Xocova - Use Following SARS-CoV-2 Positivity or Development of COVID-19 Symptoms During Post-Exposure Prophylaxis

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

SCORPIO-PEP is a phase 3 randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of XOCOVA for preventing symptomatic SARS-CoV-2 infection in household contacts (HHCs) aged ≥12 and older of individuals with symptomatic COVID-19. See the **Appendix** section of this letter for details on study design and results.[1]

- The study design did not include dose modifications or discontinuation for HHCs who tested positive for SARS-CoV-2 or developed COVID-19 symptoms during the 5-day course.[2]
- Participants (HHCs) who tested positive and developed COVID-19 were allowed to receive any locally available, standard-of-care COVID-19 treatments that were compatible with the study intervention.[2]

Primary Outcome (mITT Population)

- The proportion of participants (95% CI) with symptomatic COVID-19 through Day 10 was 2.9% in the ensitrelvir group and 9.0% in the placebo group.[1]

Secondary Outcomes in Participants with Breakthrough Infections (mITT Populations)

- Ensitrelvir had numerically lower viral RNA levels (mean [standard deviation]: 5.0 [2.0] vs 6.3 [1.9] $\log_{10}$ copies/mL) and lower symptom scores (mean [standard deviation]: 6.6 [4.7] vs 8.9 [4.9]) compared with placebo through Day 10.[3]
- The proportion of participants with sustained resolution of all COVID-19 symptoms through Day 28 was 65.5% in the ensitrelvir group and 67.4% in the placebo group.[2]

Post-hoc Analysis (ITT-BP Population)

- In a subset of participants who were RT-PCR positive at baseline based and continued with study treatment, ensitrelvir was associated with: [1-3]
    - Numerically lower rates of COVID-19 development: 17.5% (20/114) and 22% (27/123) in the ensitrelvir and placebo groups, respectively (risk ratio [RR] 0.75; 95% CI, 0.46–1.23)
    - Lower viral RNA levels (mean [standard deviation]: 5.6 [2.0] vs 6.2 [1.8] $\log_{10}$ copies/mL) through Day 10
    - Lower total symptom scores (6.2 [6.7] vs 10.3 [4.5]) through Day 10

Key Prescribing Information

The recommended dosage of XOCOVA in adults and adolescents 12 years of age and older is 375 mg (three 125-mg tablets taken together) orally on Day 1 and 125 mg (one 125-mg tablet) orally on Days 2 to 5 with or without food.[4]

2. CLINICAL TRIALS

SCORPIO-PEP

Study Design

SCORPIO-PEP 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) household contacts (HHCs) living with COVID-19-positive (local test), symptomatic index patients, when compared to placebo. This study was conducted across the US, Japan, Vietnam, Argentina, and South America from June 2023 to September 2024.[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.[1]

- The study design did not include dose modifications or discontinuation for HHCs who tested positive for SARS-CoV-2 or developed COVID-19 symptoms during the 5-day course.[1,2]
- Participants who tested positive for SARS-CoV-2 infection during the study and met the study definition for COVID-19 symptoms onset (occurrence or worsening in the case of pre-existing COVID-19-like symptoms) of ≥ 1 of the 14 specified COVID-19 symptoms for at least 48 hours) could have received any locally standard-of-care COVID-19 therapies available and indicated in their regions, as long as compatible with study intervention. Per protocol compatible therapies include, but are not limited to, anti-SARS-CoV-2 mAbs, outpatient IV remdesivir, molnupiravir, convalescent plasma, inhaled budesonide, and fluvoxamine after study enrollment.[2]
- The primary endpoint compared the proportion of participants who were infected with SARS-CoV-2 (central laboratory-confirmed [CLC]-positive RT-PCR test) and had COVID-19 symptoms onset through Day 10 in the mITT population.[1]
- As part of the secondary endpoint and a post hoc analysis, outcomes were evaluated in participants with confirmed SARS-CoV-2 infection.[1-3]
- For additional details about the study description and primary and key secondary endpoint results please see the **Appendix** of this letter.

