Xocova - Incidence of Rebound

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1. 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]

Clinical Studies

- The global, Phase 3 study, **SCORPIO-PEP** evaluated the safety and efficacy of ensitrelvir vs. placebo in the prevention of symptomatic SARS-CoV-2 infection in HHCs of people who tested positive for COVID-19.[2]
  - In the ITT baseline positive population, 17 participants (15.3%) in the ensitrelvir group and 8 participants (6.7%) in the placebo group developed SARS-CoV-2 viral RNA rebound from Day 6 up to Day 28. No participants in either group developed COVID-19 symptoms rebound during the study.[3]
- The global, Phase 3 study, **SCORPIO-HR**, assessed the clinical and antiviral effects of ensitrelvir vs placebo in nonhospitalized patients with COVID-19:[4,5]
  - Viral RNA rebound was observed in 0.6% (6/945) of ensitrelvir-treated and 1.4% (13/943) of placebo-treated participants by Day 29, none of which had symptom rebound.
- The global, Phase 3 study, **SCORPIO-SR**, assessed the clinical and antiviral effects of ensitrelvir vs placebo in patients with COVID-19, of which **Tsuge et al (2023)** conducted a post-hoc analysis assessing viral rebound and symptom occurrence up to Day 21.[6,7]
  - Viral RNA rebound was reported in 7.8% (46/590), 6.7% (38/570), and 4.7% (27/574) of patients in the ensitrelvir 125 mg, ensitrelvir 250 mg, and placebo groups, respectively. Symptom recurrence of the five COVID-19 Omicron-predominant symptoms was observed in 0%, 3.6% (1/28), and 0% of patients with viral RNA rebound in the ensitrelvir 125 mg, 250 mg, and placebo groups, with no association with rebound of viral RNA.
  - Viral titer rebound was reported in 0.3% (1/310), 0%, and 0% of patients in the ensitrelvir 125 mg, ensitrelvir 250 mg, and placebo groups, respectively.
- Nobori et al (2026) presented a pooled analysis of virologic outcomes across the Phase 3 studies, including **SCORPIO-PEP**, **SCORPIO-SR**, and **SCORPIO-HR**. Viral RNA rebound was evaluated as a post hoc analysis using study-specific definitions.[8]
  - In SCORPIO-PEP, viral RNA rebound in the mITT population (household contacts [HHCs] with a negative local test and negative central RT-PCR at baseline) was reported in 0.8% (2/242; 95% CI: 0.1%, 3.0%) of participants treated with ensitrelvir vs 1.3% (4/304; 95% CI: 0.4%, 3.3%) of participants treated with placebo. In the ITT-BP population (HHCs with a positive RT-PCR at baseline), rebound occurred in 15.3% (17/111; 95% CI: 9.2%, 23.4%) vs 6.7% (8/120; 95% CI: 2.9%, 12.7%) of participants, respectively.
  - In SCORPIO-HR, rebound rates were 2.4% (23/945; 95% CI: 1.5%, 3.6%) and 2.2% (21/943; 95% CI: 1.4%, 3.4%) with ensitrelvir and placebo, respectively.

- In SCORPIO-SR, viral RNA rebound occurred in 9.6% (33/343; 95% CI: 6.7%, 13.2%) of participants treated with ensitrelvir and 4.2% (14/334; 95% CI: 2.3%, 6.9%) of participants treated with placebo.
- Across SCORPIO-SR and SCORPIO-HR, culture-positive infectious virus was detected in 8% (7/87) of rebound cases, and viral rebound was reported not to be associated with recurrence of symptoms.

- **PLATCOV** is a global Phase 2 pharmacometric platform trial that evaluated the *in vivo* antiviral activity of oral ensitrelvir (n=197) compared with ritonavir-boosted nirmatrelvir (n=201) and no study drug (n=191) in low-risk adults with early symptomatic COVID-19.[9]
  - Both ensitrelvir and ritonavir-boosted nirmatrelvir significantly accelerated viral clearance vs no study drug; the median viral clearance half-life was 5.9 hours, 5.2 hours, and 11.6 hours, respectively. In the non-inferiority analysis, viral clearance with ensitrelvir was 16% slower (95% CrI: 5-25) than with nirmatrelvir.
  - Viral rebound occurred in 5% (10/197) of ensitrelvir-treated patients, compared with 7% in both the nirmatrelvir (15/201) and no study drug groups (13/191) (*P*=0.61). Median time to rebound was 5.9 days (IQR 5.0-6.7) with ensitrelvir, 9.9 days (6.8-13.8) with nirmatrelvir, and 6.9 days (6.0-9.0) without treatment.
  - dysgeusia was reported more often with nirmatrelvir (26%; 52/201) vs. ensitrelvir (1%; 2/197) and vs. no study drug (1%; 1/191).

Real World Studies

In Japan, XOCOVA is approved for use in both PEP and treatment of COVID-19 from the Ministry of Health, Labour, and Welfare (MHLW).[10,11] In the United States, 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] XOCOVA is not approved for the treatment of COVID-19 in the United States.

- **Yamato et al (2024)** conducted a retrospective chart review that assessed the outcomes of hospitalized, predominantly elderly patients with a range of comorbidities who were treated with ensitrelvir in Japan.[12]
  - Of the patients treated with ensitrelvir, 12.5% (4/32) experienced viral rebound; 2 had no symptoms, 2 had additional treatment with remdesivir, and 1 of those with additional treatment had a transient increase in body temperature. No disease progression was reported in either of the 4 cases.
- **Kasamatsu et al (2026)** reported a case of clinical and viral rebound following ensitrelvir treatment in a vaccinated woman in her 50s with COVID-19 and no significant comorbidities or prior history of COVID-19.[13]
  - Forty-eight hours after ensitrelvir discontinuation and initial symptom improvement, symptoms of sore throat, fever, and cough recurred, accompanied by an increase in SARS-CoV-2 antigen levels, suggesting viral rebound with symptom relapse. Within a few days, her symptoms resolved spontaneously without additional treatment.

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 HHCs of people who tested positive for COVID-19 conducted from June 2023 to September 2024.[14]

HHC participants with a negative screening test for SARS-CoV-2 infection and no symptoms, 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 72 hours of when the household member with COVID-19 began showing symptoms.[14] See **Appendix-SCORPIO-PEP** for additional study design details.

