Xocova - Use in Post-Exposure Prophylaxis

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Summary

- **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]**

- The **SCORPIO-PEP** study, a double-blind, randomized, placebo-controlled trial, evaluated the efficacy and safety of ensitrelvir when used as post-exposure prophylaxis in household contacts (HHCs) who were exposed to SARS-CoV-2.[2]
  - In the mITT population, a statistically significant risk reduction for COVID-19 was observed in the ensitrelvir group vs the placebo group at Day 10 (primary endpoint: 2.9% [30/1030] vs 9.0% [91/1011]; RR 0.33, 95% CI: 0.22–0.49, *P*<0.0001). [2]
  - In the ITT population, the proportion of HHCs that developed COVID-19 was significantly lower in the ensitrelvir group vs the placebo group (key secondary endpoint: 4.4% [52/1194] vs 10.2% [122/1193]; RR 0.43, 95% CI: 0.32–0.59, *P*<0.0001).[2,3]
  - Prespecified subgroup analysis in the mITT population showed:
    - HHCs with high risk factors and without high risk factors for severe COVID-19 had a reduced risk of COVID-19 development in the ensitrelvir vs placebo treatment groups (2.4% [9/382] vs 9.9% [37/374], RR 0.24, 95% CI: 0.12, 0.49; *P*<0.0001) and (3.2% [21/648] vs 8.5% [54/637], RR 0.39, 95% CI: 0.24, 0.62; *P*=0.0001), respectively.[2,4,5]
    - The proportion of patients that developed COVID-19 (time from initial symptom development in the index patient to post exposure prophylaxis initiation) in <48 hours and within 48–72 hours was lower in the ensitrelvir group vs the placebo group (2.5% [18/732] vs 10.3% [74/720], RR 0.26, 95% CI: 0.16-0.41) and (4.0% [12/298] vs 5.8% [17/291], RR 0.69, 95% CI: 0.33-1.42), respectively.[2,3]
    - COVID-19 development in the ensitrelvir and placebo treatment groups according to age of HHCs (<18 years, 18–64 years, and ≥65 years) was 1.6% [1/64] vs 3.7% [2/54], RR 0.42, 95% CI: 0.04-4.57, 3.0% [26/867] vs 9.0% [78/867], RR 0.34, 95% CI: 0.23-0.52, and 3.0% [3/99] vs 12.2% [11/90], RR 0.25, 95% CI: 0.08-0.82, respectively.[2,3]
  - Post-hoc analyses in the mITT population showed:
    - Numerically lower mean (SD) viral RNA levels through Day 10 were observed in the ensitrelvir group (n=30) vs placebo (n=91) among participants with breakthrough infections (5.0 [2.0] vs 6.3 [1.9] $\log_{10}$ copies/mL).[2,3]
    - Symptom scores (mean [SD]) through Day 10 were numerically lower among participants with breakthrough infections in the ensitrelvir (n=30) vs placebo (n=91) groups (6.6 [4.7] vs 8.9 [4.9]).[2,3]
  - AEs occurred in 15.1% (180/1190) patients in the ensitrelvir group and 15.5% (184/1187) in the placebo group. Two serious TEAEs occurred in each group; none were considered related to the study drug.[2]

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SCORPIO-PEP (Phase 3 Trial)



2023–2024

Study Design[2,3,6]

SCORPIO-PEP (NCT05897541) is a completed Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical study that evaluated the safety and efficacy of ensitrelvir in the prevention of symptomatic COVID-19 in COVID-negative (local test) HHCs aged ≥12 years living with COVID-19-positive index patients when compared to placebo (Figure 1).

- Ensitrelvir 375 mg was given orally once on Day 1, followed by ensitrelvir 125 mg orally once daily on Days 2–5 to HHCs in the active group, while placebo was given to the control group. Patients were followed up for up to 28 days.
- This study was conducted across the US, Japan, Vietnam, Argentina, and South Africa from June 2023 to September 2024.