Results: Primary Endpoints, Secondary Endpoints and Post-Hoc Analysis

The ITT population included HHCs who were SARS-CoV-2 negative by local testing at enrollment (N=2387; n=1194 ensitrelvir; n=1193 placebo). The primary analysis population (mITT) included those confirmed RT-PCR negative at baseline by central laboratory (n=1030 ensitrelvir; n=1011 placebo).[1]

Primary Endpoint

The proportion of participants (95% CI) who were infected with SARS-CoV-2 (CLC-positive RT-PCR test) and had COVID-19 symptoms onset through Day 10 in the mITT analysis set was 2.9% (30/1030) in the ensitrelvir group and 9.0% (91/1011) in the placebo group. The risk ratio of symptomatic COVID-19 in ensitrelvir group compared to placebo was 0.33 (0.22, 0.49).[1]

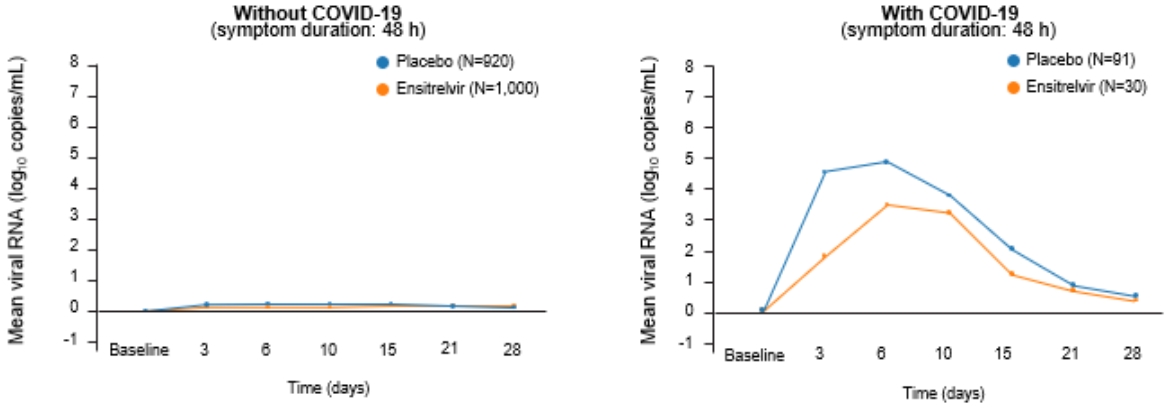
Secondary Endpoints

A fixed-sequence hierarchical testing procedure was applied to control type 1 errors for the primary and key secondary endpoints through Day 10. Therefore, this data is descriptive in nature and should be interpreted with caution. No statistical or clinical conclusions can be drawn.

SARS-CoV-2 Viral RNA (mITT)

Through Day 10, patients with breakthrough infections in the mITT population who received ensitrelvir had lower mean standard deviation (SD) viral ribonucleic acid (RNA) levels compared with those who received placebo (5.0 [2.0] vs 6.3 [1.9] log_{10} copies/mL) (See **Figure 1**).[3]

Figure 1. **Mean Viral RNA Over Time (mITT Population)[3]**



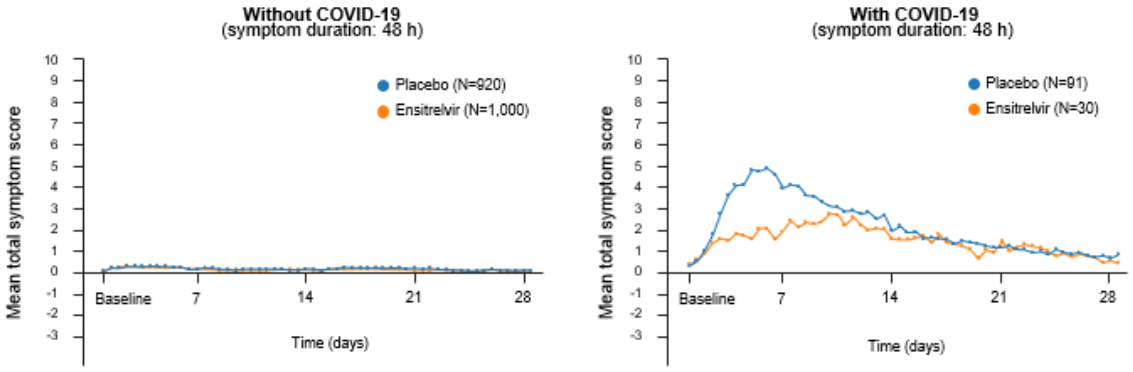
COVID-19 was defined as a central laboratory positive RT-PCR test and the occurrence (or worsening [increasing a symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
Abbreviations: h, hour; mITT, modified intention-to-treat; RNA, Ribonucleic acid
Figure adopted from Hayden et al. (Suppl 1) *NEJM*. 2026.