Viral Rebound and Symptom Recurrence Endpoints
An exploratory endpoint included the proportion of participants who had viral RNA rebound from Day 6 up to Day 28 and proportion of participants who have COVID-19 symptomatic rebound after the sustained resolution of COVID-19 symptoms through Day 28. Using viral RNA from nasopharyngeal swabs and symptoms from participants symptom diary, the proportion of participants who had viral RNA and/or COVID-19 symptom rebound was calculated.[3]

Results

Efficacy

Primary Endpoint
In the ensitrelvir group, 2.9% (30/1030) of HHCs developed symptomatic COVID-19 compared to 9.0% (91/1011) of HHC participants in the placebo group through Day 10, a 67% reduction in the risk of developing COVID-19 (risk ratio: 0.33; 95% CI: 0.22-0.49; $P < 0.0001$) in uninfected individuals (mITT population) treated after exposure.[14]

Viral Rebound and Symptom Recurrence

- In the ITT baseline positive population, 17 participants (15.3%) in the ensitrelvir group and 8 participants (6.7%) in the placebo group developed SARS-CoV-2 viral RNA rebound from Day 6 up to Day 28. No participants in either group developed COVID-19 symptoms rebound during the study.[3]

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.[14]
- 2 serious TEAEs occurred in each group and they were considered to be unrelated to the study drug.[14]
- There were no AEs that led to hospitalization and no deaths were observed in either group.[14]

SCORPIO-HR

Study Design

SCORPIO-HR (NCT05305547) is a global ongoing 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. 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.[4,5]

Ensitrelvir 375 mg was given orally once on Day 1, followed by ensitrelvir 125 mg orally once daily on Days 2-5 in the active group (N=945), while placebo (N=943) was given to the control group.[5] See **Appendix-SCORPIO-HR** for additional study design details.

Viral Rebound and Symptom Recurrence Endpoints
A secondary endpoint included the proportion of participants with negative SARS-CoV-2 viral culture on Day 4, and viral rebound and symptomatic viral rebound after treatment completion through 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 the limit of detection (LoD) or lower limit of quantification (LLoQ) if the previous value was undetected or <LLoQ. Symptomatic viral rebound was defined as viral rebound in the setting of new or worsening clinical symptoms.[5]

Results

Primary Endpoint
In the modified intent-to-treat (mITT) population, the restricted mean time to sustained symptom resolution was not significantly different between the ensitrelvir (12.5 days) and placebo (13.1 days) groups (difference, 0.6 days; 95% CI: 1.38, 0.19; *P*=0.14).[5]

Primary and key secondary endpoints were tested using a fixed-sequence hierarchical approach at two-sided significance level of 0.05. 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.[5]

Viral Rebound and Symptom Recurrence
- 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 at day 4 (see **Table 1**).[5]
- 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. Viral rebound occurred in 0.6% (6/945) of ensitrelvir-treated and 1.4% (13/943) of placebo-treated participants by Day 29.[5]
- No symptomatic viral rebound (defined as viral rebound in the setting of new or worsening clinical symptoms) was observed.[5]

Table 1. SCORPIO-HR mITT Population: Virologic Efficacy Outcomes (Secondary Endpoints)[5]

	Ensitrelvir	Placebo
Negative viral culture on Day 4[a]		
No. of participants	309	292
No. of participants with negative viral culture on Day 4 (%)	274/287 (95.5%)	210/280 (75.0%)
Viral rebound[b]		
No. of participants	945	943
No. of participants with RNA rebound (%)	6/945 (0.6)	13/943 (1.4)
Estimated difference in proportion (95% CI)	-0.7 (-1.6, 0.2)	
No. of participants with symptomatic RNA rebound	0 (0.0)	0 (0.0)
Estimated difference in proportion (95% CI)	NA (NA, NA)	

Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; NA, not applicable; RNA, ribonucleic acid.
[a] The analysis was performed on the viral culture set, which included all participants in the mITT population with detectable (above the LLoQ) viral cultures on Day 1. Missing data were excluded from the analysis, assuming that they were completely missing at random. The associated p-values were calculated using normal approximation of the binomial distribution.
[b] 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 the limit of detection or lower limit of quantification (LLoQ) if the previous value was undetected or below the LLoQ. Symptomatic viral rebound was defined as viral rebound in the setting of new or worsening clinical symptoms. The analysis was performed in the mITT population. The exact 95% CI for the absolute difference in proportions (ensitrelvir minus placebo) was calculated using the Chan and Zhang method [4], and the p-value was calculated using Fisher's exact test.
A fixed-sequence hierarchical testing procedure was applied. Since the results for the primary efficacy endpoint were not statistically significant, the results from the secondary endpoints, including viral analyses, are descriptive in nature and should be interpreted in an exploratory manner.

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 (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.[5]

COVID-19–related hospitalization was observed in 3/1037 (0.3%) ensitrelvir-treated patients and 1/1048 (0.1%) placebo-treated participant.[5]

No deaths were observed in either group.[5]

SCORPIO-SR

Study Design

The SCORPIO-SR (phase 3 part) trial is part of the phase 2/3, multicenter, randomized, double-blind, placebo- controlled clinical study and evaluated the efficacy (clinical symptom improvement and antiviral effect), and safety of ensitrelvir administered orally, once daily for five days in patients with SARS-CoV-2 infection. SCORPIO-SR was conducted in Japan, South Korea, and Vietnam during when the Omicron BA.1 variant was dominant, between February to July 2022.[6,7]

Patients were randomized 1:1:1 to receive:[7]

- Ensitrelvir 375 mg on Day 1, followed by 125 mg of once-daily ensitrelvir Days 2-5 (N=347)
- Ensitrelvir 750 mg on Day 1, followed by 250 mg of once-daily ensitrelvir Days 2-5 (N=340)
- Placebo for 5 days (N=343)

See **Appendix-SCORPIO-SR** for additional study design details.

