Xocova – Effect on SARS-CoV-2 Transmission

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). This document is being provided in response to an unsolicited request for medical information from a healthcare professional. 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

- 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 SARS-CoV-2 virus responsible for COVID-19 remains transmissible, and individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19 can potentially transmit the virus to others.[2]
- Healthcare providers should exercise clinical judgment, use existing public health guidance, and take into account individual patient factors.

Clinical Trials

Ensitrelvir has been evaluated in three Phase 3 clinical trials that assessed symptom-based outcomes as well as virologic outcomes relevant to SARS-CoV-2 replication. These studies did not assess SARS-CoV-2 transmission. Virologic and infectivity findings are provided as contextual information and should not be interpreted as direct evidence of reduced transmissibility.

- **SCORPIO-PEP** (post-exposure prophylaxis; PEP) is a global Phase 3, multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of ensitrelvir 125 mg vs placebo in preventing symptomatic COVID-19 in household contacts (HHCs) who were exposed to a person with SARS-CoV-2 infection.[3]
  - Symptomatic COVID-19 through Day 10 occurred in 2.9% (30/1030) of HHCs with ensitrelvir vs 9.0% (91/1011) with placebo (RR 0.33; 95% CI: 0.22-0.49; $P<0.0001$).[1,3]
  - Cumulative incidence of COVID-19, regardless of symptoms, remained lower with ensitrelvir vs placebo through Days 10, 15, 21, and 28.[4]
  - Among participants with breakthrough COVID-19 in the modified intention-to-treat (mITT) population, mean (SD) viral RNA levels through Day 10 were numerically lower with ensitrelvir vs placebo (5.0 [2.0] vs 6.3 [1.9] $\log_{10}$ copies/mL).[4] Among participants who developed SARS-CoV-2 infection regardless of symptoms, reductions in viral RNA shedding were greater with ensitrelvir through Days 3, 6, and 10.[1]
  - In the ITT baseline RT-PCR–positive population (ITT-BP), mean (SD) viral RNA levels through Day 10 were also numerically lower with ensitrelvir vs placebo (5.6 [2.0] vs 6.2 [1.8] $\log_{10}$ copies/mL).[4] XOCOVA use was associated with a greater mean decline in viral RNA shedding levels through Days 3 and 6, relative to placebo.[1]
  - Subgroup analysis [high-risk factors, age groups and time from symptom onset to PEP initiation (<48 hours and 48-72 hours from index symptom onset)] showed lower incidence of symptomatic COVID-19 with ensitrelvir vs placebo.[3]
  - TEAEs occurred in 15.1% (180/1190) of patients treated with ensitrelvir vs 15.5% (184/1187) of patients treated with placebo; no AEs led to hospitalization or deaths.[3]

- **SCORPIO-HR** is a global Phase 3, multicenter, randomized, double-blind, parallel-group, 24-week clinical study that assessed the clinical and antiviral effects of ensitrelvir 125 mg vs placebo in nonhospitalized patients with COVID-19 with or without high-risk factors for severe COVID-19.[5,6]
    - The restricted mean time to sustained symptom resolution in the mITT population was not significantly different between ensitrelvir (12.5 days) and placebo (13.1 days) (difference -0.6 days; 95% CI: -1.38-0.19; *P*=0.14).[5]
    - mITT population: ensitrelvir produced a larger reduction in SARS-CoV-2 viral RNA by Day 4 vs placebo, including in high-risk and standard-risk subgroups. A greater proportion of patients with positive baseline viral culture achieved a negative culture on Day 4 with ensitrelvir. Viral rebound was infrequent in both groups, with no symptomatic rebound occurring in either group.[5,6]
    - AEs occurred in 61.5% (638/1037) of patients with ensitrelvir vs 60.6% (635/1048) with placebo; no deaths were observed in either group.[5]

- The Phase 3 part (**SCORPIO-SR**) of the Phase 2/3 clinical study conducted in Asia evaluated clinical symptom improvement, antiviral effect, and safety of ensitrelvir 125 mg, 250 mg, or placebo.[7]
    - In the primary analysis population (<72 hours from onset), the median time to resolution of five COVID-19 symptoms was significantly reduced with ensitrelvir 125 mg (*P*=0.04).[7]
    - Ensitrelvir 125 mg resulted in a significantly greater reduction in viral RNA levels by Day 4 vs placebo and a shorter median time to first negative viral titer. SARS-CoV-2 RNA levels remained lower through Day 9, and viral titers remained lower through Day 6 with ensitrelvir, compared to placebo.[7,8]
    - Most treatment-related AEs were mild; decreased HDL was the most common TRAE. Two SAEs occurred (one in each arm), which were not considered treatment-related.[7]

Real World Evidence

- **Ikeuchi et al (2025)** conducted a retrospective cohort study using the JMDC administrative claims database in Japan to evaluate the comparative effectiveness of different antiviral treatments on household transmission of SARS-CoV-2 during the Omicron XBB- predominant period. The study included 5398 married-couple households in which the index patient received an antiviral agent on day 0. Household transmission, defined as a COVID-19 diagnosis in the partner between days 2-7, occurred in 21.2% (1143/5398) of households. The cumulative 7-day transmission rate was lower among the 73 index patients who were hospitalized and initiated antiviral therapy on day 0, compared with 5325 outpatients (11.0% vs 21.5%; *P*=0.035). Among outpatients, transmission rates were similar across antiviral groups, including molnupiravir (21.3%), ensitrelvir (21.6%), and nirmatrelvir/ritonavir (22.8%), with no significant differences observed between them (*P*=0.74). Multivariable analyses reported an adjusted hazard ratio of 0.98 (95% CI: 0.86-1.12) for ensitrelvir when using molnupiravir as a reference, compared to 1.10 (95% CI: 0.86-1.40) for nirmatrelvir/ritonavir. Safety outcomes were not reported.[9]

- **Hirai et al (2025)** conducted a retrospective, single-centre study in Japan evaluating the viral load dynamics in 407 vaccinated healthcare workers (HCWs) with mild COVID-19 treated with ensitrelvir (n=205) for 5 days vs symptomatic therapy (n=202) alone. Please note that this study did not evaluate SARS-CoV-2 transmissibility; it assessed infectivity via symptom improvement and viral load. The following results are provided as contextual information. Improvement of major respiratory symptoms by days 5-8 occurred in 91.2% of patients treated with ensitrelvir vs 45.0% of those receiving symptomatic therapy (*P*<0.01). Viral RNA levels decreased in both groups, with higher mean Ct values observed with ensitrelvir vs symptomatic therapy at days 5-8 (28.1 vs 24.4; *P*<0.01) and days 9-12 (30.6 vs 29.2; *P*=0.018). Ct values >30 were achieved in a greater proportion of patients treated with ensitrelvir vs symptomatic therapy (38.0% vs 9.9% at days 5-8; 77.8% vs

42.3% at days 9-12; *P*<0.01 for each comparison). In multivariate logistic regression analysis, ensitrelvir use was independently associated with achieving Ct >30 on days 5-8 (adjusted OR 6.498; 95% CI: 2.902-14.549; *P*<0.01). No adverse events, hospitalizations, exacerbations, or all-cause mortality were reported across both treatment groups.[10]

Preclinical Study

- **Nakashima et al (2024)** conducted an *in vivo* hamster aerosol transmission study to evaluate whether ensitrelvir reduces SARS-CoV-2 shedding in infected hamsters (Index animals) and prevents aerosol transmission to naïve hamsters (Contact animals).[11]
  - Post-infection treatment of Index hamsters with oral ensitrelvir at doses of 12.5, 50, or 200 mg/kg resulted in dose-dependent reductions in viral replication in the lungs and nasal lavage fluid (NALF), along with decreased viral shedding. Reduced shedding in Index hamsters resulted in lower transmission rates in Contact hamsters.[11]
  - In the pre-exposure prophylaxis setting, Contact hamsters received subcutaneous ensitrelvir at 250 or 750 mg/kg prior to exposure, which reduced infection in a dose-dependent manner, reduced lung and NALF transmission ratios, and reduced SARS-CoV-2-associated lung pathology compared with vehicle.[11]
  - No toxicity or adverse events were reported.[11]

2. CLINICAL STUDIES

Ensitrelvir has been evaluated in three Phase 3 clinical trials that assessed symptom-based outcomes as well as virologic outcomes relevant to SARS-CoV-2 replication. These studies did not assess SARS-CoV-2 transmission. Virologic and infectivity findings are provided as contextual information and should not be interpreted as direct evidence of reduced transmissibility.