Among mITT participants who developed SARS-CoV-2 infection through Day 10, regardless of symptoms, reductions in viral RNA shedding levels in nasopharyngeal samples were greater with ensitrelvir group compared to the placebo group by 1.45, 1.24, and 0.94 log10 copies/mL through Days 3, 6, and 10, respectively.[4]

Symptom Analysis in HHCs (mITT)

The mean total symptom score (SD) observed in the ensitrelvir group in breakthrough infections in the mITT population was 6.6 (4.7) while the mean total symptom score observed in the placebo group was 8.9 (4.9) through Day 10 (See **Figure 2**).[3]

Figure 2. Total Symptom Score Over Time (mITT Population)[3]



COVID-19 was defined as a central laboratory positive RT-PCR test and the occurrence (or worsening [increasing a symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
Abbreviations: h, hour; mITT, modified intention-to-treat; RNA, Ribonucleic acid
Figure adopted from Hayden et al. (Suppl 1) *NEJM*. 2026.

In an impression questionnaire in the mITT population, participants in the ensitrelvir group largely reported no or only mild symptoms over the past 24 hours on Day 10, whereas the placebo group showed a higher proportion of mild to moderate symptoms, with a small number still reporting severe symptoms. Central-laboratory confirmed COVID-19 RT-PCR positivity or negativity was not reported (see **Table 2**).[2]

The proportion of participants with sustained resolution of all COVID-19 symptoms through Day 28 in the mITT analysis set who tested positive for SARS-CoV-2 and experienced symptomatic COVID-19 (defined as a CLC-positive RT-PCR test and new or worsened ≥1 of 14 specified COVID-19 symptoms for at least 48 hours) was 65.5% (19/29) in the ensitrelvir group and 67.4% (58/86) in the placebo group. The risk ratio for sustained resolution of all COVID-19 symptoms was 1.01 (95% CI: 0.58, 1.75).[2]

Table 2. Global Impression Questionnaire (GIQ) Scores and Change from Baseline (mITT)[2a]

Timepoint: Day 10	Ensitrelvir (N=1030)	Placebo (N=1011)	Total (N=2041)
Severity of Overall COVID-19 Symptoms (Past 24 Hours) (# responses)	24	68	92
0 - None	13 (54.2)	15 (22.1)	28 (30.4)
1 - Mild	9 (37.5)	44 (64.7)	53 (57.6)
2 - Moderate	2 (8.3)	8 (11.8)	10 (10.9)
3 - Severe	0	1 (1.5)	1 (1.1)