Primary Endpoint[2]

- The proportion of HHCs in the mITT population with COVID-19 development through Day 10, defined as having a positive central RT-PCR and ≥1 of the 14 symptoms of COVID-19 lasting at least 48 hours.
  - This includes the worsening (higher symptom score than baseline) of preexisting COVID-19-like symptoms.

Key Secondary Endpoint[2,3]

- The proportion of HHCs in the ITT population with COVID-19 development through Day 10, defined as having a positive central RT-PCR and ≥1 of the 14 symptoms of COVID-19 lasting at least 48 hours.
  - This includes the worsening (higher symptom score than baseline) of preexisting COVID-19-like symptoms.

Secondary Endpoints[2,3,7]

- The proportion of HHCs infected with SARS-CoV-2 through Day 10, 15, 21 or 28 regardless of COVID-19 symptom occurrence.
- The time to the first positive RT-PCR result through Day 10.
- The proportion of HHCs with a positive RT-PCR result through Day 10.
- Changes in SARS-CoV-2 viral RNA levels.
- The proportion of HHCs with asymptomatic COVID-19 development through Day 10.
- The proportion of HHCs with prolonged resolution of all COVID-19 symptoms through Day 28.
- The proportion of HHCs with prolonged resolution of each COVID-19 symptom through Day 28.
- The change in the COVID-19 symptom total score through Day 10.
- The time from the first confirmed COVID-19 test until the onset of ≥1 COVID-19 symptom through Day 28.
- The time from first confirmed COVID-19 test until COVID-19 symptom development through Day 28
- The proportion of HHCs with hospitalization or death (from any cause) through Day 28
- The plasma levels of ensitrelvir at visits 2 or 3, and Event-Driven.
- The proportion of HHCs developing TEAEs through Day 28.

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SCORPIO-PEP (Phase 3 Trial)

Figure 1. SCORPIO-PEP Study Design[2,3,6]

Key Eligibility Criteria

Index Participant:

- Any age (pediatric or adult)
- Have at least 1 COVID-19 symptom due to current SARS-CoV-2 infection, within 24 hours before providing informed consent
- Must have positive SARS-CoV-2 local test from any respiratory tract specimen collected pre-randomization
- Have a potential study participant who can participate in the study after onset of COVID-19 symptoms in an index participant

Study Participant:

- Aged ≥12 years
- Randomized 72 hours from onset of COVID-19 symptoms in the index participant
- Negative screening on local test for SARS-CoV-2 infection from any respiratory tract specimen
- Must not be considered to have SARS-CoV-2 infection and: no measured fever + no COVID-19 symptoms at screening
- Has lived in household with index participant and will continue to live in same household and share common areas until end of study

Key Exclusion Criteria

- Tested positive for SARS-CoV-2 in the past 6 months
- Underlying disease requiring systemic corticosteroids (excluding topical), antipyretics /analgesics, or immunosuppressants
- Known current renal impairment (CrCl <30 mL/min) or requiring dialysis
- Severe liver dysfunction
- Received convalescent plasma or other anti-SARS-CoV-2 biologic products within 3 months of the screening visit
- Received approved, authorized, or investigational anti-SARS-CoV-2 mAbs in the last 3 months [3]
- Received any SARS-CoV-2 vaccine in the last 6 months or is expected to receive a SARS-CoV-2 vaccine or other postexposure prophylaxis treatments until the end of the study
- Use of strong CYP3A inducer or products containing St. John's wort within 14 days prior to enrollment
- Exposed to an investigational drug within 30 days or 5 half-lives of the drug prior to screening
- Positive urine pregnancy test at screening or lactating
- Known allergy/sensitivity or any hypersensitivity to components of ensitrelvir or placebo

Randomization

Ensitrelvir (once daily for 5 days)

Placebo (once daily for 5 days)