SCORPIO-PEP (Global Phase 3 Study)

Study Design

SCORPIO-PEP (NCT05897541) is a global Phase 3 trial that evaluated the safety and efficacy of ensitrelvir in preventing symptomatic SARS-CoV-2 infection in household contacts (HHCs) of people who tested positive for COVID-19 (index patients), conducted from June 2023 to September 2024, across the U.S., Japan, Vietnam, Argentina, and South Africa. The study was conducted when Omicron variant infection was predominant, and most participants were vaccinated (see **SCORPIO-PEP Appendix** for more information on study design).[3,12]

HHC participants aged ≥12 years had a negative local screening test for SARS-CoV-2 infection (antigen or RT-PCR) and no symptoms and also received a confirmatory central PCR test at baseline. HHCs 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 day 1 and 125 mg days 2-5) or placebo once daily for 5 days. Study participants began treatment within 72 hours of when the index patient with COVID-19 began showing symptoms.[3]

HHCs were required to have lived with the index patient and to continue living in the same household, sharing common areas (e.g., dining rooms and bathrooms), from within 72 hours after onset of COVID-19 symptoms in the index patient through the end of the study.[3] Only 1 index patient was permitted from each household. In the case of multiple members in the household with confirmed SARS-CoV-2 infection, the household member with the earliest positive test for SARS-CoV-2 (a nucleic acid amplification test or antigen test) or the earliest onset of COVID-19 symptoms was considered the index patient.[3,4]

- As an exploratory assessment, spike gene sequence analysis was performed on nasopharyngeal swabs from participants who tested positive for SARS-CoV-2 and from their corresponding index patient. Results are not currently available
- A participant exposure questionnaire captured the duration of time spent with the index patient, infection-prevention measures, and frequency of contact (e.g., shared meals). Results are not currently available

The ITT population was defined as all randomized HHCs and the mITT population was defined as all HHCs randomly assigned to the study intervention who were SARS-CoV-2-negative on both a local test and a central RT-PCR test at baseline.[3]

The primary endpoint was the proportion of HHCs with COVID-19 development (central laboratory–confirmed RT-PCR positivity of SARS-CoV-2 and ≥1 of the 14 COVID-19 symptoms lasting ≥48 hours) through Day 10 in the mITT population. The key secondary endpoint evaluated the same outcome through Day 10 in the ITT population. Other relevant analyses included the cumulative incidence of COVID-19, regardless of symptoms, through Days 10-28 in the mITT population, SARS-CoV-2 viral RNA over time in the mITT and ITTBP populations, and subgroup analyses according to age, presence of predefined risk factors for severe COVID-19, and time from symptom onset in the index patient to initiation of post-exposure prophylaxis in the mITT population.[3,4]

SCORPIO-PEP did not assess SARS-CoV-2 viral titers. SCORPIO-PEP was not designed to assess COVID-19 transmission.

Results

Baseline Characteristics

The total mITT population included 1030 HHCs treated with ensitrelvir and 1011 HHCs who received a placebo. The baseline demographics and characteristics of the HHCs in the ensitrelvir and placebo groups were similar, and the majority of participants were in the United States (67.2% and 67.6%, respectively).[3]

Efficacy

Primary Endpoint: 2.9% (30/1030) of HHCs in the ensitrelvir group developed symptomatic COVID-19 compared to 9.0% (91/1011) of HHC participants on placebo through day 10, a 67% significant reduction in the risk of developing COVID-19 (RR 0.33, 95% CI: 0.22-0.49; P<0.0001) in uninfected individuals (mITT population) treated after exposure.[1,3]

Key secondary analysis, ITT (through Day 10)[1,3]
In the overall ITT population (all randomized HHCs, including those with central RT-PCR positivity at baseline), symptomatic COVID-19 through Day 10 occurred in 4.4% (52/1194) with ensitrelvir vs 10.2% (122/1193) with placebo (RR 0.43; 95% CI: 0.32-0.59; *P*<0.0001).

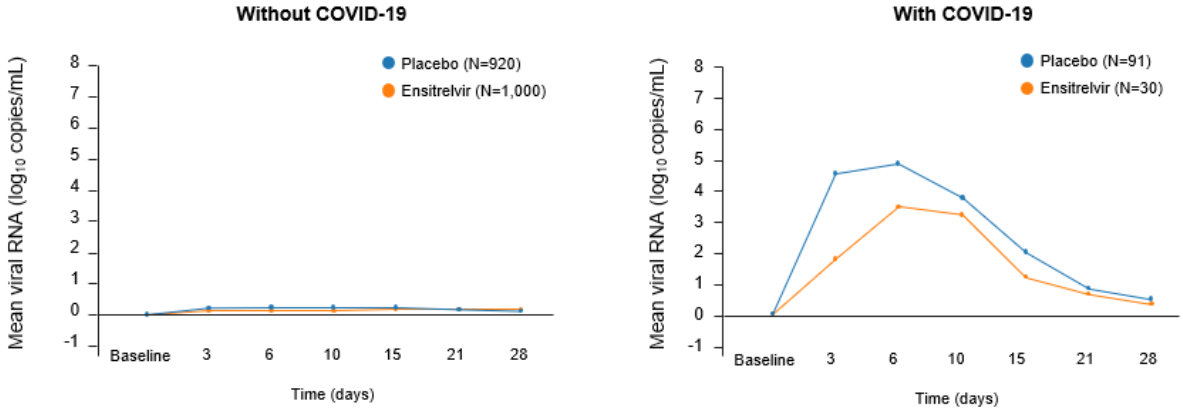
Contextual evidence related to SARS-CoV-2 replication, infectivity, and transmission

The following data were not adjusted for multiplicity; therefore, no clinical or statistical conclusions can be made, and data should be interpreted with caution.

- **Cumulative incidence of COVID-19, regardless of symptoms (mITT; Days 10-28)**[4]
  In the mITT population, cumulative COVID-19, regardless of symptoms, remained lower with ensitrelvir vs placebo at later time points:
  - Day 10: 14.0% (144/1030) vs 21.5% (217/1011); RR 0.66; 95% CI: 0.55-0.79)
  - Day 15: 17.8% (183/1030) vs 25.8% (261/1011); RR 0.69; 95% CI: 0.59-0.81)
  - Day 21: 21.5% (221/1030) vs 29.0% (293/1011); RR 0.74; 95% CI: 0.64-0.86)
  - Day 28: 24.6% (253/1030) vs 31.5% (318/1011); RR 0.78; 95% CI: 0.68-0.90)

- **SARS-CoV-2 viral RNA (mITT)**
  - Through Day 10, participants with breakthrough COVID-19 in the mITT population who received ensitrelvir had numerically lower mean (SD) viral RNA levels compared with those who received placebo (5.0 [2.0] vs 6.3 [1.9] $\log_{10}$ copies/mL; see **Figure 1**).[4]
  - Among mITT participants who developed SARS-CoV-2 infection through Day 10, regardless of symptoms, mean reductions in viral RNA shedding levels in nasopharyngeal samples were greater with ensitrelvir compared with placebo by 1.45, 1.24, and 0.94 $\log_{10}$ copies/mL through Days 3, 6, and 10, respectively.[1]