Viral Rebound and Symptom Recurrence Endpoints

Tsuge et al (2023) conducted a post hoc analysis assessing viral rebound and symptom recurrence up to Day 21.[6]

- Viral RNA rebound was assessed on Day 9, 14, and 21, defined as ≥1.0 $\log_{10}$ copies/mL increase from the previous visit.[6]
- Viral titer rebound was assessed at the same visits, defined as ≥1.0 $\log_{10}$ ($TCID_{50}$/mL) after the viral titer at the previous visit was undetected.[6]
- Symptom recurrence was evaluated both in five and 12 target symptoms (the study required one of 12 typical COVID-19 symptoms for enrolment, and five symptoms were found to predominate during the Omicron era) defined as at least one moderate or severe symptom persisting for ≥24 hours after Day 6 in patients who had experienced symptom resolution by Day 5.[6]
    - The five COVID-19 symptoms were stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness.
    - The other seven (of the 12 typical symptoms) were shortness of breath, muscle or body aches, headache, chills or shivering, nausea, vomiting, or diarrhea.

Results

Among the 1821 patients enrolled in the study, 1769 completed the study and 1030 were randomized in less than 72 hours of disease onset (primary analysis population). Baseline demographics and disease characteristics of patients, including mean viral RNA level, were similar between the ensitrelvir and placebo groups.[7]

Primary Endpoint

- The time to resolution of five COVID-19 symptoms (primary endpoint) was significantly reduced with ensitrelvir 125 mg vs placebo in the primary analysis population (P = 0.04 with a Peto-Prentice generalized Wilcoxon test) (See **Table 2**).[7]

Table 2. Time to Resolution of 5 COVID-19 Symptoms in SCORPIO-SR[7,a]

	COVID-19 Onset to Randomization: <72 h (Primary Analysis)[b]		
	Ensitrelvir 125 mg (n=347)	**Ensitrelvir 250 mg (n=340)**	**Placebo (n=343)**
Kaplan-Meier estimator (h)			
Median (95% CI)	167.9 (145.0, 197.6)	171.2 (150.8, 190.3)	192.2 (174.5, 238.3)
Difference from placebo (95% CI)	−24.3 (−78.7, 11.7)	−21.0 (−73.8, 7.2)	-
Stratified Peto-Prentice's generalized Wilcoxon test[c]			
P-value (two-tailed)	0.04	0.0203	-

The efficacy analysis group comprised of the ensitrelvir 125 mg treatment arm and placebo arm.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 19; h, hours; ITT, intention-to-treat; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Five COVID-19 symptoms were runny or stuffy nose, sore throat, cough, feeling hot or feverish, and malaise (fatigue). [b]Analysis in the ITT population (all cases confirmed positive for SARS-CoV-2 viral RNA at baseline) with any of the 5 symptoms at baseline. [c]Adjusted for SARS-CoV-2 vaccination status.

Viral Rebound and Symptom Recurrence
Results for these endpoints are observational in nature; as such, they should be interpreted with caution.

In patients with viral RNA data from days 6-9 onwards, viral RNA rebound by PCR testing was observed in 7.8% of patients in the 125 mg group (46/590), 6.7% in the 250 mg group (38/570), and 4.7% in the placebo group (27/574).[6]

- Based on the five COVID-19 Omicron-predominant symptoms, of the patients with viral RNA rebound, 0%, 3.6% (1/28) and 0% of patients had symptom recurrence in the ensitrelvir 125 mg, 250 mg, and placebo groups, respectively.
- Based on the 12 typical COVID-19 symptoms, of the patients with viral RNA rebound, there was no symptom recurrence in the 125 mg, 250 mg, and placebo groups, respectively.
- There was no obvious difference in symptom recurrence in treatment group and placebo group (**Table 3**). Symptom recurrence was not associated with rebound of viral RNA.

Table 3. SCORPIO-SR: Percentage of Symptoms Recurrence with or without Viral RNA Rebound (ITT Population)[6]

	Ensitrelvir 125 mg		Ensitrelvir 250 mg		Placebo	
Target: 5 symptoms	No rebound	Rebound	No rebound	Rebound	No rebound	Rebound
	1.3% (5/384)	0.0% (0/33)	0.8% (3/394)	3.6% (1/28)	0.8% (3/382)	0.0% (0/19)
Target: 12 symptoms	No rebound	Rebound	No rebound	Rebound	No rebound	Rebound
	1.4% (5/363)	0.0% (0/30)	0.8% (3/387)	0.0% (0[a]/26)	1.6% (6/374)	0.0% (0/19)

Abbreviations: ITT, intent-to-treat; RNA, ribonucleic acid.
The five COVID-19 symptoms were stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness and the 12 symptoms also include shortness of breath, muscle or body aches, headache, chills or shivering, nausea, vomiting, or diarrhea (besides the 5 symptoms above). Numerator: The number of subjects that experienced symptom recurrence after Day 6. Denominator: The number of subjects that experienced symptom resolution and obtained symptom data after Day 6.
[a] One subject who did not experience 12 symptom resolution by Day 6 was excluded.

For the modified ITT (mITT) population, viral titer rebound was observed at 0.3% (1/310) of patients in the ensitrelvir 125 mg group, 0% (0/292) in the ensitrelvir 250 mg group, and 0% (0/319) in the placebo group.[6]

Safety
Most treatment-related adverse events (TRAEs) were mild in severity, and a decrease in high-density lipoprotein (HDL) was the most commonly reported TRAE. There were two serious adverse events (AEs) reported in the study (one in the ensitrelvir 125 mg arm and one in the placebo arm), both of which were judged as not treatment related.[7]

Pooled Analysis of Phase 3 Clinical Trials

Nobori et al. (2026) presented a pooled analysis of virologic outcomes across the Phase 3 clinical studies, including SCORPIO-PEP, SCORPIO-SR, and SCORPIO-HR. Pre-defined analyses evaluated viral RNA copy number and infectious virus titer, while viral RNA rebound was assessed as a post hoc analysis.[8]

Across the Phase 3 studies, ensitrelvir treatment was associated with lower viral RNA copy number vs placebo across standard-risk and high-risk populations and irrespective of time from symptom onset.[8]

- In SCORPIO-PEP, differences in mean viral RNA copy number for ensitrelvir vs placebo in the mITT population (HHCs with a negative local test and negative central RT-PCR at baseline; ensitrelvir: N=1030; placebo: N=1011) were −1.45 $\log_{10}$ RNA copies/mL on Day 3

(ensitrelvir: n=139; placebo: n=210) and −1.24 $\log_{10}$ RNA copies/mL on Day 6 (ensitrelvir: n=138; placebo: n=206) and in the ITT-BP population (HHCs with a positive RT-PCR test at baseline; ensitrelvir: N=114; placebo: N=123) were: −1.49 $\log_{10}$ RNA copies/mL on Day 3 (ensitrelvir: n=112; placebo: n=117) and −0.63 $\log_{10}$ RNA copies/mL on Day 6 (ensitrelvir: n=109; placebo: n=118).