Primary Endpoint

- Number of participants in mITT population with a negative SARS-CoV-2 infection screening via RT-PCR at baseline with COVID-19 development (CLC RT-PCR positivity of SARS-CoV-2 and ≥1 of the 14 COVID-19 symptoms lasting ≥48 hours, or a worsening symptom score from baseline in the case of preexisting symptoms) Day 1 through Day 10

Key Secondary Endpoint

- Number of participants in the ITT population (all randomized HHCs, including those who were RT-PCR-positive at baseline) with COVID-19 development (CLC RT-PCR positivity of SARS-CoV-2 and ≥1 of the 14 COVID-19 symptoms lasting ≥48 hours, or a worsening symptom score from baseline in the case of preexisting symptoms) Day 1 through Day 10

Abbreviations: CLC, central laboratory-confirmed; COVID-19, Coronavirus disease 19; CrCl, creatinine clearance; CYP3A, cytochrome P450 enzyme 3A4; mAbs, monoclonal antibodies; mITT, modified intention-to-treat; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

mITT population and ITT population. [2,3]

- The mITT population included all randomized HHCs with central laboratory-confirmed SARS-CoV-2 negativity by RT-PCR at baseline.*
- The ITT population included all randomized HHCs, including those with central laboratory RT-PCR positivity at baseline.

*Participants with local (-) and central (+) were excluded from the mITT population.

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SCORPIO-PEP (Phase 3 Trial)

Baseline Characteristics

- The total mITT population included 1030 HHCs (COVID-19-negative individuals living with COVID-19-positive index patients) treated with ensitrelvir and 1011 HHCs given placebo. An index patient was defined as the first person in a household with documented COVID-19.[2]
- Among the index patients, 1319 patients were enrolled; 56.0% were female, and the majority of patients resided in the US (55.0%). Antiviral therapy was reported in 18.7% of index patients, most commonly ensitrelvir (13.6%). Approximately 83% of index patients had more than one HHCs.[2]
- Among HCCs, baseline characteristics were generally similar between treatment groups. Overall, 59.3% of HHCs were female, the mean age was 42.4 years, and 9.3% were aged ≥65 years; majority of participants were in the US (67.2%). Most HHCs (71.1%) were enrolled less than 48 hours from symptom onset in the index patient. Approximately 37% had high-risk factors for severe illness, most commonly obesity, smoking, and age >65 years. More than 98% of HHCs were positive for antinucleocapsid or antispike antibodies or both.[2] Two (0.2%) patients in the ensitrelvir treatment group had immunocompromising conditions.[1] While HHCs were ineligible to enter the study if they had received a SARS-CoV-2 vaccine within the previous 6 months[2], prior COVID-19 vaccination was reported in 70% of patients in both groups overall.[1,2]

Efficacy Results: Primary Endpoint

- In the mITT population, a statistically significant risk reduction for symptomatic COVID-19 was observed in the ensitrelvir group vs the placebo group through Day 10 (2.9% vs 9.0%, RR, 0.33; 95% CI: 0.22–0.49, *P*<0.0001) (Table 1 and Figure 2).[2]

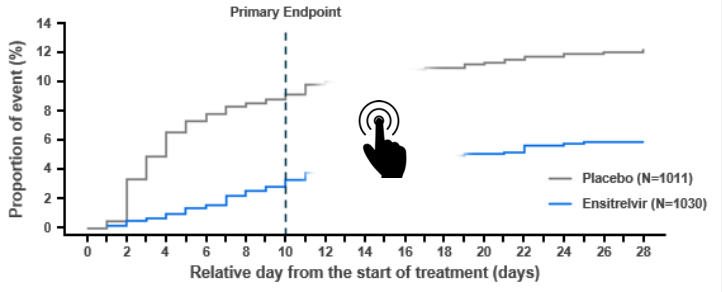
Efficacy Results: Key Secondary Endpoint