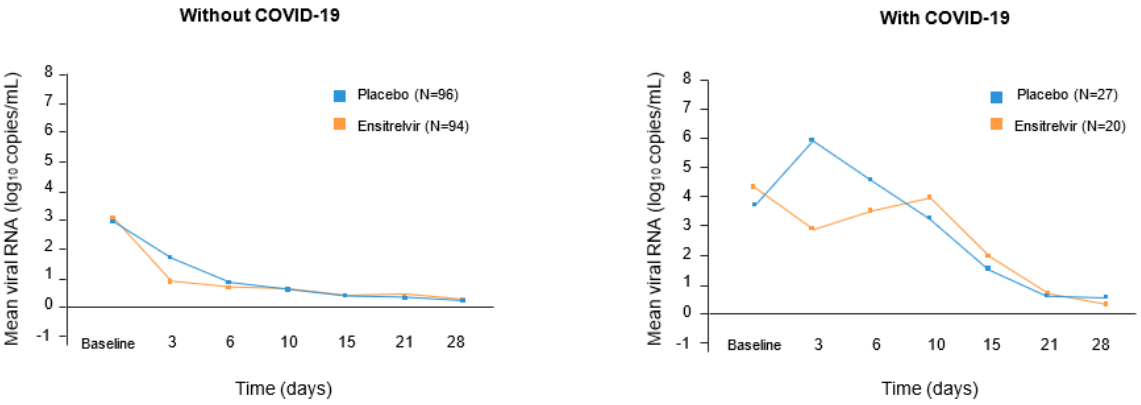
Figure 1: Mean Viral RNA Over Time (mITT Population)[4]



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; mITT, modified intention-to-treat; RNA, ribonucleic acid
Figure adapted from Hayden et al. *NEJM (Suppl).* 2026.

- **SARS-CoV-2 viral RNA [ITT baseline RT-PCR-positive (ITT-BP) population]**[4]
  - Among participants in the ITT baseline RT-PCR-positive population, the ensitrelvir group showed numerically lower mean (SD) viral RNA levels through Day 10 compared with placebo (5.6 [2.0] vs 6.2 [1.8] $\log_{10}$ copies/mL; see **Figure 2**).[4]
  - Among the ITT-BP population, XOCOVA use was associated with a 1.36 and 0.49 $\log_{10}$ copies/mL greater mean decline in viral RNA shedding levels in nasopharyngeal samples through Days 3 and 6, respectively, relative to placebo.[1]

Figure 2: Mean Viral RNA Over Time (ITT-BP Population)[4]



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 (Suppl).* 2026.

- **Subgroup analysis, high-risk vs without high-risk HHCs (mITT)**[3]
  - Among HHCs with ≥1 predefined high-risk factor for severe COVID-19 (e.g., BMI ≥30 kg/m^2, smoking, age ≥65 years, heart disease, diabetes), symptomatic COVID-19 through Day 10 occurred in 2.4% (9/382) with ensitrelvir vs 9.9% (37/374) with placebo (RR 0.24; 95% CI: 0.12-0.49).
  - In HHCs without high-risk factors, COVID-19 occurred in 3.2% (21/648) vs 8.5% (54/637), respectively (RR 0.39; 95% CI: 0.24-0.62).

- **Subgroup analysis, age of HHCs (mITT)**[3]
  - In HHCs aged <18 years, symptomatic COVID-19 occurred in 1.6% (1/64) with ensitrelvir vs 3.7% (2/54) with placebo (RR 0.42; 95% CI: 0.04-4.57).
  - In HHCs aged 18-64 years, symptomatic COVID-19 occurred in 3.0% (26/867) vs 9.0% (78/867), respectively (RR 0.34; 95% CI: 0.23-0.52).
  - Among those ≥65 years, COVID-19 occurred in 3.0% (3/99) vs 12.2% (11/90), respectively (RR 0.25; 95% CI: 0.08-0.82).

- **Subgroup analysis, time from symptom onset in index patient to PEP initiation (mITT)**[3]
  - For HHCs enrolled <48 hours from index symptom onset, symptomatic COVID-19 through Day 10 occurred in 2.5% (18/732) with ensitrelvir vs 10.3% (74/720) with placebo (RR 0.26; 95% CI: 0.16-0.41).
  - For those enrolled at 48-72 hours, COVID-19 occurred in 4.0% (12/298) vs 5.8% (17/291), respectively (RR 0.69; 95% CI: 0.33-1.42).

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 in the safety analysis set, with 1 event in each group leading to discontinuation of treatment.[3]
- Two serious TEAEs occurred in each group, and they were considered to be unrelated to the study drug.[3]
- There were no AEs that led to hospitalization, and no deaths were observed in either group.[3]

SCORPIO-HR (Global Phase 3 Study)

Study Design

SCORPIO-HR (NCT05305547) is a global Phase 3, multicenter, randomized, double-blind, parallel-group, 24-week clinical study that assessed the clinical and antiviral effects of ensitrelvir (375 mg orally on day 1 and 125 mg orally once daily on days 2-5) vs placebo for 5 days in nonhospitalized patients aged ≥18 years with COVID-19 with or without high-risk factors for severe COVID-19 (see **SCORPIO-HR_Appendix** for more information on study design).[5,6,13]

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 the Omicron variant infection was predominant and among a mostly vaccinated population.[5,6,13]

The mITT population was the primary analysis population, and it was defined as all patients who were randomized and received ≥1 dose of treatment ≤3 days from when symptoms began. The viral culture analysis included participants in the mITT population with detectable viral culture at baseline.[5]

The primary endpoint was the restricted mean time to sustained resolution of 15 COVID-19 symptoms through Day 29 in the mITT population. Other relevant endpoints included the change in SARS-CoV-2 RNA levels from Day 1 to Day 4 (mITT), the proportion of participants with negative SARS-CoV-2 viral culture on Day 4 (mITT), and viral rebound and symptomatic viral rebound through Day 29 (mITT).[5,6]

SCORPIO-HR was not designed to assess COVID-19 transmission.

Results

Efficacy

Primary Endpoint: In the 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]

Contextual evidence related to SARS-CoV-2 replication, infectivity, and transmission

- **Change in SARS-CoV-2 RNA levels from Day 1 to Day 4[5,6]**
  In the mITT population, ensitrelvir produced a larger reduction in viral RNA levels by Day 4 compared with placebo. Ensitrelvir: least-squares mean (LSM) change of -2.71 $\log_{10}$ copies/mL vs placebo: LSM change of -1.99 $\log_{10}$ copies/mL; difference: 0.72 $\log_{10}$ copies/mL (95% CI: 0.55 to 0.90).
  - Subgroup results:
    - High-risk: difference in LSM of 0.63 $\log_{10}$ copies/mL (95% CI: 0.35 to 0.91).
    - Standard-risk: difference in LSM of 0.76 $\log_{10}$ copies/mL (95% CI: 0.54 to 0.98).

- **Viral culture results on Day 4[5]**
  Among participants in the mITT population who had a positive viral culture at baseline, a greater proportion had negative viral culture on Day 4 with ensitrelvir (95.5% [274/287]) vs placebo (75.0% [210/280]).

- **Viral rebound through Day 29[5,6]**
  - Viral rebound was assessed in the mITT population and defined as an increase in quantitative viral RNA by ≥1.0 $\log_{10}$ from the previous quantifiable value or to ≥1.0 $\log_{10}$ above the lower limit of quantification (LLoQ) when the previous value was undetectable or below the LLoQ.
  - Rebound rates: 0.6% (6/945) with ensitrelvir vs 1.4% (13/943) with placebo.
  - No symptomatic viral rebound, defined as viral rebound accompanied by new or worsening clinical symptoms, was reported in either group.

Safety[5]

- AEs occurred in 638 patients treated with ensitrelvir (61.5%; n=1037), and 635 patients treated with placebo (60.6%; n=1048).
- TRAEs occurred in 86/1037 (8.3%) of patients treated with ensitrelvir and 74/1048 (7.1%) of patients that were given placebo.
- Serious TEAE occurred in 5/1037 (0.5%) of the ensitrelvir-treated participants and 6/1048 (0.6%) of the patients given placebo.
- No serious TRAEs occurred in either group.
- COVID-19-related hospitalization was observed in 3/1037 (0.3%) ensitrelvir-treated patients and 1/1048 (0.1%) placebo treated participant.
- No deaths were observed in either group through Day 29.

