and "felt no fatigue" with ensitrelvir compared to placebo. Further detailed analysis is planned, including additional analysis of the long COVID-19 endpoints at 24 weeks.[3]

Safety:

In the safety population (n=2085), adverse events in the ensitrelvir group (n=1037) and the placebo group (n=1048) were assessed through Day 29.[2]

Adverse events occurred in 638 patients treated with ensitrelvir (61.5%; n=1037), and 635 patients treated with placebo (60.6%; n=1048) (**Table 2**). Treatment-related adverse events occurred in 86 (8.3%) of patients treated with ensitrelvir and 74 (7.1%) of patients that were given placebo. Serious treatment-emergent adverse events (TEAE) occurred in 5 (0.5%) of the ensitrelvir-treated participants and 6 (0.6%) of the patients given placebo. No serious treatment-related adverse events occurred in either group.[2]

COVID-19–related hospitalization was observed in 3 (0.3%) ensitrelvir-treated patients and 1 (0.1%) placebo-treated participant.[2]

Adverse events in the safety analysis population through Day 29 can be seen in **Table 3**

No deaths were observed in either group.[2]

Table 2. SCORPIO-HR: Summary of AEs in the Safety Analysis Population through Day 29[2,a]

n (%)	Ensitrelvir 125 mg (n=1037)	Placebo (n=1048)	Total (n=2085)
TEAEs	638 (61.5)	635 (60.6)	1273 (61.1)
Serious TEAEs other than death[b]	5 (0.5)	6 (0.6)	11 (0.5)
Maximum event Grade 3 or 4	116 (11.2)	151 (14.4)	267 (12.8)
TEAEs leading to permanent discontinuation	6 (0.6)	5 (0.5)	11 (0.5)
Treatment-related AEs	86 (8.3)	74 (7.1)	160 (7.7)
Serious TEAEs other than death[b]	0	0	0
TEAEs leading to permanent discontinuation	2 (0.2)	2 (0.2)	4 (0.2)
Event leading to treatment interruption	2 (0.2)	1 (0.1)	3 (0.1)
COVID-19–related hospitalizations	3 (0.3)	1 (0.1)	4 (0.2)
Death	0	0	0

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; COVID-19, coronavirus disease 19; TEAE, treatment-emergent adverse event.

[a]The safety analysis population included participants who received at least 1 dose of ensitrelvir or placebo and were analyzed according to the study intervention that the participants received rather than the intervention to which they were randomized to. The severity of adverse events was graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) [26].

[b]Overall, 11 (0.5%) participants reported 14 SAEs: increased alanine aminotransferase, increased aspartate aminotransferase. increased hepatic enzyme, decreased lymphocyte count, acute myocardial infarction, pericarditis, appendicitis, lower respiratory tract infection, cerebral atrophy, migraine, abdominal pain, pyrexia, dyslipidemia, and myalgia.

Table 3. Adverse Events in the Safety Analysis Population Through Day 29[a4]

System organ class	Ensitrelvir (n=1037)	Placebo (n=1048)	Total (n=2085)
Treatment-related adverse events leading to treatment discontinuation			
Gastrointestinal disorders	1 (0.1)	2 (0.2)	3 (0.1)
Diarrhoea	0	1 (0.1)	1 (0.0)
Nausea	1 (0.1)	0	1 (0.0)
Vomiting	0	2 (0.2)	2 (0.1)
Investigations	0	1 (0.1)	1 (0.0)
Blood pressure increased	0	1 (0.1)	1 (0.0)
Skin and subcutaneous tissue disorders	1 (0.1)	0	1 (0.0)
Pruritus	1 (0.1)	0	1 (0.0)
Serious adverse events through Day 29			
Gastrointestinal disorders	0	1 (0.1)	1 (0.0)
Abdominal pain	0	1 (0.1)	1 (0.0)
General disorders and administration site conditions	1 (0.1)	0	1 (0.0)
Pyrexia	1 (0.1)	0	1 (0.0)
Cardiac disorders	1 (0.1)	1 (0.1)	2 (0.1)
Acute myocardial infarction	0	1 (0.1)	1 (0.0)
Pericarditis	1 (0.1)	0	1 (0.0)
Infections and infestations	0	2 (0.2)	2 (0.1)
Appendicitis	0	1 (0.1)	1 (0.0)
Lower respiratory tract infection	0	1 (0.1)	1 (0.0)
Investigations	2 (0.2)	1 (0.1)	3 (0.1)
Alanine aminotransferase increased	0	1 (0.1)	1 (0.0)
Aspartate aminotransferase increased	0	1 (0.1)	1 (0.0)
Hepatic enzyme increased	1 (0.1)	0	1 (0.0)
Lymphocyte count decreased	1 (0.1)	0	1 (0.0)
Metabolism and nutrition disorders	0	1 (0.1)	1 (0.0)
Dyslipidaemia	0	1 (0.1)	1 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.1)	0	1 (0.0)
Myalgia	1 (0.1)	0	1 (0.0)
Nervous system disorders	1 (0.1)	1 (0.1)	2 (0.1)
Cerebral atrophy	1 (0.1)	0	1 (0.0)
Migraine	0	1 (0.1)	1 (0.0)

Table adapted from Luetkemeyer et al. *Clin Infect Dis*. 2025

[a]The safety analysis population included participants who received at least 1 dose of ensitrelvir or a placebo and were analyzed according to the study intervention the participants received rather than the intervention to which they were randomized. Participants with multiple events within a category were counted only once for that category. The severity of adverse events was graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017)

3. 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.[5]

CONTRAINDICATIONS

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[5]

XOCOVA is contraindicated in patients taking drugs that are[5]:

- 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.[5]

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.

4. LITERATURE SEARCH, ABBREVIATIONS, AND REFERENCES

LITERATURE SEARCH

As of March 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) failed to identify any relevant references regarding ensitrelvir and SCORPIO-HR. 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	LSM	least-squares mean
(ACTIV)-2	Accelerating COVID 19 Therapeutic Interventions and Vaccines	MHLW	Ministry of Health, Labour, and Welfare
ACTG	AIDS Clinical Trials Group	mITT	modified intention-to-treat
AIDS	acquired immunodeficiency syndrome	NIH	National Institutes of Health
ANCOVA	analysis of covariance	PCR	polymerase chain reaction
CI	confidence interval	PK	pharmacokinetic
COVID-19	coronavirus disease 2019	RMSD	restricted mean symptom duration
D	day	RNA	ribonucleic acid
h	hours	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
IQR	interquartile range	SCORPIO-HR	Stopping COVID-19 pRogression with early Protease InhibitOr-High Risk
KM	Kaplan-Meier	TEAE	treatment-emergent adverse event
LLoQ	lower limit of quantification	ULoQ	upper limit of quantification
LoD	limit of detection	US	United States

REFERENCES

1. A study to compare S-217622 with placebo in non-hospitalized participants with COVID-19 (SCORPIO-HR). Accessed March 6, 2023. https://clinicaltrials.gov/ct2/show/NCT05305547?term=nCT05305547&draw=2&rank=1

2. 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*. 2025;doi:/10.1093/cid/ciaf029/8017725
3. Shionogi provides updates from SCORPIO-HR, a global phase 3 study of ensitrelvir for non-hospitalized participants with COVID-19. May 13, 2024. Accessed May 13, 2024. https://www.shionogi.com/global/en/news/2024/05/E_20240513_1.html
4. 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;(Suppl)doi:10.1093/cid/ciaf029
5. Xocova® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.

ENCLOSURE

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