- In SCORPIO-SR, (ensitrelvir: N=607; placebo: N=608), differences in LS mean viral RNA copy number were −1.57 $\log_{10}$ RNA copies/mL on Day 4 (ensitrelvir: n=398; placebo: n=395) and −1.35 $\log_{10}$ RNA copies/mL on Day 6 (ensitrelvir: n=399; placebo: n=391).
- In SCORPIO-HR (ensitrelvir: N=1042; placebo: N=1051), differences in LS mean viral RNA copy number were −0.72 $\log_{10}$ RNA copies/mL on Day 4 (ensitrelvir: n=798; placebo: n=821) and −0.30 $\log_{10}$ RNA copies/mL on Day 8 (ensitrelvir: n=840; placebo: n=840).

Infectious virus titer was assessed in SCORPIO-SR and SCORPIO-HR but not in SCORPIO-PEP. Culture-positive infectious virus on Day 4 was detected in 4.1% (8/197) of participants treated with ensitrelvir compared with 31.9% (66/207) of participants treated with placebo in SCORPIO-SR, and in 4.5% (13/287) vs 25.0% (70/280), respectively, in SCORPIO-HR.[8]

Rate of Viral RNA Rebound

Viral RNA rebound was evaluated as a post hoc analysis using study-specific definitions across the Phase 3 studies.[6]

- In SCORPIO-PEP, viral RNA rebound was assessed through Day 28 in both the mITT and the ITT-BP populations.[8]
  - mITT population:[8]
    - Viral RNA rebound occurred in 0.8% (2/242) of participants treated with ensitrelvir (95% CI: 0.1%, 3.0%) and 1.3% (4/304) of participants treated with placebo (95% CI: 0.4%, 3.3%).
    - Viral RNA rebound was defined as ≥1.0 $\log_{10}$ RNA copies/mL increase with ≥3.27 $\log_{10}$ RNA copies/mL observed, compared with the lowest viral RNA with ≥1.0 $\log_{10}$ RNA copies/mL decrease from the peak viral RNA within all time points after the peak viral RNA visit (defined as the earliest visit at which a larger viral RNA value was observed than both of the previous non-missing visit and the next non-missing visit where the viral RNA was ≥3.27 $\log_{10}$ RNA copies/mL).
      - If the viral RNA value was negative and <LLoQ, the viral RNA was imputed as 0 and 1.97 (=$\log_{10}$ [$10^{2.27}$/2]) $\log_{10}$ RNA copies/mL, respectively.
  - ITT-BP population:[8]
    - Viral RNA rebound occurred in 15.3% (17/111) of participants treated with ensitrelvir (95% CI: 9.2%, 23.4%) and 6.7% (8/120) of participants treated with placebo (95% CI: 2.9%, 12.7%).
    - Viral rebound was defined as: (a) viral RNA on Day 6 <LLoQ and ≥LLoQ at any subsequent visit through Day 28 or viral RNA on Day 6 ≥LLoQ and ≥0.5 $\log_{10}$ RNA copies/mL increase at any subsequent visit through Day 28, (b) viral RNA on Day 10 <LLoQ and ≥LLoQ at any subsequent visit through Day 28 or viral RNA on Day 10 ≥LLoQ and ≥0.5 $\log_{10}$ RNA copies/mL increase at any subsequent visit through Day 28.
      - If the viral RNA value was negative and <LLoQ, the viral RNA was imputed as 0 and 1.97 (=$\log_{10}$ [$10^{2.27}$/2]) $\log_{10}$ RNA copies/mL, respectively.

- In SCORPIO-HR, viral RNA rebound occurred in 2.4% (23/945) of participants treated with ensitrelvir (95% CI: 1.5%, 3.6%) and 2.2% (21/943) of participants treated with placebo (95% CI: 1.4%, 3.4%).[8]
    - Viral RNA rebound was defined as an increase of ≥1.0 $\log_{10}$ from the previous non-missing visit value when the previous visit was detected or an increase to ≥LLoQ + 1.0 $\log_{10}$ when the previous non-missing visit value was below LLoQ or an increase to ≥LoD + 1.0 $\log_{10}$ when the previous non-missing visit was undetected (2.0 $\log_{10}$ was used as LLoQ and LoD for viral RNA rebound assessment).
- In SCORPIO-SR, viral RNA rebound occurred in 9.6% (33/343) of participants treated with ensitrelvir (95% CI: 6.7%, 13.2%) and 4.2% (14/334) of participants treated with placebo (95% CI: 2.3%, 6.9%).[8]
    - Viral RNA rebound through Days 6 to 21 was defined as ≥ 1.0 $\log_{10}$ RNA copies/mL with ≥3.27 $\log_{10}$ RNA copies/mL observed at any visit after Day 9 compared to the previous nonmissing visit (i.e. Day 6 or after) at which viral RNA was detected or ≥3.27 $\log_{10}$ RNA copies/mL (2.27 + 1 $\log_{10}$ RNA copies/mL) observed at any visit after Day 9 compared to the previous non-missing visit (i.e. Day 6 or after) at which viral RNA was below LLoQ or undetected.
        - If the viral RNA value was negative and <LLoQ, the viral RNA was imputed as 0 and 1.97 (=$\log_{10}$ [102.27/2]) $\log_{10}$ RNA copies/mL, respectively.
        - Analysis population is the full mITT set (randomized and administered within ≤3 days from onset) with baseline viral culture detected.

