Xocova - Clinical Trial Program

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

- Shionogi conducted a Phase 2/3 clinical study in Asia to evaluate the efficacy, safety, and pharmacokinetics (PK) of ensitrelvir (125 and 250 mg) given orally, once daily for 5 days vs placebo in patients with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection.[1-5]
- SCORPIO-HR 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 five days) vs placebo in nonhospitalized patients with COVID-19 with or without high risk factors for severe COVID-19.[6,7]
- SCORPIO-PEP is a global Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical study that evaluated the safety and efficacy of ensitrelvir (oral once daily for 5 days) in the prevention of symptomatic COVID-19 from household contacts of people who tested positive for COVID-19, when compared to placebo.[8-10]
- Shionogi conducted a Phase 3, randomized, double-blind, placebo-controlled clinical study that evaluated the safety and efficacy of treatment with ensitrelvir (oral once daily for 5 days) vs. placebo in children (6 to 11 years of age) who were SARS-CoV-2 positive within 72 hours before randomization and with at least 1 moderate or severe COVID-19 symptom at screening.[11,12]
- Shionogi conducted a Phase 1 clinical study in Japan to assess safety, tolerability, and PK of single and multiple ascending oral doses of ensitrelvir in healthy participants, as well as the effect of food, the comparison of PK of ensitrelvir in healthy Japanese and White participants, and the drug-drug interaction (DDI) potential of ensitrelvir co-administered with cytochrome P450 3A (CYP3A) substrates in healthy adults.[13-15]
- A Phase 1 study conducted in Japan to assess the DDI potential of ensitrelvir co-administered with transporter substrates in healthy Japanese patients[16]
- A Phase 1 study to assess safety, tolerability, and PK of ensitrelvir in participants with renal impairment was conducted in the US.[17,18]
- A Phase 1 study to assess safety, tolerability, and PK of ensitrelvir in participants with mild and moderate hepatic impairment was conducted in the US.[19,20]
- A Phase 1 study to assess drug-drug interactions of ensitrelvir combined with oral contraceptives in healthy adult females conducted in the US.[21,22]

2. CLINICAL DEVELOPMENT PROGRAM

The ensitrelvir Clinical Development Program is summarized in **Table 1** and **Table 2**.

Table 1. Phase 2/3, Phase 3 and Phase 2 Studies

Study Name	Study Description	Primary Endpoint	Regions of Study	Age Population
Phase 2/3 Study[1,2,4,5,23] (jRCT2031210350)	Phase 2/3, multicenter, randomized, DB, PC clinical study that evaluated the efficacy and safety of two different doses of ensitrelvir (125 mg or 250 mg) vs placebo administered orally, once daily for 5 days in patients with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection regardless of risk factors for progressing to severe disease		Asia	≥12 to <70 years
Phase 2a part[1,23]	An exploratory analysis of patients with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection. Majority of patients were infected with the Delta variant and vaccinated	Change from baseline in SARS-CoV-2 viral titer at each time point	Japan	
Phase 2b part[1,4]	Included patients with mild-to-moderate COVID-19. Most patients were infected with the Omicron variant BA.1 and >80% of patients were vaccinated	Time-weighted average change in total score of 12 COVID-19 symptoms from Day 1 up to Day 6; Change from baseline on Day 4 in SARS-CoV-2 viral titer	Japan, South Korea	
Phase 3 part (SCORPIO-SR)[1,5]	Included patients with mild-to-moderate COVID-19. Most patients were infected with Omicron variant BA.2 and >90% vaccinated	Time to resolution of five COVID-19 symptoms	Japan, Vietnam, South Korea	
Phase 2b/3 part[1,2]	An exploratory analysis of a subset of patients from SCORPIO-SR who tested positive for SARS-CoV-2 but were asymptomatic or had only mild symptoms. Most patients were infected with the Omicron variant and >90% were vaccinated	Proportion of participants with occurrence of symptoms if they were originally asymptomatic or worsening of COVID-19 symptoms if they originally only had mild symptoms at enrollment by Day 10	Japan, Vietnam, South Korea	
SCORPIO-HR[6,7] (NCT05305547)	Phase 3, randomized, DB, PC, multicenter, 24-week clinical study that evaluated the safety, clinical and antiviral effects of ensitrelvir (oral once daily for 5 days) vs placebo in nonhospitalized patients with confirmed symptomatic COVID-19 with or without high risk factors for severe COVID-19. It is a part of the ACTIV clinical trials portfolio, overseen by the ACTG and supported by the NIH	Median time to sustained symptom resolution	North America, South America, Europe, Asia, and Africa	≥18 years
SCORPIO-PEP[8-10] (NCT05897541)	Phase 3, randomized, DB, PC, multicenter clinical study that evaluated the safety and efficacy of ensitrelvir (oral once daily for 5 days) in the prevention of symptomatic COVID-19 from household contacts of people who tested positive for COVID-19, when compared to placebo	Number of participants in the mITT population with a negative screening SARS-CoV-2 infection who are infected with SARS-CoV-2 and have COVID-19 symptoms onset (from Day 1 through Day 10)	North America, Europe, South America, Africa, Asia	≥12 years

Pediatric trial[11,12] (jRCT2031230140)	Phase 3, randomized, DB, PC clinical study evaluated the safety and efficacy of treatment with ensitrelvir (oral once daily for 5 days) vs. placebo in children who were SARS-CoV-2 positive within 72 hours before randomization and with at least 1 moderate or severe COVID-19 symptom at screening	Adverse events, laboratory tests, vital signs, and plasma concentration of ensitrelvir	Japan	≥6 to ≤11 years

All studies listed above have been completed.
Abbreviations: ACTG, AIDS Clinical Trials Group; ACTIV, Accelerating COVID-19 Therapeutic Interventions and Vaccines; COVID-19, coronavirus disease 19; DB, double-blind; DRS-60, Days to Recovery Scale assessed over 60 days; mITT, modified intention-to-treat; NIH, National Institutes of Health; PC, placebo-controlled; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoC, standard of care.