SCORPIO-SR (Phase 3 Study)

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 in patients aged 12-69 years with mild-to-moderate COVID-19. Eligible patients had tested positive for SARS-CoV-2 within 120 hours before randomization and were randomized 1:1:1 to receive ensitrelvir 125 mg (375 mg on Day 1 and 125 mg once daily on Days 2-5), ensitrelvir 250 mg (750 mg on Day 1 and 250 mg once daily on Days 2-5), or matching placebo for 5 days. The primary analysis population included patients randomized within <72 hours of disease onset. The study was conducted in Japan, South Korea, and Vietnam from February to July 2022 during the Omicron variant-predominant period in a mostly vaccinated population (see **SCORPIO-SR_Appendix** for more information on study design).[7]

The primary endpoint was time to resolution of the composite of 5 COVID-19 symptoms from the ITT population (all patients who tested positive for SARS-CoV-2 RNA at baseline). Other relevant endpoints in the ITT population included the change from baseline in SARS-CoV-2 RNA levels on Day 4, the time to first negative SARS-CoV-2 viral titer, and SARS-CoV-2 RNA levels and viral titers over time.[7,8]

The ITT population included all patients who tested positive for SARS-CoV-2 RNA at baseline. The mITT population included patients who tested positive for SARS-CoV-2 RNA and had a detectable SARS-CoV-2 viral titer at baseline. The primary analysis population for the primary endpoint and key secondary endpoints included patients in the ITT population who were randomized within <72 hours of disease onset.[7]

SCORPIO-SR was not designed to assess COVID-19 transmission.

Results

Efficacy

Primary Endpoint: The time to resolution of five COVID-19 symptoms 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 1**).[7]

Table 1. Time to Resolution of 5 COVID-19 Symptoms in SCORPIO-SR[7a]

	COVID-19 Onset to Randomization: <72 h (Primary Analysis Population)[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	-

Table adopted from Yotsuyanagi et al. *JAMA Netw Open*. 2024.
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.

Contextual evidence related to SARS-CoV-2 replication, infectivity, and transmission

- **Change in SARS-CoV-2 RNA levels from baseline to Day 4 (primary analysis population)[7,8]**
  In the primary analysis population (<72 hours), ensitrelvir resulted in a significantly greater reduction in viral RNA levels by Day 4 compared with placebo. Ensitrelvir 125 mg: Least squares mean (LSM) (SE) -2.48 (0.08) $\log_{10}$ copies/mL vs placebo: LSM (SE) -1.01 (0.08) $\log_{10}$ copies/mL, *P*<0.001 (95% CI: -1.63 to -1.31).
  - In the ≤120-hour ITT population, ensitrelvir 125 mg produced a substantially larger reduction in viral RNA levels by Day 4 compared with placebo. Ensitrelvir 125 mg: LSM change of -2.46 (0.06) $\log_{10}$ copies/mL vs placebo: -1.26 (0.06) $\log_{10}$ copies/mL; difference: -1.20 (0.06) $\log_{10}$ copies/mL (95% CI: -1.32 to -1.08; *P*<0.001).

- **Time to first negative SARS-CoV-2 viral titer (primary analysis population)[7,8]**
  A significant difference was observed between the groups. Ensitrelvir 125 mg: median 36.2 hours (95% CI: 23.4-43.2) vs Placebo: median 65.3 hours (95% CI 62.0-66.8), difference: -29.1 hours (95% CI: -42.3 to -21.1), *P*<0.001.
  - Similar results were obtained for patients randomized within 120 hours of disease onset.

- **SARS-CoV-2 RNA levels and viral titers over time (primary analysis population)[7,8]**
  Across all timepoints, SARS-CoV-2 RNA levels remained lower in the ensitrelvir 125 mg group vs placebo up to Day 9, and viral titers remained lower up to Day 6, irrespective of time to randomization.

Safety

- Most TRAEs were mild in severity, and a decrease in HDL was the most commonly reported TRAE.[7]
- There were two SAEs 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]

3. REAL WORLD EVIDENCE STUDIES

Retrospective Cohort Study on Household Transmission of COVID-19

Ikeuchi et al. (2025) conducted a retrospective cohort study using the JMDC administrative claims database in Japan to examine the comparative effectiveness of antiviral treatment (molnupiravir, ensitrelvir, nirmatrelvir/ritonavir, and remdesivir) on household transmission of SARS-CoV-2 during the Omicron XBB-predominant period (April 1, 2023 to August 31, 2023). Married-couple households were eligible if one partner was diagnosed with COVID-19 and received antiviral therapy on day 0. Exclusion criteria included households in which both partners were diagnosed on day 0-1, where the index case (first diagnosed partner) had been hospitalized prior to day 0, or where >1 antiviral was prescribed simultaneously.[9]

The primary endpoint was household transmission, defined as a COVID-19 diagnosis in the partner between day 2 and day 7 of the index case diagnosis. Kaplan-Meier curves were used to visualize the time to secondary infection, and log-rank tests were used to compare the antiviral treatment groups. Cox proportional hazards models were used to estimate adjusted hazard ratios for secondary household transmission, accounting for potential confounders, including antiviral treatment group, age, sex, prior COVID-19 infection, hospitalization, and immunocompromised conditions.[9]

Results

Baseline Characteristics

In total, 5398 households were included in the final analysis. Most index cases were treated as outpatients (98.6%; n=5325), while 1.4% (n=73) were hospitalized and treated with antivirals on day 0. Antiviral agents prescribed in the outpatient setting included 3,093/5,398 (57.3%) for molnupiravir, 1,907/5,398 (35.3%) for ensitrelvir, 323/5,398 (6.0%) for nirmatrelvir/ritonavir, and 2/5,398 (0.0%) for remdesivir.[9]

Table 2. Antiviral Distribution in Outpatient and Inpatient Settings[9]

Index patient	Total	Household transmission		
	N=5398	No (n=4255)	Yes (n=1143)	*P* value
Outpatient Treatment	5,325 (98.6%)	4,190 (98.5%)	1,135 (99.3%)	0.031
Molnupiravir	3,093 (57.3%)	2,440 (57.3%)	653 (57.1%)	0.90
Ensitrelvir	1,907 (35.3%)	1,498 (35.2%)	409 (35.8%)	0.72
Nirmatrelvir/ritonavir	323 (6.0%)	250 (5.9%)	73 (6.4%)	0.52
Remdesivir	2 (0.0%)	2 (0.0%)	0 (0.0%)	0.46
Inpatient Treatment	73 (1.4%)	65 (1.5%)	8 (0.7%)	0.031
Molnupiravir	16 (0.3%)	15 (0.4%)	1 (0.1%)	0.22
Ensitrelvir	1 (0.0%)	1 (0.0%)	0 (0.0%)	1.00
Nirmatrelvir/ritonavir	3 (0.1%)	3 (0.1%)	0 (0.0%)	1.00
Remdesivir	53 (1.0%)	46 (1.1%)	7 (0.6%)	0.15

Data are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables. P values were calculated using the Mann–Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Table adapted from Ikeuchi et al. *BMC Infectious Diseases.* 2025.

Efficacy

- Household transmission occurred in 21.2% (1143/5398) of households by day 7. The cumulative 7-day transmission rate, estimated using the Kaplan-Meier method, was 11.0% (95% CI: 5.7-20.8; n=73) among index patients who were hospitalized and began antiviral therapy on day 0, compared with 21.5% (95% CI: 20.4-22.6; n=5325) among outpatients (log-rank test, *P*=0.035) (see **Figure 3A**).[9]
- Transmission rate by antiviral treatment group among the outpatients was:[9]
  - Molnupiravir: 21.3% (n=3093; 95% CI: 19.9-22.8)
  - Ensitrelvir: 21.6% (n=1907; 95% CI: 19.8-23.6)

- Nirmatrelvir/ritonavir: 22.8% (n=323; 95% CI: 18.6-27.8)
  - No significant difference was observed among oral antivirals, log-rank test *P*=0.74 (see **Figure 3B**).