- Overall, the proportion of HHCs from the ITT population that developed symptomatic COVID-19 through day 10 was significantly lower in the ensitrelvir group vs the placebo group (4.4% [52/1194], 95% CI: 3.27–5.67 vs 10.2% [122/1193], 95% CI: 8.56–12.09; RR 0.43, 95% CI: 0.32–0.59, *P*<0.0001).[2,3]

Table 1. Proportion of HHCs with Symptomatic COVID-19 Development Through Day 10 (mITT)[2,3]

Timepoint	Ensitrelvir Events (%) [95% CI][a] (N=1030)	Placebo Events (%) [95% CI][a] (N=1011)	RR[b] [95% CI][c]	*P* Value[d]
COVID-19 development	30 (2.9) [1.97–4.13]	91 (9.0) [7.31–10.94]	0.33 [0.22–0.49]	<0.0001

Figure 2. HHCs with Symptomatic COVID-19 Development Through Day 28 (mITT)[5]



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SCORPIO-PEP (Phase 3 Trial)

Table 1. Proportion of HHCs with Symptomatic COVID-19 Development Through Day 10 (mITT)[2,3]

Timepoint	Ensitrelvir Events (%) [95% CI][a] (N=1030)	Placebo Events (%) [95% CI][a] (N=1011)	RR[b] [95% CI][c]	*P* Value[d]
COVID-19 development	30 (2.9) [1.97–4.13]	91 (9.0) [7.31–10.94]	0.33 [0.22–0.49]	<0.0001

Abbreviations: CI, confidence interval; COVID-19, Coronavirus disease 2019; GEE, generalized estimating equation; HHC, household contact; mITT, modified intention-to-treat; RoW, rest of world; RR, risk ratio.
[a]CI for the proportion of participants with symptomatic COVID-19 using the Clopper-Pearson method.
[b]RR based on the GEE Poisson regression model with covariates of time from symptom onset in the index patient to the enrollment (<48 hours/≥48 hours) and the pooled geographic regions (North America/Japan/RoW).
[c]CI calculated from GEE Poisson regression model.
[d]*P* value for the log coefficient of treatment effect equal to zero in the GEE Poisson regression model.
Table adapted from Hayden et al. *NEJM.* 2026.

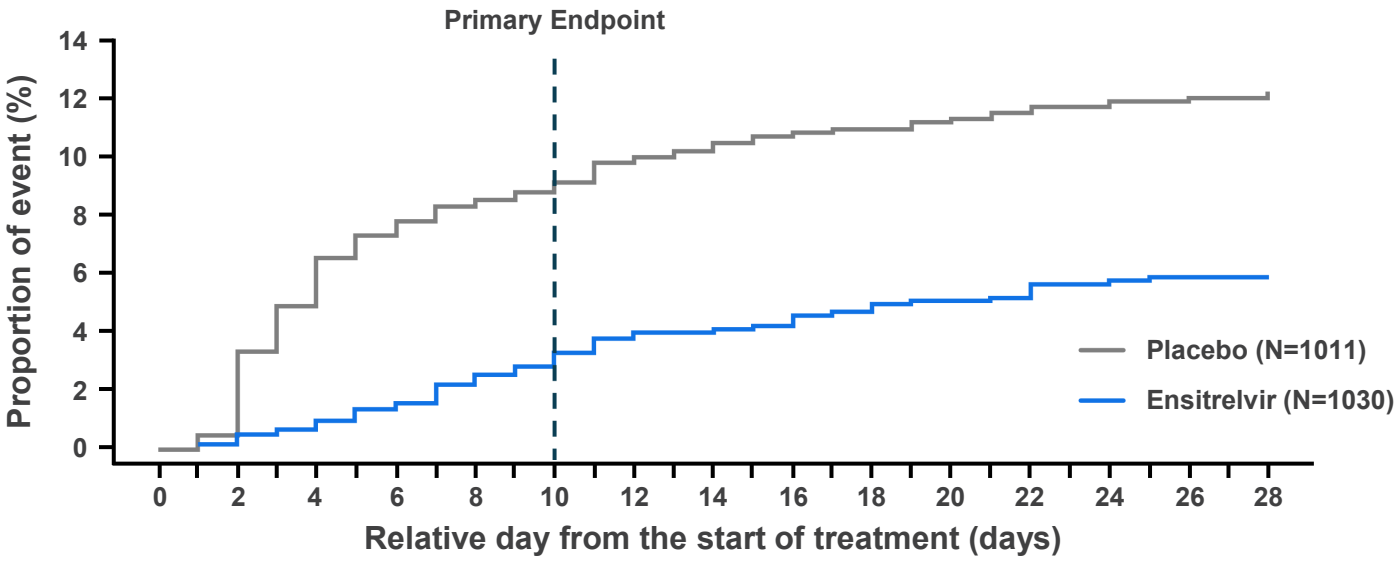
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Figure 2. HHCs with Symptomatic COVID-19 Development Through Day 28 (mITT)[5]