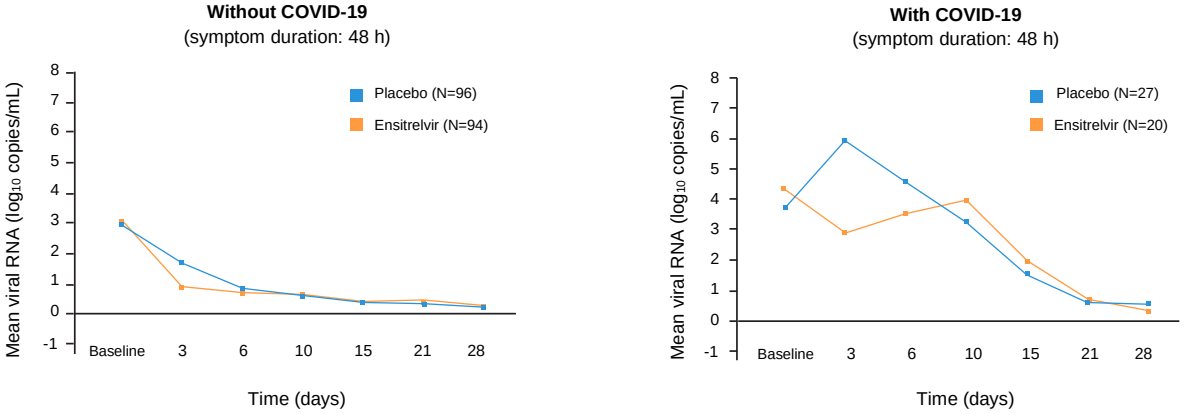
[a]The denominator for each GIQ question is the number of participants from each treatment group and scheduled timepoint who provided a response.

Post-hoc Analysis

A subset of participants were RT-PCR positive at baseline based on central testing (ITT baseline RT-PCR–positive population [ITT-BP]; n=114 ensitrelvir; n=123 placebo), continued with ensitrelvir treatment, and were evaluated in a post-hoc analysis.[1,3]

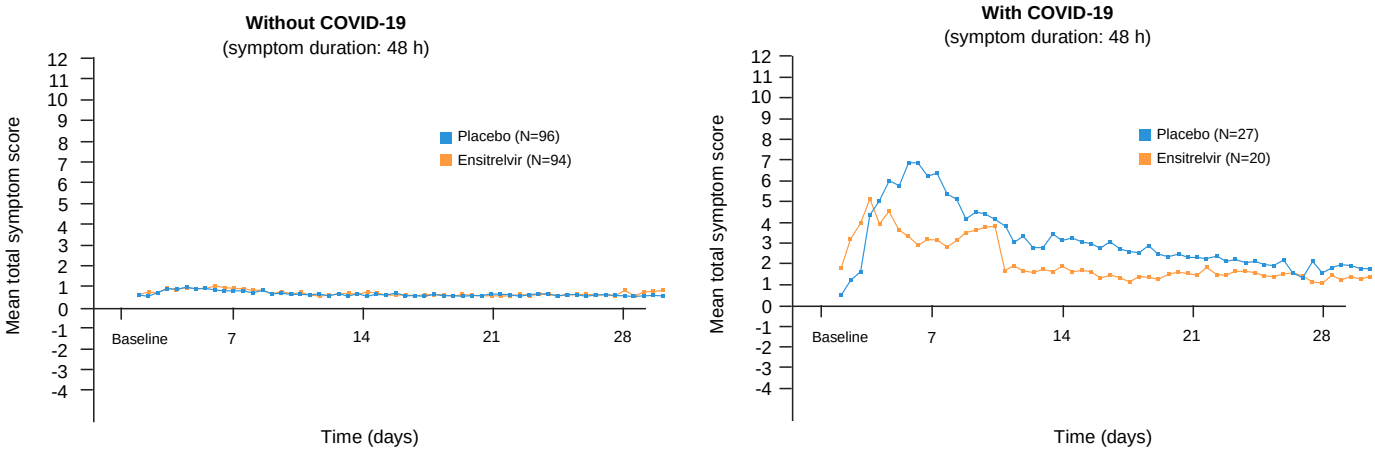
- In the ITT-BP population, 17.5% (20/114) and 22% (27/123) of participants developed COVID-19 in the ensitrelvir and placebo groups, respectively (RR 0.75; 95% CI, 0.46–1.23). COVID-19 was defined as a central laboratory positive RT-PCR test and the occurrence (or worsening [increasing a symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
- Among those in the ITT-BP population, the ensitrelvir group showed numerically lower mean (SD) viral RNA levels (5.6 [2.0] vs 6.2 [1.8] log_{10} copies/mL) through day 10 vs placebo (**Figure 3**).
- In the ensitrelvir group a numerically lower mean (SD) total symptom scores was seen (6.2 [6.7] vs 10.3 [4.5]) through day 10 relative to placebo for the ITT-BP population (**Figure 4**).