Among viral RNA rebound cases across SCORPIO-SR and SCORPIO-HR, cell culture infectious virus was detected in 8% (7/87) of rebound cases across ensitrelvir (375 mg and 125 mg) and placebo groups. The authors additionally reported that viral rebound was not associated with recurrence of symptoms.[8]

Phase 2 Clinical Study

PLATCOV Trial

Study Design

PLATCOV (NCT05041907) is an ongoing, Phase 2, open-label, multicentre, randomized, controlled, adaptive, pharmacometric platform trial established to assess the in vivo antiviral activity of potential COVID-19 treatments in low-risk adults with early symptomatic infection. The broader PLATCOV platform operates across Thailand, Brazil, Nepal, and Laos. The ensitrelvir versus ritonavir-boosted nirmatrelvir comparison was conducted among participants enrolled in Thailand and Laos between March 17, 2023, and April 21, 2024.[9]

The study enrolled previously healthy adults aged 18-60 years who presented within <4 days of symptoms of COVID-19 with confirmed SARS-CoV-2 infection by antigen or PCR testing. Exclusion criteria included the use of concomitant medications, the presence of chronic diseases, or other clinically significant comorbidities.[9]

Participants were randomized to receive: [9]

- Oral ensitrelvir (n=197): 375 mg loading dose on Day 1 followed by 125 mg once daily for the next 4 days (Days 2-5)
- Oral ritonavir-boosted nirmatrelvir (n=201): 300 mg nirmatrelvir + 100 mg ritonavir twice daily for 5 days
- No study drug (n=191)
- All patients received standard symptomatic treatment with paracetamol.

Among the 589 patients in the modified intention-to-treat (mITT) population, 545 (93%) patients had received at least one COVID-19 vaccine dose. The mean interval from symptom onset to randomization was 1.8 days (SD 0.8), and the geometric mean baseline viral load was 5.1 $\log_{10}$ genomes/mL (SD 1.4). Baseline viral load in the ensitrelvir group was 0.3 log10 genomes/mL lower than in the ritonavir-boosted nirmatrelvir group and the no study drug group.[9]

Results

Efficacy

Primary Endpoint: The primary endpoint was the oropharyngeal viral clearance rate measured between Day 0 and Day 5, estimated using a Bayesian hierarchical linear model on log10 viral load density.[9]

- Both ensitrelvir and ritonavir-boosted nirmatrelvir accelerated the viral clearance compared with the no study drug group. The median estimated viral clearance half-life was 5.9 hours (IQR 4.0-8.6) for ensitrelvir (n=197), 5.2 hours (IQR 3.8-6.6) for nirmatrelvir (n=201), and 11.6 hours (IQR 8.1-14.5) for the no study drug group (n=191).
- Compared with the no drug group, the viral clearance rate was 82% faster (95% credible interval [CrI]: 61-104) with ensitrelvir and 116% faster (95% CrI: 91-142) with nirmatrelvir. In the non-inferiority assessment, viral clearance with ensitrelvir was 16% slower (95% CrI: 5-25) than with nirmatrelvir (<0.86 probability than the 10% non-inferiority margin).

Viral Rebound and Symptom Recurrence

Viral rebound was defined as a mean daily oropharyngeal eluate viral load of <100 genomes per mL for at least 2 consecutive days that then rose to >1000 genomes per mL at any time thereafter.[9]

- Viral rebound occurred in 10 of 197 (5%) patients in the ensitrelvir group, 15 of 201 (7%) patients in the nirmatrelvir group, and 13 of 191 (7%) patients in the no study drug group (*P*=0.61).
- The median time to viral rebound (exploratory *post-hoc* analysis) was 5.9 days (IQR 5.0-6.7) for the ensitrelvir group, 9.9 days (IQR 6.8-13.8) for the nirmatrelvir group, and 6.9 days (IQR 6.0-9.0) for the no study drug group (see **Figure 1**).
- No patients developed severe disease, although specific data regarding clinical outcomes on the patients who experienced rebound are unavailable. Seven patients were hospitalized - 2 had fatigue related to covid (1 in the nirmatrelvir group and 1 in the no study drug group) and one had a likely DDI (nirmatrelvir group). Others were considered unrelated to COVID or the study drug.

Figure 1. Viral Rebound in Ensitrelvir vs Nirmatrelvir vs No Study Drug Groups.[9]

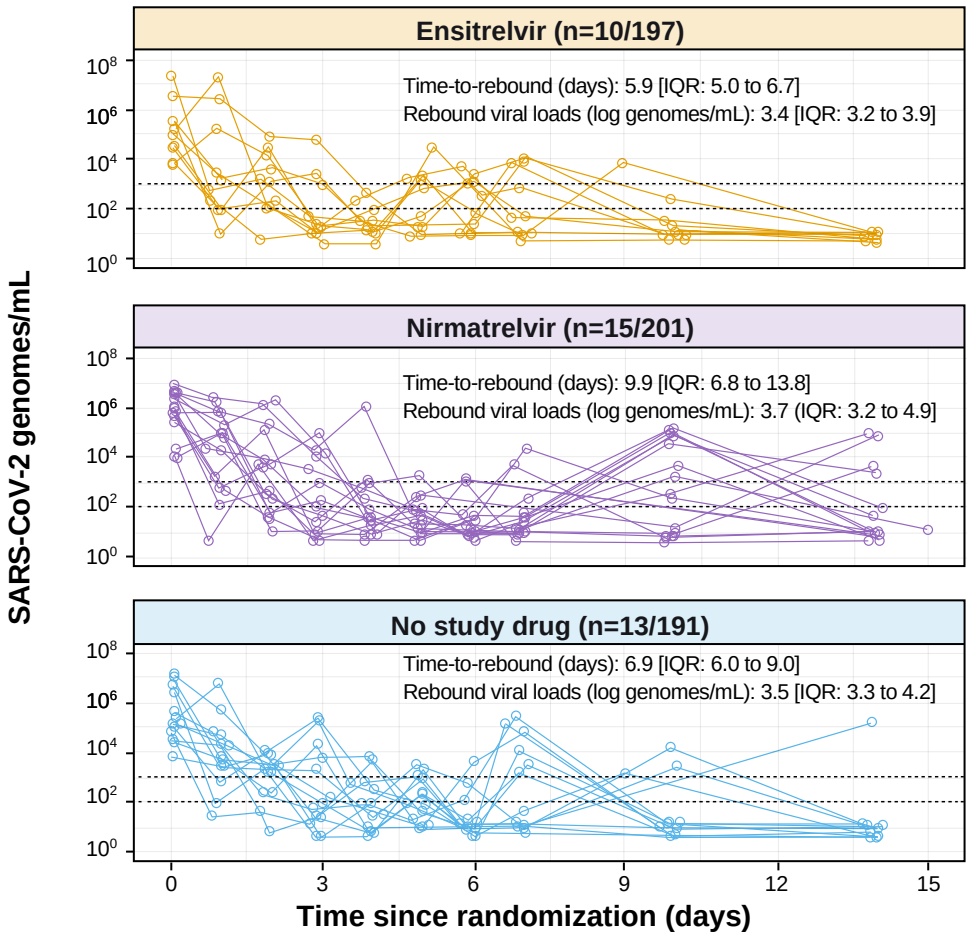


Figure adapted from Schilling et al. *Lancet Infect Dis.* 2025.
Abbreviations: IQR, interquartile range.