Data labeled as a primary endpoint was multiplicity controlled. All other comparisons presented here were not adjusted for multiplicity; therefore, no clinical or statistical conclusions can be made, and data should be interpreted with caution

Abbreviations: COVID-19, Coronavirus disease 2019; HHC, household contact; mITT, modified intention-to-treat.
Participants who were randomized but did not receive treatment were excluded from this analysis.
Figure adapted from Shinkai et al. CROI. 2025.

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SCORPIO-PEP (Phase 3 Trial)

Efficacy Results: Prespecified Subgroup Analyses

- Prespecified subgroup analyses in the mITT population are provided that looked at HHCs with or without high risk for COVID-19 (**Table 2**), at time from initial symptom onset in the index patient to PEP (**Table 3**), and the effect of the HHC according to age (**Table 4**).[2-5]

Subgroup analyses were not controlled for multiplicity and are exploratory in nature. Additionally, findings derived from observational data should be interpreted with caution, and no definitive conclusions can be drawn.

Table 2. HHCs With or Without High Risk for Severe COVID-19 Subgroup Analysis (mITT)[2,4,5]

	Ensitrelvir (N=1030)	Placebo (N=1011)
High Risk*, n (%) COVID-19 development	382 9 (2.4)	374 37 (9.9)
RR[a]	0.24	
95% CI[a]	0.12–0.49	
P value[b]	<0.0001 (nominal)	
High Risk absent, n (%) COVID-19 development		637 54 (8.5)
RR[a]	0.39	
95% CI[a]	0.24–0.62	
P value[b]	0.0001 (nominal)	

Table 3. Time from Initial Symptom Development in Index Patient to Post-Exposure Prophylaxis Subgroup Analysis (mITT)[2,3]

	Ensitrelvir (N=1030)	Placebo (N=1011)
Less than 48 hours, n COVID-19 onset, n (%)	732	720 74 (10.3)
RR[a] (95% CI)	0.26 (0.16–0.41)	
Between 48-72 hours, n COVID-19 onset, n (%)		291 17 (5.8)
RR[a] (95% CI)	0.69 (0.33–1.42)	

Table 4. Effect of HHC According to Age Subgroup Analysis (mITT)[2,3]

	Ensitrelvir (N=1030)	Placebo (N=1011)
Age less than 18 years, n COVID-19 development, n (%)	64 1 (1.6)	54 2 (3.7)
RR[a] (95% CI)	0.42 0.04–4.57	
Age 18–64 years, n COVID-19 development, n (%)		867 78 (9)
RR[a] (95% CI)	0.34 0.23–0.52	
Age ≥65 years, n COVID-19 development, n (%)		90 11 (12.2)
RR[a] (95% CI)	0.25 0.08–0.82	

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Table 2. HHCs With or Without High Risk for Severe COVID-19 Subgroup Analysis (mITT)[2,4,5]