Figure 3. Cumulative Probability of COVID-19 Diagnosis in Household Partners (A) Comparing Index Patients Who Were Hospitalized on Day 0 With Those Treated as Outpatients (B) Based on Antiviral Agent Administered to the Index Patient.[9]

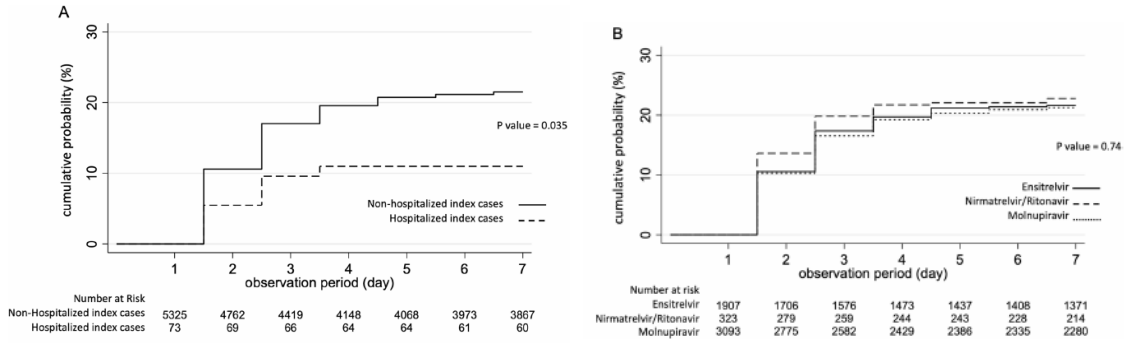


Figure adopted from Ikeuchi et al. *BMC Infectious Diseases.* 2025, under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

- Cox proportional hazard analysis results:[9]
  - When antiviral agents were evaluated using molnupiravir as the reference, the multivariable Cox analysis reported an adjusted hazard ratio (aHR) of 0.98 (95% CI: 0.86-1.12) for ensitrelvir and 1.10 (95% CI: 0.86-1.40) for nirmatrelvir/ritonavir (see **Table 3**).
  - Additional variables associated with transmission included:
    - Prior COVID-19 infection in the index patient (aHR 0.50, 95% CI: 0.33-0.76; *P*=0.001)
    - Prior COVID-19 infection in the partner (aHR 0.31, 95% CI: 0.21-0.45; *P*<0.001)
    - Age ≥61 years versus <49 years (aHR 0.84, 95% CI: 0.71-1.00; *P*=0.051)
    - Male sex of the index patient (aHR 1.43, 95% CI: 1.26-1.63; *P*<0.001)
  - For index patients hospitalized on day 0 (mostly treated with remdesivir), aHR for household transmission was 0.51 (95% CI: 0.25-1.03; *P*=0.062).

Table 3. Cox Proportional Hazard Models for Household Transmission of COVID-19[9]

		Univariable		Multivariable	
	Events/ Total	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Outpatient molnupiravir	653/3093	Reference			
Outpatient ensitrelvir	409/1907	1.02 (0.90–1.16)	0.74	0.98 (0.86–1.12)	0.79
Outpatient nirmatrelvir/ritonavir	73/323	1.09 (0.86–1.39)	0.47	1.10 (0.86–1.40)	0.45
Outpatient remdesivir	0/2	NA	NA	NA	NA
Hospitalized and treated on day 0	8/73	0.50 (0.25–1.00)	0.052	0.51 (0.25–1.03)	0.062

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable.
Table adapted from Ikeuchi et al. *BMC Infectious Diseases.* 2025.

- In the sensitivity analysis that excluded 19 households where the index patient was hospitalized between days 1 and 7, and 2 households where the partner was hospitalized for non-COVID-19 reasons during the same period, the findings were consistent with the main analysis, as follows:[9]
  - Cumulative day-7 transmission rates were 21.5% (95% CI: 20.4-22.7) for outpatients versus 11.0% (95% CI: 5.7-20.8; *P*=0.034) for hospitalized patients.

- Antiviral-specific rates for outpatients were 21.3% (95% CI: 19.9-22.8) for molnupiravir, 21.7% (95% CI: 19.9-23.6) for ensitrelvir, and 22.9% (95% CI: 18.7-28.0) for nirmatrelvir/ritonavir, *P*=0.70.

Safety

- Safety outcomes or adverse events associated with any of the antivirals were not reported in the publication.[9]

Retrospective Study on Viral Load Dynamics in Healthcare Workers with Mild COVID-19

Hirai et al. (2025) conducted a retrospective, single-center, observational study in Japan between November 2022 to May 2024 to compare the viral load dynamics in healthcare workers (HCWs) with mild COVID-19 treated with ensitrelvir for 5 days versus symptomatic therapy alone. Key exclusion criteria included asymptomatic infection, moderate-to-severe disease; cycle threshold (Ct) value ≥30 at diagnosis, symptom duration >72 hours at presentation, and use of other COVID-19 antivirals (nirmatrelvir/ritonavir or molnupiravir).[10]

The primary endpoint was achieving Ct >30 (threshold indicating low viral infectivity) on days 5-8 or 9-12 after symptom onset. Patients who achieved Ct >30 on days 5-8 were compared with those who did not, and multivariate logistic regression analysis was conducted to identify factors independently associated with achieving Ct >30 on days 5-8. Secondary endpoints included COVID-19-related hospitalization, disease worsening, and all-cause mortality within 30 days of onset.[10]

Please note that this study did not evaluate SARS-CoV-2 transmissibility; it assessed infectivity via symptom improvement and viral load. The following results are provided as contextual information.

Results

Baseline Characteristics

In total, 407 HCWs with mild RT-PCR-confirmed COVID-19 were included: 202 in the symptomatic therapy group and 205 in the ensitrelvir group. All participants were vaccinated. Risk factors for severe COVID-19 were similarly distributed between the two groups (ensitrelvir: 7.3% (n=15) vs symptomatic therapy: 8.9% (n=18; *P*=0.556).[10]

Among patients assessed on Days 5-8, the mean Ct value at diagnosis was significantly lower in the ensitrelvir group than in the symptomatic therapy group (15.5±3.6 vs 17.1±4.4; *P*<0.01).[10]

Among patients assessed on Days 9-12, the mean Ct value at diagnosis was also numerically lower in the ensitrelvir group (15.2±3.4 vs 16.9±4.5), although the difference was not statistically significant (*P*=0.131).[10]

Efficacy

- Ct values increased in both groups indicating that viral RNA levels decreased in both arms from baseline (**baseline values** are provided above).[10]
  - Days 5-8:
    - Mean Ct values were 28.1±4.5 (ensitrelvir; n=187) vs 24.4±4.7 (symptomatic therapy; n=91); *P*<0.01
    - 38.0% (71/187) of patients treated with ensitrelvir achieved a PCR cycle threshold value >30, indicating low infectivity, versus 9.9% (9/91) in the symptomatic therapy group (*P*<0.01).
  - Days 9-12:
    - Mean Ct values were 30.6±1.8 (ensitrelvir; n=18) vs 29.2±4.0 (symptomatic therapy; n=111); *P*=0.018

        - 77.8% (14/18) of the ensitrelvir group reached Ct >30 compared to 42.3% (47/111) in the symptomatic group (P<0.01).
    - Patients who achieved Ct >30 (n=80) on days 5-8 were compared with those who did not (Ct <30, n=198). Multivariate logistic regression analysis showed that ensitrelvir use was independently associated with achieving Ct >30 on days 5-8 (adjusted OR: 6.498; 95% CI: 2.902-14.549; P<0.01), with shorter time from symptom onset to PCR testing also predicting viral clearance.
- Symptom improvement within 5-8 days was reported by 91.2% (187/205) of the ensitrelvir group, significantly higher than the 45.0% (91/202) observed in the symptomatic therapy group (P<0.01).[10]
- Improvement of major respiratory symptoms (cough, sore throat, nasal symptoms, etc.) within 5-8 days of onset was reported in 91.2% (187/205) of patients in the ensitrelvir group vs 45.0% (91/202) of patients in the symptomatic therapy group (P<0.01).[10]