Safety

- Drug interaction was reported for 1 patient in the nirmatrelvir group.[9]
- Dysgeusia was reported in 2/197 (1%) patients in the ensitrelvir group versus 52/201 (26%) patients in the nirmatrelvir group and 1/191 (1%) patients in the no study drug group.[9]

3. REAL WORLD STUDIES/CASE REPORT

In Japan, XOCOVA is approved for use in both PEP and treatment of COVID-19 from the Ministry of Health, Labour, and Welfare (MHLW).[10,11] In the United States, 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] XOCOVA is not approved for the treatment of COVID-19 in the United States.

Retrospective Chart Review in Hospitalized Patients

Yamato et al. (2024) conducted a single-center, retrospective chart review assessing the outcomes of hospitalized patients with severe comorbidities treated with ensitrelvir in a real-world setting in the Rinku General Medical Center in Izumisano, Japan between November 2022 and April 2023 (n=32).[12]

Patients received daily oral treatment with ensitrelvir over 5 days with a 375 mg loading dose on Day 1 and 125 mg maintenance dose on Days 2 to 5. Antiviral activity was indicated by polymerase chain reaction or antigen testing, and investigator assessments of clinical improvement were used to assess effectiveness. Viral clearance was defined as an antigen level of <89.73 pg/mL, and viral rebound was defined as an increase of antigen level of ≥89.73 pg/mL after viral clearance.[12]

At the start of ensitrelvir treatment, 21 (65.6%) patients had mild COVID-19 disease severity; 4 (12.5%) had moderate I and 7 (21.9%) had moderate II severity (classified according to the MHLW guidelines in Japan).[12]

- After ensitrelvir treatment, 56.3% (18/32) of patients had viral clearance by Day 6 and 78.1% (25/32) of patients had viral clearance at final measurement.
- All patients experienced clinical improvement by Day 5.
- Four patients experienced viral rebound (**Table 4**):
  - Two (Patient 9 and 14) had no symptom rebound or additional treatment
  - One (Patient 25) had no symptom rebound but received a six-day course of remdesivir
  - One (Patient 28) had a transient increase of body temperature ≥37.5 °C and received a five-day course of remdesivir before achieving viral clearance
  - No disease progression was reported in these four cases
- No ensitrelvir treatment-related AEs were observed, and ensitrelvir treatment was not discontinued for any patient
- No patients were admitted to the ICU, no patients progressed to severe disease over the course of the study and no patients died up to Day 14

Table 4. Yamato 2024: Virology Outcomes for Patients with Viral Rebound[12]

Patient	Underlying Diseases	Prior SARS-CoV-2 Treatment	Days From Start of Ensitrelvir Administration															Treatment Outcome by Day 6[a]	Treatment Outcome at Final Measurement[a]	Viral Rebound
			Day -1 and Day 0	Day 1	Day 2	Day 3	Day 4	Day 5 (EOT)	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14			
			Quantitative Viral Antigen (pg/mL)																	
9[b,d]	AAV, CKD, DM, HTN	Remdesivir[c] Molnupiravir Tixagevimab/ cilgavimab	5000	5000		2587.88		4.77	1210.73		5000	5000	5000							Viral Rebound (at Day 6)
14[b]	Pulmonary metastasis from cancer of the sigmoid colon, suspected catheter-related BSI, chronic gastritis, angina pectoris, dyslipidemia, T2D	Remdesivir[c] Casirivimab/ imdevimab	5000	5000			87.07	25.39	8.50	6.81	7.94	94.59	0.14	2.29	0.05	1.73	0.57	Viral Clearance	Viral Clearance	Viral Rebound (at Day 9)
25	T2D, chronic renal failure, angina pectoris, hypothyroidism, post-cerebral infarction status, hemodialysis	Remdesivir Casirivimab/ imdevimab	5000		267.69		38.25				84.65	301			38.23	2.40	8.13	Viral Clearance	Viral Clearance	Viral Rebound (at Day 9)
28	Acute renal failure, empyema, HTN, hemodialysis	Casirivimab/ imdevimab		PCR Ct 16.6	5000			168.50			86.65	1.39	14.97	6.59	496.04					Viral Rebound[e] (at Day 12)

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; BSI, bloodstream infection; CKD, chronic kidney disease; Ct, cycle threshold; DM, diabetes mellitus; EOT, end of treatment; HTN, hypertension; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T2D, Type 2 diabetes.
Patients received ensitrelvir on Days 1-5. Shading represents days the patient was hospitalized.
[a]Viral clearance defined as an antigen level of <89.73 pg/mL; viral rebound defined as an increase of antigen level of >89.73 pg/mL after viral clearance.
[b]Patient was included in the subgroup analysis. [c]Patient received ≥3 days of remdesivir. [d]Patient received rituximab at Day -48. [e]Viral clearance documented on Day 15 and Day 16.

Case Report of Viral Rebound in a Vaccinated Patient

Kasamatsu et al. (2026) reported a case of clinical and viral rebound following ensitrelvir treatment in a vaccinated Japanese woman in her 50s with COVID-19 who had received 6 vaccine doses (last dose administered 6 months prior), with no significant comorbidities or prior history of COVID-19. Ensitrelvir was initiated following a positive SARS-CoV-2 PCR test with an initial Ct value of 31.97 and mild sore throat. The sore throat improved on the following day,, and her symptoms resolved following completion of the 5-day ensitrelvir treatment course. A quantitative antigen test on her Day 6 follow up visit showed a low value of 144.8 pg/mL.[13]

However, 48 hours after discontinuation of ensitrelvir (Day 7), sore throat recurred along with fever (37.9°C) and cough. Quantitative SARS-CoV-2 antigen levels were >5000 pg/mL on Day 7, while the Ct value changed from 31.97 to 16.6, suggesting viral rebound with symptom relapse. No radiographic evidence of pneumonia was observed, and symptoms resolved spontaneously within a few days without additional treatment.[13]

4. 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:

- 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]

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.