	Ensitrelvir (N=1030)	Placebo (N=1011)
High Risk*, n (%) **COVID-19 development**	382 9 (2.4)	374 37 (9.9)
RR[a]	0.24	
95% CI[a]	0.12–0.49	
***P* value[b]**	<0.0001 (nominal)	
High Risk absent, n (%) **COVID-19 development**	648 21 (3.2)	637 54 (8.5)
RR[a]	0.39	
95% CI[a]	0.24–0.62	
***P* value[b]**	0.0001 (nominal)	

Abbreviations: CLC, central laboratory-confirmed; COVID-19, Coronavirus disease 2019; GEE, generalized estimating equation; HHC, household contact; mITT, modified intention-to-treat; RT-PCR, reverse transcriptase polymerase chain reaction.
COVID-19 development was defined as a CLC positive RT-PCR test and the occurrence (or worsening [increase in symptom score from baseline] in the case of preexisting COVID-19-like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
[a]RR and its 95% CI was calculated by GEE Poisson regression model.
[b]*P* value for the log coefficient of the treatment effect equal to 0 in the GEE Poisson regression model. These are nominal *P* values since subgroup analyses were not controlled for multiplicity.
*High-risk was defined ≥1 of the following risk factors: BMI ≥30 kg/m2, smoking (current or former), age (≥65 years), heart disease, diabetes (type 1 or type 2).
Table adapted from Hayden et al. *NEJM.* 2026, Hayden et al. ESCMID. 2025, and Shinkai et al. CROI. 2025.

Subgroup analyses were not controlled for multiplicity and are exploratory in nature. Additionally, findings derived from observational data should be interpreted with caution, and no definitive conclusions can be drawn.

An analysis looking at the time from initial symptom development in the index patient to PEP is provided in Table 3.

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Table 3. Time from Initial Symptom Development in Index Patient to Post-Exposure Prophylaxis Subgroup Analysis (mITT)[2,3]

	Ensitrelvir (N=1030)	Placebo (N=1011)
Less than 48 hours, n	732	720
COVID-19 onset, n (%)	18 (2.5)	74 (10.3)
RR[a]	0.26	
(95% CI)	(0.16–0.41)	
Between 48-72 hours, n	298	291
COVID-19 onset, n (%)	12 (4)	17 (5.8)
RR[a]	0.69	
(95% CI)	(0.33–1.42)	

Abbreviations: CI, confidence interval; CLC, central laboratory-confirmed; COVID-19, Coronavirus disease 2019; GEE, generalized estimating equation; mITT, modified intention-to-treat; RR, risk ratio; RT-PCR, reverse transcriptase polymerase chain reaction.
COVID-19 development was defined as a CLC positive RT-PCR test and the occurrence (or worsening [increase in symptom score from baseline] in the case of preexisting COVID-19-like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
[a]RR and its 95% CI was calculated by GEE Poisson regression model.
Table adapted from Hayden et al. *NEJM.* 2026.

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Table 4. Effect of HHC According to Age Subgroup Analysis (mITT)[2,3]

	Ensitrelvir (N=1030)	Placebo (N=1011)
Age less than 18 years, n	64	54
COVID-19 development, n (%)	1 (1.6)	2 (3.7)
RR[a] (95% CI)	0.42 (0.04–4.57)	
Age 18–64 years, n	867	867
COVID-19 development, n (%)	26 (3)	78 (9)
RR[a] (95% CI)	0.34 (0.23–0.52)	
Age ≥65 years, n	99	90
COVID-19 development, n (%)	3 (3)	11 (12.2)
RR[a] (95% CI)	0.25 (0.08–0.82)	

Abbreviations: CI, confidence interval; CLC, central laboratory-confirmed; COVID-19, Coronavirus disease 2019; GEE, generalized estimating equation; HHC, household contact; mITT, modified intention-to-treat; RR, risk ratio; RT-PCR, reverse transcriptase polymerase chain reaction. COVID-19 development was defined as a CLC positive RT-PCR test and the occurrence (or worsening [increase in symptom score from baseline] in the case of preexisting COVID-19-like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
[a]RR and its 95% CI was calculated by GEE Poisson regression model.
Table adapted from Hayden et al. *NEJM.* 2026.