Figure 3. Mean Viral RNA Over Time in ITT-BP Population[3]



COVID-19 was defined as a central laboratory positive RT-PCR test and the occurrence (or worsening [increasing a symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
Abbreviations: COVID-19, coronavirus disease 2019; h, hour; ITT; intention-to-treat; ITT-BP, ITT baseline reverse transcriptase-polymerase chain reaction positive; RNA, ribonucleic acid.
Figure adapted from Hayden et al. *NEJM (supplement).* 2026.

Figure 4. Total Symptom Score Over Time in ITT-BP Population.[3]



COVID-19 was defined as a central laboratory positive RT-PCR test and the occurrence (or worsening [increasing a symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.

Abbreviations: COVID-19, coronavirus disease 2019; h, hour; ITT; intention-to-treat; ITT-BP, ITT baseline reverse transcriptase-polymerase chain reaction positive.

Figure adapted from Hayden et al. *NEJM (supplement).* 2026.

Safety Results

Treatment-emergent adverse events (TEAEs) occurred in 15.1% (180/1190) and 15.5% (184/1187) of patients in the safety analysis set of the ensitrelvir and placebo groups, respectively.[1]

Safety data are provided in **Table 3** and **Table 4**.

Table 3. TEAEs in the Safety Analysis Set[1]

TEAEs n (%)	Ensitrelvir (N=1190)[a]	Placebo (N=1187)[a]
Any TEAEs	180 (15.1)	184 (15.5)
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 TEAE leading to hospitalization	0	0
Any TEAEs leading to study discontinuation	0	1 (<0.1)
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 adopted from Hayden et al. *NEJM*. 2026.

Table 4. TEAEs in the Safety Analysis Set for SCORPIO-PEP[1]

TEAEs (≥1%) by preferred term	Ensitrelvir (N=1190)[a]	Placebo (N=1187)[a]
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)

Abbreviations: TEAE, treatment-emergent adverse event
[a]N represents the number of participating HHCs with each type of adverse event. Percentages are based on the number of participating HHCs in the safety analysis set within each treatment group.
Table adopted from Hayden et al. *NEJM*. 2026.

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.[4]

Contraindications

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[4]

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.[4]

Recommended Dosage

The recommended dosage of XOCOVA in adults and adolescents 12 years of age and older is 375 mg (three 125-mg tablets taken together) orally on Day 1 and 125 mg (one 125-mg tablet) orally on Days 2 to 5 with or without food.[4]

Begin XOCOVA as soon as possible and within 72 hours following contact with an individual who has COVID-19. The tablets should be taken at approximately the same time each day. If a dose of XOCOVA is missed, take the missed dose as soon as possible on the same day, and then take the next dose as scheduled the following day.[4]

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

As of February 2026, a computerized search of the published medical literature using internal and external databases (eg, PubMed®) failed to identify any additional relevant references regarding information on ensitrelvir and use following a SARS-CoV-2 positivity test during 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

AE	adverse event	n	number of participants
AUC	area under the curve	PCR / RT-PCR	reverse transcription polymerase chain reaction
CI	confidence interval	NP	nasopharyngeal
CLC	central laboratory-confirmed	PEP	post-exposure prophylaxis
COVID-19	coronavirus disease 2019	RR	risk ratio
GEE	generalized estimating equations	RNA	ribonucleic acid
HHC	household contact	SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
IV	intravenous	SAS	safety analysis set
ITT	intent-to-treat	SCORPIO-PEP	Stopping COVID-19 progression with early protease inhibitor-post-exposure prophylaxis
ITT-BP	ITT baseline RT-PCR positive	SD	standard deviation
mITT	modified intention-to-treat	TEAE / TEAEs	treatment-emergent adverse event(s)
N	total number of participants	US	United States

REFERENCES

1. 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. doi:10.1056/NEJMoa2509306.
2. Ensitrelvir Data on File 8. Shionogi Inc.
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 1):S1-S34. doi:10.1056/NEJMoa2509306.
4. XOCOVA® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.