5. LITERATURE SEARCH, ABBREVIATIONS, & REFERENCES

Literature Search

As of August 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has identified additional relevant references regarding ensitrelvir and incidence of rebound. For your review, these references are listed in the bibliography that follows:

- Nair MS, Luck MI, Huang Y, Sabo Y, Ho DD. Persistence of an infectious form of SARS-CoV-2 after protease inhibitor treatment of permissive cells in vitro. *The Journal of Infectious Diseases*. 2025;231(1):e68-e76. doi:10.1093/infdis/jiae385. [Web Link].
- Abe S, Leshan W, Suzuki Y, et al. Real world effectiveness of early ensitrelvir treatment in patients with SARS-CoV-2, a retrospective case series. *New Microbes New Infect*. 2024;62:101522. doi:10.1016/j.nmni.2024.101522. [Web Link]

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	HTN	hypertension
AAV	ANCA-associated vasculitis	ICU	intensive care unit
(ACTIV)-2	Accelerating COVID 19 Therapeutic Interventions and Vaccines	ITT	intent-to-treat
ACTG	AIDS Clinical Trials Group	LLoQ	lower limit of quantification
AE	adverse event	LoD	limit of detection
AIDS	acquired immunodeficiency syndrome	MHLW	Ministry of Health, Labour, and Welfare
ANCA	anti-neutrophil cytoplasmic antibody	mITT	modified intention-to-treat
BSI	bloodstream infection	NIH	National Institutes of Health
CI	confidence interval	PCR	polymerase chain reaction
CKD	chronic kidney disease	PK	pharmacokinetic
COVID-19	coronavirus disease 2019	RNA	ribonucleic acid
Ct	cycle threshold	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
D	day	T2D	Type 2 diabetes
DM	diabetes mellitus	$TCID_{50}$	50% tissue culture infectious dose
EOT	end of treatment	TEAE	treatment-emergent adverse event
h	hours	US	United States
HDL	high-density lipoprotein	TRAE	treatment-related adverse event

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7. Yotsuyanagi H, Ohmagari N, Doi Y, et al. Efficacy and safety of 5-day oral ensitrelvir for patients with mild to moderate COVID-19 the SCORPIO-SR randomized clinical trial. *JAMA Netw Open*. 2024;7(2):e2354991. doi:10.1001/jamanetworkopen.2023.54991.
8. Nobori H, Sakaguchi H, Luetkemeyer A, et al. Ensitrelvir treatment of COVID-19 across multiple global phase 3 trials resulted in reduced culture positivity and RNA copy number with minimal viral rebound. Poster presented at: ESCMID 2026; April 17 - 21, 2026 2026; Munich, Germany.
9. Schilling WHK, Jittamala P, Wongnak P, et al. Antiviral efficacy of oral ensitrelvir versus oral ritonavir-boosted nirmatrelvir in COVID-19 (PLATCOV): an open-label, phase 2, randomised, controlled, adaptive trial. *Lancet Infect Dis*. 2025;26(2):139-147. doi:10.1016/s1473-3099(25)00482-7
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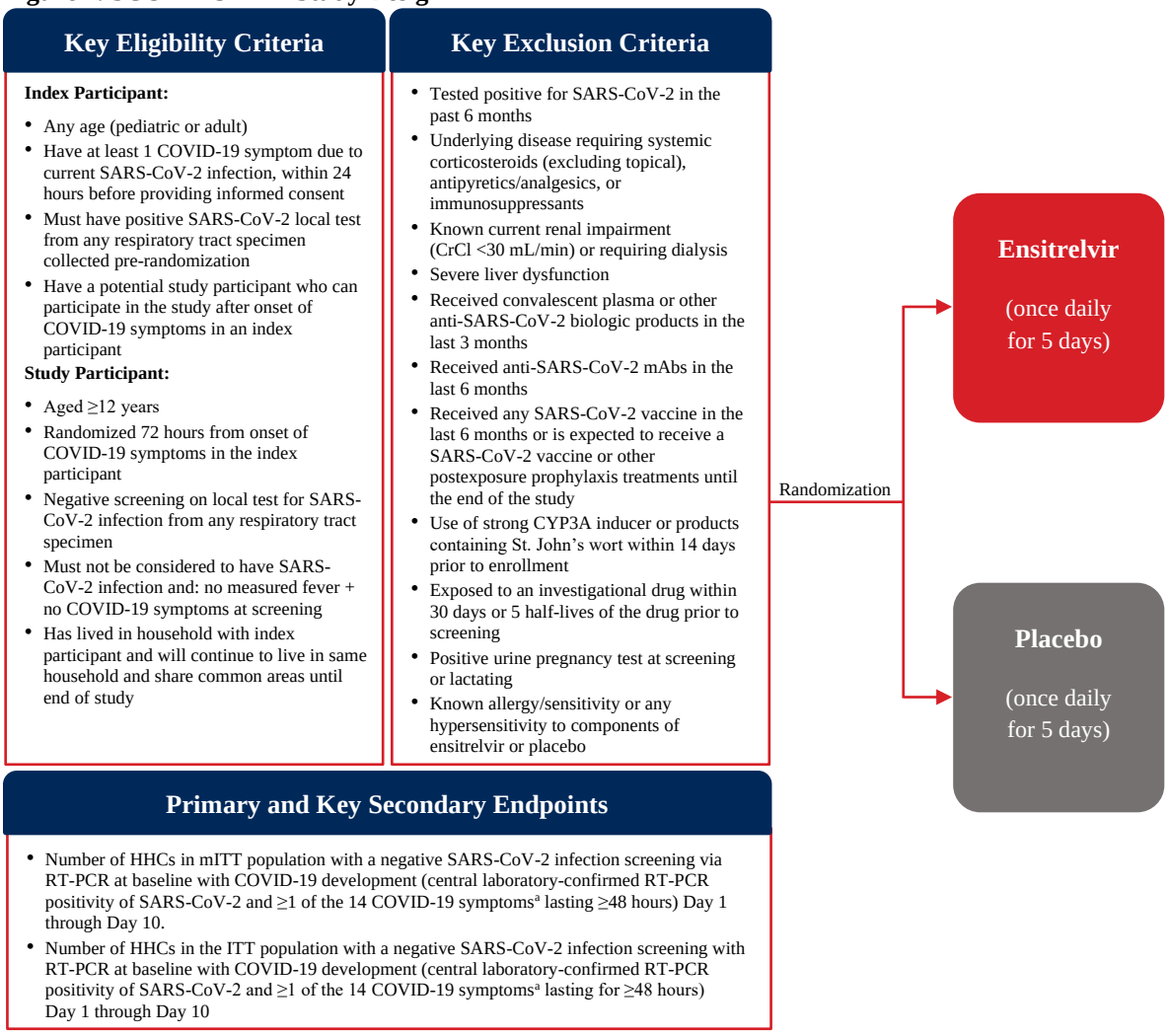
ENCLOSURE