Subgroup analyses were not controlled for multiplicity and are exploratory in nature. Additionally, findings derived from observational data should be interpreted with caution, and no definitive conclusions can be drawn.

Efficacy Results: Subgroup Analysis

- A subgroup analysis that looked at HHCs with or without a high risk for COVID-19 in the mITT population is provided in Table 2.
- An analysis looking at the time from initial symptom development in the index patient to PEP is provided in Table 3.

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SCORPIO-PEP (Phase 3 Trial)

Efficacy Results: Post-Hoc Analyses

- Among breakthrough infections in the mITT population, mean (SD) viral RNA levels through Day 10 were numerically lower in the ensitrelvir group (n=30) compared with the placebo (n=91) group (5.0 [2.0] vs 6.3 [1.9] log_{10} copies/mL).[2,3]
- Among breakthrough infections in the mITT population, mean (SD) total symptom scores through Day 10 were numerically lower in the ensitrelvir group (n=30) compared with the placebo (n=91) group (6.6 [4.7] vs 8.9 [4.9]).[2,3]

Post-hoc analyses were exploratory in nature and not controlled for multiplicity; therefore, data should be interpreted with caution.

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SCORPIO-PEP (Phase 3 Trial)

Safety Results

- AEs occurred in 15.1% of patients in the ensitrelvir group and 15.5% in the placebo group.[2]
- Safety data are provided in **Table 5**.[2]

Table 5. TEAEs in the Safety Analysis Set[2]

TEAE, n (%)	Ensitrelvir (N=1190)[a]	Placebo (N=1187)[a]
Any TEAEs	180 (15.1)	184 (15.5)
TEAEs ≥1%		
Headache	35 (2.9)	30 (2.5)
Diarrhea	21 (1.8)	15 (1.3)
Nasopharyngitis	16 (1.3)	15 (1.3)
Cough	14 (1.2)	7 (0.6)
Influenza	13 (1.1)	19 (1.6)
Fatigue	13 (1.1)	12 (1.0)
Oropharyngeal pain	11 (0.9)	17 (1.4)
Any serious TEAEs	2 (0.2)	2 (0.2)
Any study drug-related TEAEs	19 (1.6)	21 (1.8)
Any study drug-related serious TEAES	0	0
Any TEAEs leading to treatment discontinuation	1 (<0.1)	1 (<0.1)
Any TEAEs leading to study discontinuation	0	1 (<0.1)
COVID-19-related hospitalization	0	0
COVID-19-related Death	0	0

Abbreviations: AE, adverse event; HHC, household contact; SAS, safety analysis set; TEAEs, treatment-emergent adverse events.
[a]n represents the number of participating HHCs with each type of AE, and percentages are based on the number of participating HHCs in the SAS within each treatment group.
Table adapted from Hayden et al. *NEJM*.2026.

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Relevant Prescribing Information

Indication 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:

- 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:

Section 6.1 - Clinical Trials Experience

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]