ENCLOSURE

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

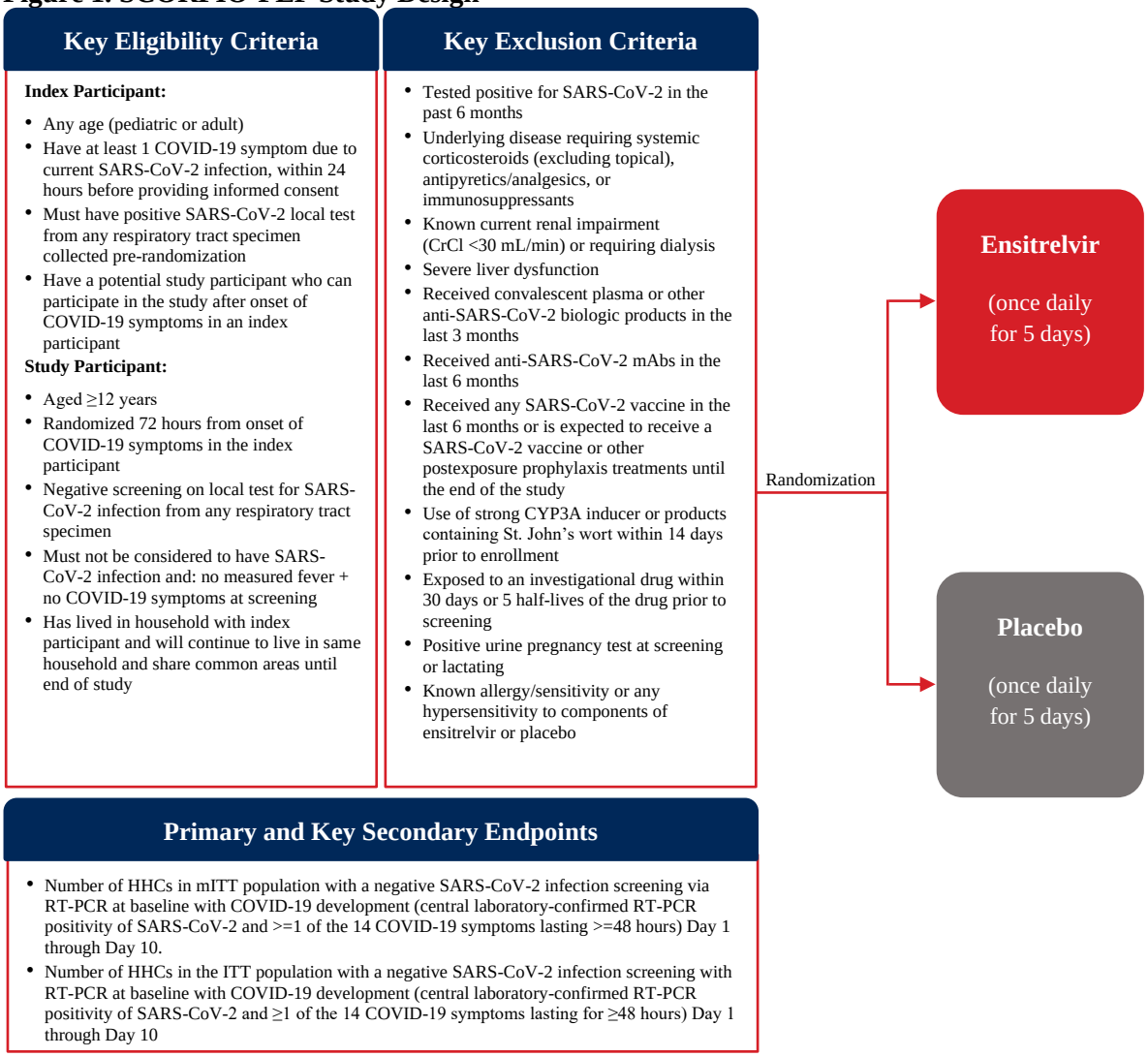
Appendix

Study Design

SCORPIO-PEP (Global Phase 3 Study)

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 on Day 1 and 125 mg on Days 2-5) or placebo once daily for 5 days. Study participants began treatment within 3 days of when the household member with COVID-19 began showing symptoms.[1]

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



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.