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

APPENDIX

SCORPIO-PEP (Global Phase 3 Study)

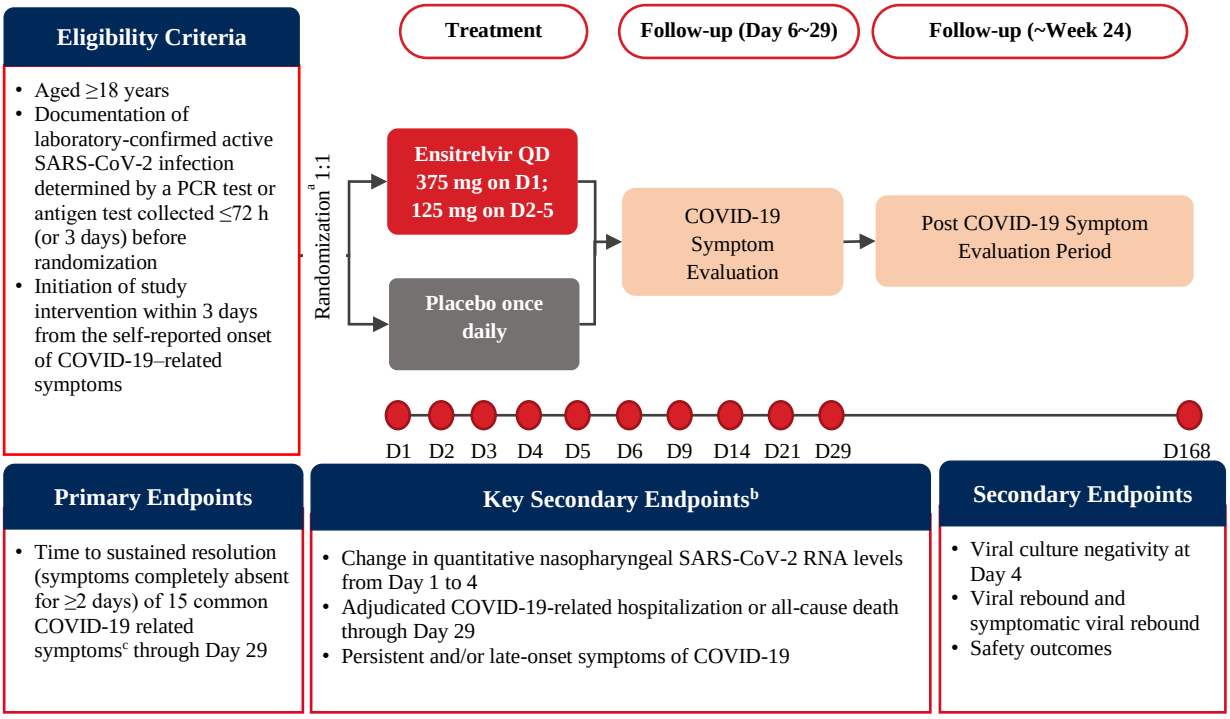
Figure 1. SCORPIO-PEP Study Design[2,15]



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

SCORPIO-HR (Global Phase 3 Study)

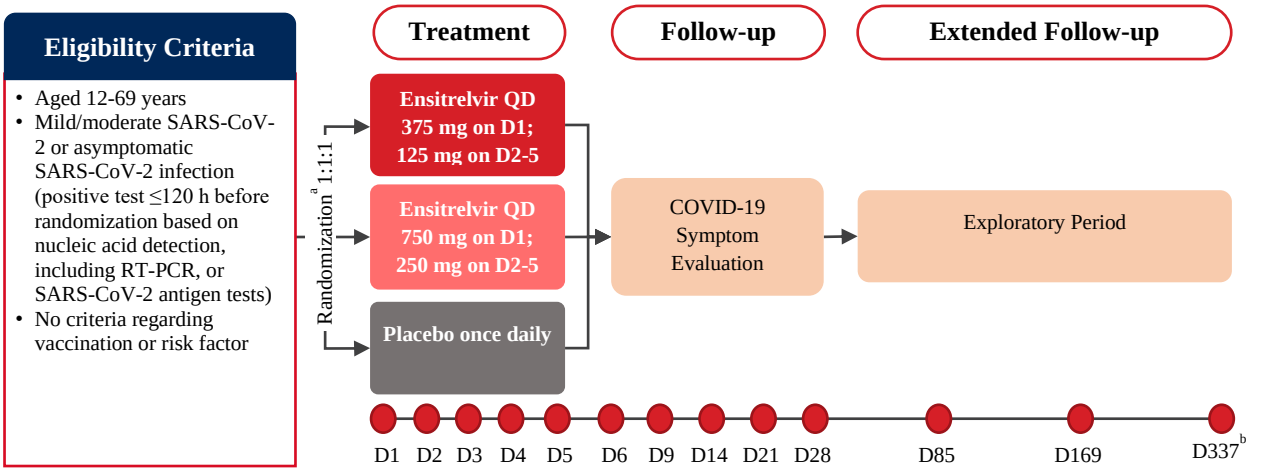
Figure 2. SCORPIO-HR Study Design[4,5]



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

SCORPIO-SR (Phase 3 Study)

Figure 3. Phase 2/3 Study, Phase 3 Part[7,16]



Phase 3 Endpoints

Population: Mild/moderate

Primary:

- Time to resolution of 5 COVID-19 symptoms[a]

Secondary outcomes included:

- Change from baseline in SARS-CoV-2 viral RNA on D4, time to first negative SARS-CoV-2 viral titer (key endpoints), and safety by D28

Abbreviations: COVID-19, coronavirus disease 19; D, Day; RNA, ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]5 COVID-19 symptoms were runny or stuffy nose, sore throat, cough, feeling hot or feverish, and malaise (fatigue).