Section 14.1 - Post-Exposure Prophylaxis of COVID-19

Trial SCORPIO-PEP was a randomized, double-blind, placebo-controlled, multinational post-exposure prophylaxis trial in 5 countries [NCT05897541] evaluating XOCOVA in asymptomatic standard- or high-risk adult and adolescent subjects considered not to have SARS-CoV-2 infection. Eligible subjects were 12 years of age or older, had a negative screening test for SARS-CoV-2 as determined by nucleic acid amplification test or antigen test at the local laboratory, and lived in a household with the index patient for the duration of the study. The trial excluded individuals who were using or were anticipating use of any medications prohibited with XOCOVA. The primary endpoint was the incidence of COVID-19 (defined as the onset of COVID-19 symptoms with duration for at least 48 hours and RT-PCR-confirmed SARS-CoV-2 infection) within 10 days of randomization in the modified intention-to-treat (mITT) population, which excluded subjects subsequently found to be SARS-CoV-2 RT-PCR-positive at baseline by central laboratory testing. A key secondary endpoint, which was the same as the primary endpoint but analyzed in the intention-to-treat (ITT) population, was evaluated in all subjects (including those subsequently found to be RT-PCR-positive at baseline by central laboratory testing).[1]

Subjects were randomized (1:1) to study intervention (XOCOVA 375 mg on Day 1 followed by 125 mg on Days 2-5 or matching placebo on Days 1-5) and enrolled within 72 hours of symptom onset in an index patient of COVID-19 within their household.[1]

A total of 2387 subjects were randomized to receive either XOCOVA or placebo. Baseline demographic and disease characteristics were balanced between the XOCOVA and placebo arms.[1]

The primary and key secondary endpoints were met. A 67% reduction in confirmed symptomatic COVID-19 (with symptom duration of at least 48 hours) on Day 10 (primary endpoint) was achieved with XOCOVA (relative risk ratio, 0.33; 95% CI, 0.22, 0.49; p <0.0001). For the key secondary endpoint (Day 10 [ITT population]), the risk reduction with XOCOVA was 57% (relative risk ratio: 0.43, 95% CI: [0.32, 0.59], p<0.0001).[1]

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.

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Xocova - Use in Post-Exposure Prophylaxis

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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.**

Literature Search

As of May 2026, a computerized search of the published medical literature using PubMed® has failed to identify any additional relevant references regarding information on ensitrelvir and its use in post-exposure prophylaxis.

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	KM	Kaplan-Meier
AE	adverse event	MHLW	Ministry of Health, Labour, and Welfare
BMI	body mass index	mITT	modified intention-to-treat
CI	confidence interval	PK	pharmacokinetic
CLC	central laboratory-confirmed	RoW	rest of world
COVID-19	Coronavirus disease 2019	RR	risk ratio
CrCl	creatinine clearance	RT-PCR	reverse transcriptase polymerase chain reaction
CYP3A4	cytochrome P450 enzyme 3A4	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
GEE	generalized estimating equation	SAS	safety analysis set
HHC	household contact	SD	standard deviation
IP	index patient	TEAE	treatment-emergent adverse event
ITT	intent-to-treat	US	United States

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References

1. XOCOVA® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.
2. Hayden FG, Shinkai M, Clark TW, et al. Ensitrelvir for Covid-19 Postexposure Prophylaxis in Household Contacts. New England Journal of Medicine. 2026;394(19):1905-1915 [Web Link].
3. Hayden FG, Shinkai M, Clark TW, et al. Ensitrelvir for Covid-19 postexposure prophylaxis in household contacts. New England Journal of Medicine. 2026;394(19)(Suppl):S1-S33 [Web Link].
4. Hayden FG, Ohmagari N, Clark TW, et al. Ensitrelvir for the prevention of COVID-19 among household contacts: key subgroup analyses of SCORPIO-PEP phase 3 study. Oral presentation presented at: ESCMID 2025; April 11 - 15, 2025; Vienna, Austria.
5. Shinkai M, Clark TW, Luetkemeyer A, et al. Ensitrelvir to Prevent COVID-19 in Households: SCORPIO-PEP Phase III Placebo-Controlled Trial Results. Oral presentation presented at: CROI; March 9 - 12, 2025; San Francisco, CA.
6. Phase 3 Study of S-217622 in Prevention of Symptomatic SARS-CoV-2 Infection (SCORPIO-PEP). Accessed September 19, 2023 [Web Link].
7. Ensitrelvir Data on File 8. Shionogi Inc.

ENCLOSURE

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

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