Safety

- Across both treatment groups, no adverse events, hospitalizations or exacerbations within 14 days of diagnosis, or all-cause 30-day mortality after COVID-19 treatment were observed.[10]

4. PRECLINICAL STUDY

Hamster Aerosol Transmission Model Evaluating Ensitrelvir

Nakashima et al. (2024) conducted an *in vivo* hamster aerosol transmission study to evaluate if ensitrelvir reduces SARS-CoV-2 shedding in infected hamsters (Index animals) and prevents aerosol transmission to naïve hamsters (Contact animals). Male Syrian index hamsters were intranasally inoculated with 1×10^3 $TCID_{50}$ of SARS-CoV-2 Delta strain and co-housed with Contact hamsters for 12 hours in a dual-cage system separated by 2 cm, allowing aerosol transmission, but preventing direct contact. Infection was assessed using nasal lavage fluid (NALF), lung tissues, and body weight measurements.[11]

Two experimental settings were evaluated:[11]

1. Post-infection treatment of Index hamsters: Index hamsters received oral ensitrelvir at 12.5, 50, or 200 mg/kg (3 doses administered from 8 hours post-infection through Day 1).

2. Pre-exposure prophylaxis in Contact hamsters: Contact hamsters received subcutaneous ensitrelvir at 250 or 750 mg/kg 12 hours prior to co-housing with infected Index hamsters.

Results

Efficacy

Post-infection treatment of Index hamsters:[11]

- Ensitrelvir reduced viral replication in the lungs and NALF in Index hamsters in a dose-dependent manner (see **Figure 4A**).
- Viral shedding from Index hamsters was suppressed with increasing doses of ensitrelvir treatment, resulting in decreased transmission to Contact hamsters with increasing doses of ensitrelvir in Index hamsters (**Figure 4B**).

Figure 4. Effects of Ensitrelvir on SARS-CoV-2 Shedding from Index Hamsters: (A) Virus Levels on Day 2 in the NALF and Lungs of Index Hamsters (B) Virus Levels on Day 5 in the NALF and Lungs of Contact hamsters.[11]

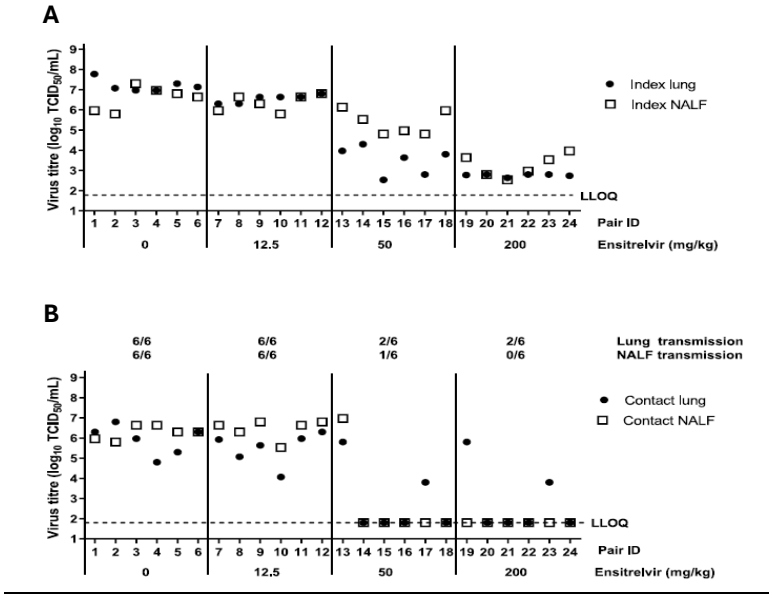


Figure adopted from Nakashima et al. *Antiviral Research.* 2024 under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0).
The dashed lines in the graphs indicate the LLOQ of the assay (1.80 $\log_{10}$ $TCID_{50}$/mL).
Abbreviations: LLOQ, lower limit of quantification; NALF, nasal lavage fluid; $TCID_{50}$, 50% Tissue Culture Infectious Dose.

Pre-exposure prophylaxis in Contact hamsters:[11]

Viral infection in the lungs and NALF of Contact hamsters:[11]

- Prophylactic ensitrelvir prior to exposure reduced SARS-CoV-2 infection in Contact hamsters in a dose-dependent manner. Lung and NALF transmission ratios were lower in the 250 mg/kg and 750 mg/kg ensitrelvir groups compared with the vehicle group (see **Figure 5**).

Viral replication/pathogenesis in Contact hamsters receiving 750 mg/kg ensitrelvir:[11]

- Contact hamsters prophylactically treated with 750 mg/kg ensitrelvir, corresponding to an approximate unbound plasma concentration of 100 ng/mL, were protected against body-weight loss compared with vehicle-treated controls. In contrast, prophylactic treatment with 250 mg/kg ensitrelvir, corresponding to an approximate unbound plasma concentration of 20 ng/mL, did not protect against body-weight loss (see **Figure 5**).
- Prophylactic ensitrelvir reduced SARS-CoV-2 infection in Contact hamsters in a dose-dependent manner. Lung and NALF transmission ratios were lower with 250 and 750 mg/kg ensitrelvir than with vehicle; the NALF transmission rate decreased from 100% (6/6) with vehicle to 2/6 with 750 mg/kg ensitrelvir (see **Figure 4**).
- Contact hamsters receiving 750 mg/kg ensitrelvir showed reduced SARS-CoV-2-associated lung pathology (indicated with suppression of increased lung weight) compared with Contact hamsters receiving vehicle, where SARS-CoV-2 exposure led to increased lung weights (see **Figure 6**). Viral RNA was detected in the lungs of 2 Contact hamsters receiving 750 mg/kg ensitrelvir; however, lung-weight increases remained suppressed.

Figure 5. Effect Of Prophylactic Administration of Ensitrelvir on Virus Levels in the Lungs and NALF of Contact Hamsters.[11]

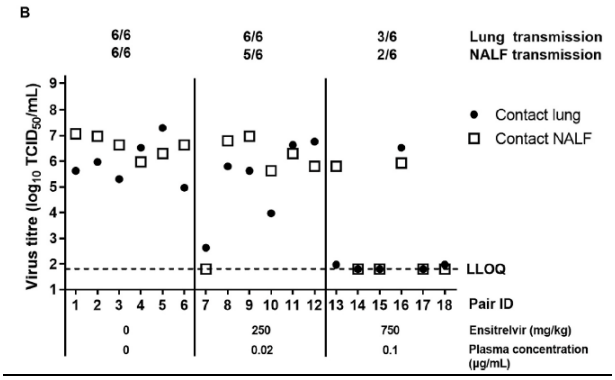


Figure adopted from Nakashima et al. *Antiviral Research.* 2024 under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0).
The dashed lines in the graphs indicate the LLOQ of the assay (1.80 $\log_{10}$ $TCID_{50}$/mL).
Abbreviations: LLOQ, lower limit of quantification; NALF, nasal lavage fluid; $TCID_{50}$, 50% Tissue Culture Infectious Dose.