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Primary Endpoint: The primary endpoint was the proportion of HHCs in the mITT population (all randomized HHCs who were RT-PCR-negative for SARS-CoV-2 at baseline) with symptomatic COVID-19 development through Day 10, defined as having a positive central RT-PCR and ≥1 of the 14 symptoms of COVID-19 lasting for more than 48 hours. This includes the worsening (higher symptom score than baseline) of preexisting COVID-19-like symptoms.[1]

Secondary Endpoints in participants with breakthrough infection included:

- Comparison of ensitrelvir with placebo in reducing SARS-CoV-2 viral RNA levels in nasopharyngeal (NP) swabs through Day 10 in participants who tested positive for SARS-CoV-2.[2]
- Evaluated COVID-19 symptom resolution and improvement through Day 28 in participants who tested positive for SARS-CoV-2 through Day 10, defined as having a central laboratory-confirmed (CLC)-positive RT-PCR test.[2]

Post-Hoc Analyses: A supplemental analysis was conducted in the ITT baseline positive population (ITT-BP), defined as the subset of ITT participants with a positive baseline SARS-CoV-2 screening result by central laboratory RT-PCR, with the sample collected on or before randomization.[1,3]

A fixed-sequence hierarchical testing procedure was applied to control type 1 errors for the primary and key secondary endpoints through Day 10. Therefore, data from secondary endpoints and post-hoc analyses are descriptive in nature and should be interpreted with caution. No statistical or clinical conclusions can be drawn.

Primary and Key Secondary Endpoint Results

Baseline Characteristics

Baseline characteristics of the HHCs in both groups were similar. Majority of participants were in the US (67.2% and 67.6%, respectively). HHCs were enrolled <48 hours from symptom onset in the index patient in 71.1% and 71.2% of participants in the ensitrelvir and placebo groups, respectively. HHCs that were considered "high risk" made up 37.1% and 37.0% of the ensitrelvir and placebo groups, respectively.[1]

Efficacy Results

Primary Endpoint: The proportion of participants with symptomatic COVID-19 through Day 10 in the mITT analysis set was 2.9% [30/1030] in the ensitrelvir group and 9.0% [91/1011] in the placebo group (**Table 1**).[1]

Table 1. Risk for Symptomatic COVID-19* Through Day 10 (mITT Analysis Set)[1]

	Ensitrelvir Group N=1030 n (%)	Placebo Group N=1011 n (%)	Total N=2041 n (%)
Endpoint Status			
No symptomatic COVID-19	1000 (97.1)	920 (91.0)	1920 (94.1)
Symptomatic COVID-19	30 (2.9)	91 (9.0)	121 (5.9)
[95% CI][a]	[1.97, 4.13]	[7.31, 10.94]	[4.94, 7.04]
Risk Ratio[b]	0.33		
[95% CI][c]	[0.22, 0.49]		
***P*-value[d]**	<0.0001		

Abbreviations: CI, confidence interval; CLC, central laboratory-confirmed; COVID-19, coronavirus disease 2019; GEE, generalized estimating equations; mITT, modified intention-to-treat; RT-PCR, reverse transcription polymerase chain reaction

*Symptomatic COVID-19 was defined as a CLC-positive RT-PCR test and the occurrence (or worsening [increasing a symptom score from baseline] in the case of pre-existing COVID-19-like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for at least 48 hours.

[a]Confidence intervals for proportion of participants with symptomatic COVID-19 use the Clopper-Pearson method.

[b]Risk ratio (relative risk) of symptomatic COVID-19 in participants randomized to ensitrelvir vs participants randomized to placebo from GEE Poisson regression model.

[c]Confidence interval calculated from GEE Poisson regression model.

[d]p-value for the log coefficient of treatment effect equal to zero in GEE Poisson regression model.

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).[1]

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[1]
- 2 serious TEAEs occurred in each group and they were considered to be unrelated to the study drug[1]
- There were no AEs that led to hospitalization and no deaths were observed in either group[1]

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