Table 2. Phase 1 Studies

Study Name	Study Description	Regions of Study	Age Population
A Phase 1 Study of S-217622 in Healthy Adult Participants[13-15,a] (jRCT2031210202)	A seven-part study to assess the safety, tolerability, and PK of single and multiple doses of ensitrelvir in healthy participants, as well as the effect of food, the comparison of PK of ensitrelvir in healthy Japanese and White participants, and DDI potential of ensitrelvir with CYP3A substrates	Japan	
Part 1: Single-ascending–dose part	Single-center, randomized, DB, PC study in Japanese healthy adult male participants who were administered a single oral dose of ensitrelvir in the fasted state; consisted of six cohorts (A, B, C, D, E, and J); in Cohort C, the effect of food was investigated in a two-group, two-period crossover design		≥20 to ≤55 years
Part 2: Multiple-ascending–dose part	Multicenter, randomized, DB (open-label for midazolam in Cohort G), PC study in Japanese and White healthy adult male participants and in Japanese healthy adult female participants who were administered multiple ascending doses of ensitrelvir in the fasted state; consisted of five cohorts (F to H, N and O)		≥20 to ≤55 years
Part 3: Drug-drug interaction part	Multicenter, single-arm, open-label study in Japanese healthy adult male participants who were coadministered ensitrelvir and either dexamethasone or prednisolone; consisted of two cohorts (L and M)		≥20 to ≤55 years
Part 4: Food-effect part	Single-center, randomized, open-label, two-group two-period crossover study in Japanese healthy adult participants who were administered ensitrelvir in the fasted state or after a high-calorie, high-fat breakfast; consisted of a single cohort (P)		≥20 to ≤55 years
Part 5: White/multiple-ascending–dose part	Single-center, randomized, DB, PC study in White healthy adult participants who were administered multiple ascending doses of ensitrelvir; consisted of two cohorts (Q and R)		≥20 to ≤55 years
Part 6: Elderly part	Single-center, randomized, DB, PC study in healthy elderly participants who were administered ensitrelvir; consisted of a single cohort (S)		≥65 years
Part 7: DDI of S-217622 (125-mg tablets) with midazolam	Single-center, single-arm, open-label study in Japanese healthy adult participants who were coadministered ensitrelvir 125 mg and midazolam; consisted of a single cohort (T)		≥20 to ≤55 years
Evaluation of Drug-Drug Interactions of Ensitrelvir, a SARS-CoV-2 3CL Protease Inhibitor, With Transporter Substrates Based on In Vitro and Clinical Studies[16] (jRCT2031210595)	Single-center, single-arm, open-label study in Japanese healthy adult participants who were coadminstered ensitrelvir 500 mg and a cocktail of medications including digoxin, rosuvastatin, and metformin	Japan	≥20 to ≤55 years

A Study to Assess S-217622 in Participants With Renal Impairment and Healthy Participants [17,18] (NCT05363215)	Phase 1, open-label, parallel-group study to assess the PK, safety, and tolerability of ensitrelvir in participants with mild, moderate, and severe renal impairment, and control participants with normal renal function	United States	≥18 to ≤80 years
A Study to Assess S-217622 in Participants With Mild and Moderate Hepatic Impairment and Healthy Control Participants[19,20] (NCT05409911)	Phase 1, open-label, parallel-group study to assess the PK, safety, and tolerability of ensitrelvir in participants with mild and moderate hepatic impairment, and control participants with normal hepatic function	United States	≥18 to ≤80 years
A Study to Assess Drug-Drug Interactions of S-217622 in Combination with Oral Contraceptives in Healthy Adult Females[21,22] (NCT06775730)	A Phase 1, interventional study in adult females that evaluated DDIs between multiple doses of a combined oral contraceptive and ensitrelvir high dose and multiple doses of ensitrelvir low dose.	United States	≥18 to ≤35 years

Abbreviations: CYP3A, cytochrome P450 3A; DB, double-blind; DDI, drug-drug interactions; PC, placebo-controlled; PK, pharmacokinetics.
[a]Please note that the three publications that report on the various parts of this phase 1 study use differing nomenclature. Therefore, we have used our own method of numbering the study parts for added clarity.

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.[24]

CONTRAINDICATIONS

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[24]

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.[24]

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, & REFERENCES

LITERATURE SEARCH

As of February 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) failed to identify any additional relevant references regarding information on ensitrelvir's clinical trial program. 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	MHLW	Ministry of Health, Labour and Welfare
ACTG	AIDS Clinical Trials Group	mITT	modified intention-to-treat
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines	NDA	New Drug Application
COVID-19	coronavirus disease 19	NIH	National Institutes of Health
CYP3A	cytochrome P450 3A	PC	placebo-controlled
D	day	PK	pharmacokinetics
DB	double-blind	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
DDI	drug-drug interaction	SCORPIO-PEP	Stopping COVID-19 pRogression with early Protease InhibitOr-Post-Exposure Prevention
DRS-60	Days to Recovery Scale assessed over 60 days	SCORPIO-HR	Stopping COVID-19 pRogression with early Protease InhibitOr-High Risk
h	hours	SoC	standard of care
ITT	intention-to-treat	US	United States

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Enclosure

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