Figure 6. Effect of Prophylactic Administration of Ensitrelvir on Virus Replication and SARS-CoV-2-Induced Pathogenesis in Contact Hamsters: (A) Mean Group Lung Weights and (B) Lung Weights of Individual Contact Hamsters.[11]

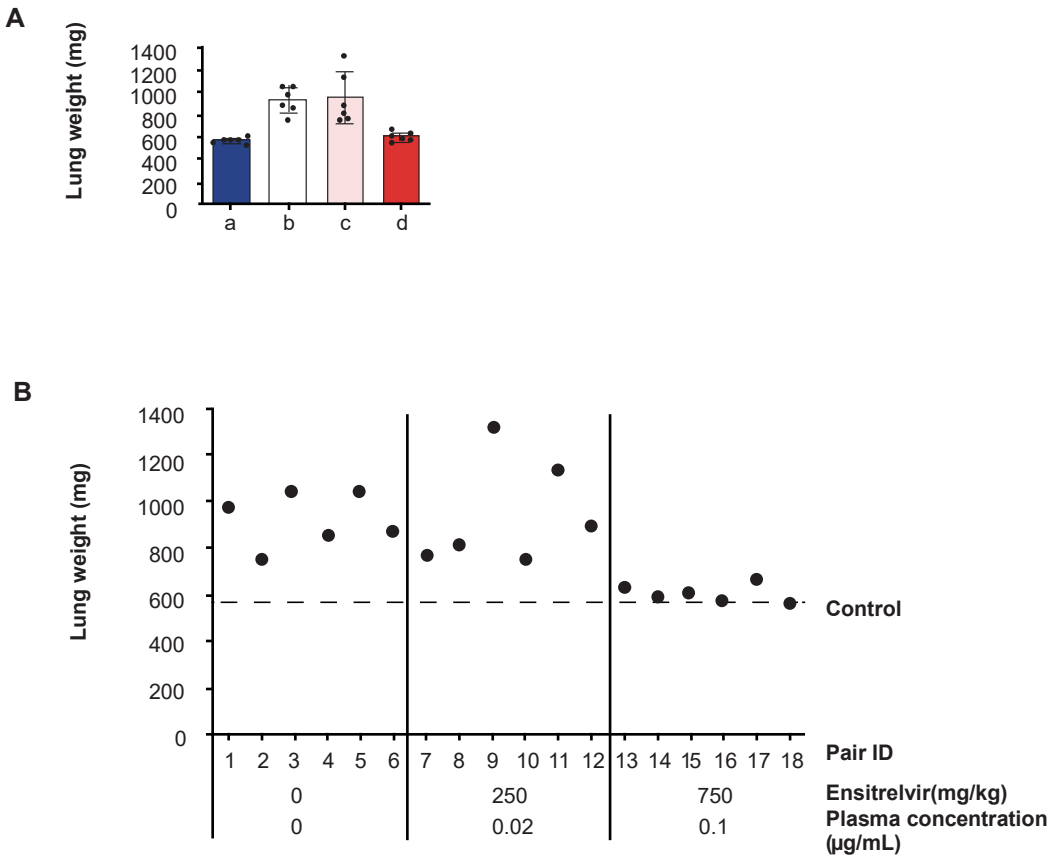


Figure adapted from Nakashima et al. *Antiviral Research.* 2024 under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0).

Figure A: The bar graphs indicate mean group lung weights. The dots indicate lung weights of individual animals in each group.

**P*<0.001 (Dunnett's test comparison with "group b" Contact hamsters co-housed with infected Index hamsters).

The groups were:

(a) Contact hamsters administered vehicle and co-housed with non-infected Index hamsters

(b) Contact hamsters administered vehicle and co-housed with SARS-CoV-2-infected Index hamsters

(c) Contact hamsters administered 250 mg/kg ensitrelvir and co-housed with SARS-CoV-2-infected Index hamsters

(d) Contact hamsters administered 750 mg/kg ensitrelvir and co-housed with SARS-CoV-2-infected Index hamsters

Figure B: The dots indicate lungs that were positive for virus infection based on qRT-PCR analysis. The dashed line indicates the mean lung weight of the Contact hamsters that were cohoused with non-infected Index hamsters administered vehicle only (Control).

Abbreviations: qRT-PCR, quantitative Reverse Transcription Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

Safety

- No toxicity or adverse events were reported in the publication.[11]

5. 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]

As stated in Section 12.4 of the XOCOVA Full Prescribing Information:

Microbiology - Antiviral Activity

Clinical Antiviral Activity

In Trial SCORPIO-PEP, among mITT subjects who developed SARS-CoV-2 infection (regardless of symptoms) through Day 10, XOCOVA use was associated with a 1.45, 1.24, and 0.94 $\log_{10}$ copies/mL greater mean decline in viral RNA shedding levels in nasopharyngeal samples through Days 3, 6, and 10, respectively, relative to placebo. In addition, among subjects who had a negative screening test for SARS-CoV-2 at the local laboratory, but were subsequently found to be RT-PCR-positive at baseline by central laboratory testing (i.e., the ITT baseline positive population), XOCOVA use was associated with a 1.36 and 0.49 $\log_{10}$ copies/mL greater mean decline in viral RNA shedding levels in nasopharyngeal samples through Days 3 and 6, respectively, relative to placebo.[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.

6. LITERATURE SEARCH, ABBREVIATIONS, & REFERENCES

LITERATURE SEARCH

As of July 2026, a computerized search of the published medical literature using internal and external databases (eg, PubMed®) has identified an additional relevant reference regarding the ability of ensitrelvir to reduce transmission. For your review, these references are listed in the bibliography that follows:

Yamaguchi D, Saito MM, Hata A, et al. Modeling the Impact of Ensitrelvir on SARS-CoV-2 Dynamics and Its Application for Assessment of Transmission Mitigation of Patients with COVID-19. *Infect Dis Ther*. 2024;13(11):2377-2393. doi:10.1007/s40121-024-01046-6 [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 it should not be considered all-inclusive.

ABBREVIATIONS

3CL	3-chymotrypsin-like
ACTG	AIDS Clinical Trials Group
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AE	adverse event
aHR	adjusted hazard ratio
AOR	adjusted odds ratio
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 19
Ct	cycle threshold
HCCc	household contacts
HCWs	healthcare workers
HDL	high-density lipoprotein
ITT	intention-to-treat
LLoQ	lower limit of quantification
LSM	least-squares mean
MHLW	Ministry of Health, Labour and Welfare
mITT	modified intention-to-treat
NALF	nasal lavage fluid
NIH	National Institutes of Health
OR	odds ratio
PEP	post-exposure prophylaxis
PK	pharmacokinetic
RNA	ribonucleic acid
RR	risk ratio
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse events
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SE	standard error
TEAE	treatment-emergent adverse events
TRAE	treatment-related adverse events

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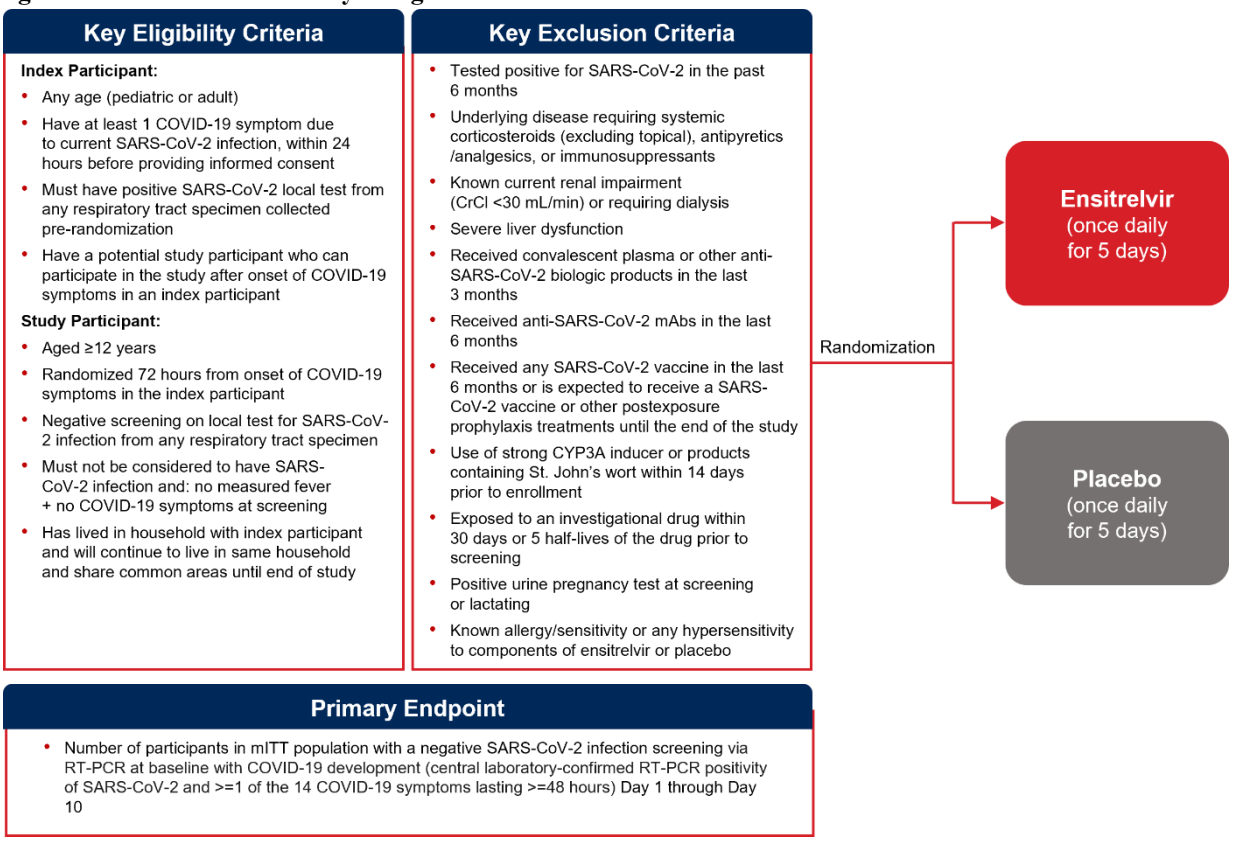
ENCLOSURE

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

APPENDIX

SCORPIO-PEP (Global Phase 3 Study)

Figure 3. SCORPIO-PEP Study Design[3,4,14]

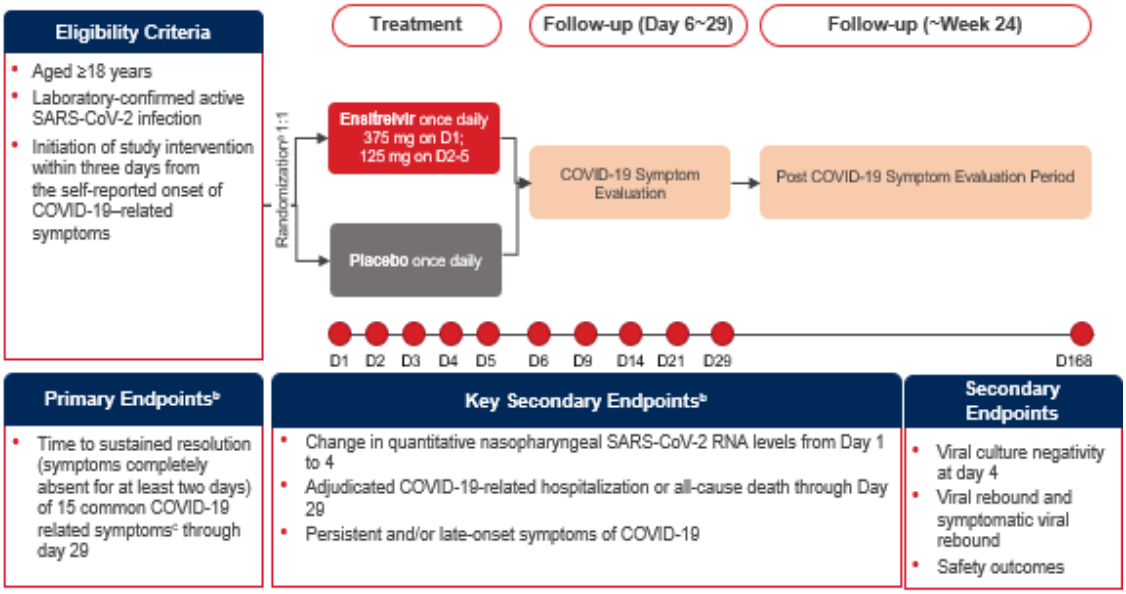


Abbreviations: COVID-19, coronavirus disease; CrCl, creatinine clearance; CYP3A, cyctochrome P450 3A; mAbs, monoclonal antibodies; mITT, modified intention-to-treat; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
Note: mITT population 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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SCORPIO-HR (Global Phase 3 Study)

Figure 4. SCORPIO-HR Study Design[5,6,13]



Abbreviations: COVID-19, coronavirus disease; D, day; h, hours; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]N=~2000; ~1000 patients in each treatment arm

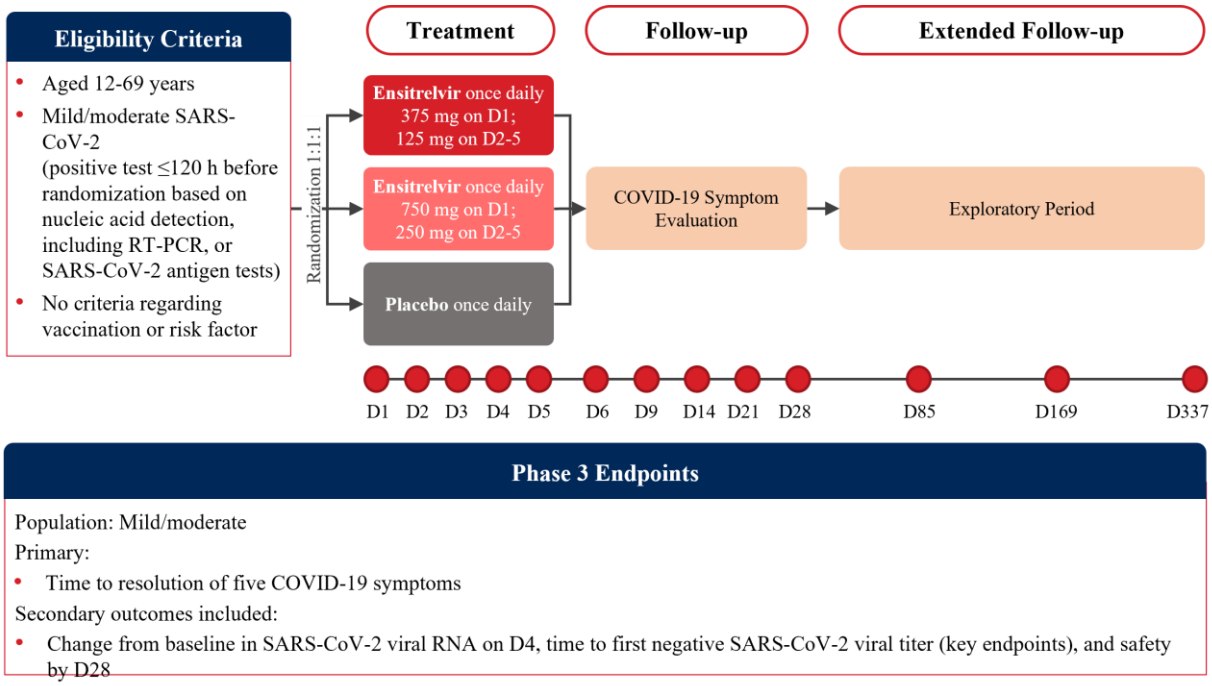
[b]Primary and key secondary endpoints were tested using a fixed-sequence hierarchical approach at two-sided significance level of 0.05.

[c]15 COVID-19 symptoms: stuffy nose, runny nose, cough, sore throat, low energy or tiredness, feeling hot or feverish, shortness of breath or difficulty breathing, chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, loss of taste and loss of smell.

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SCORPIO-SR (Phase 3 Study)

Figure 5. SCORPIO-SR Study Design[7,8]



Abbreviations: COVID-19, coronavirus disease 2019; D, day; RNA, ribonucleic acid; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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