Xocova – Use in Treatment

This medical response contains information in addition to that provided in the XOCOVA® (ensitrelvir) tablets, for oral use Full Prescribing Information approved by the U.S. Food and Drug Administration (FDA). Shionogi does not recommend the use of XOCOVA in any manner other than as described in the Full Prescribing Information. **Please read the attached XOCOVA Full Prescribing Information**.

1. SUMMARY

- XOCOVA is not indicated for the treatment of COVID-19. XOCOVA is indicated for post-exposure prophylaxis (PEP) of COVID-19 in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19. [1]
- Information from studies evaluating XOCOVA for the treatment of COVID-19 is provided below.

Clinical Trials

- The Phase 3 study, **SCORPIO-PEP**, evaluated the efficacy of ensitrelvir for the prevention of symptomatic infection in COVID-negative household contacts (HHCs) living with COVID-positive index patients.[2]
  - The ITT population included HHCs who were SARS-CoV-2 negative by local testing at enrollment (N=2387; n=1194 ensitrelvir; n=1193 placebo). The primary analysis population (mITT) included those confirmed RT-PCR negative at baseline by central laboratory (n=1030 ensitrelvir; n=1011 placebo).[2]
  - A subset of participants were RT-PCR positive at baseline based on central testing (ITT baseline RT-PCR–positive population [ITT-BP]; n=114 ensitrelvir; n=123 placebo), continued with ensitrelvir treatment, and were evaluated in a post-hoc analysis.[2]
  - In the ITT-BP population, COVID-19 developed in 17.5% (20/114) and 22% (27/123) of participants in the ensitrelvir and placebo groups, respectively (risk ratio [RR] 0.75; 95% CI, 0.46–1.23); ensitrelvir was also associated with numerically lower mean (SD) viral RNA levels (5.6 [2.0] vs 6.2 [1.8] $\log_{10}$ copies/mL) and total symptom scores (6.2 [6.7] vs 10.3 [4.5]) through Day 10.[2,3]
  - In the mITT population, a statistically significant risk reduction for COVID-19 was observed in the ensitrelvir group vs the placebo group at Day 10 (primary endpoint 2.9% [30/1030] vs 9.0% [91/1011], RR 0.33; 95% CI: 0.22-0.49, $P<0.0001$).[2]
  - Treatment-emergent adverse events (TEAEs) occurred in 15.1% and 15.5% of patients in the ensitrelvir and placebo groups, respectively.[2]

- The global, Phase 3 study, **SCORPIO-HR**, assessed the clinical and antiviral effects of ensitrelvir vs placebo in nonhospitalized patients.[4,5]
  - The primary endpoint for SCORPIO-HR, time to sustained resolution of 15 common COVID-19 related symptoms (completely absent for at least 2 days) demonstrated a numerical reduction for ensitrelvir compared to placebo, but was not statistically significant.[4]
  - Most TEAEs were mild to moderate in severity, and no serious adverse events (SAEs) were considered treatment-related. There were no deaths observed in either group through Day 29.[4]

- **SCORPIO-SR** (Phase 3) is part of the Phase 2/3, multicenter, randomized, double-blind, placebo-controlled clinical study that evaluated the efficacy (clinical symptom improvement and antiviral effect), and safety of ensitrelvir administered orally, once daily for 5 days in patients with mild-to-moderate SARS-CoV-2 infection.[6,7]
  - In the primary analysis population (<72 hours from onset), the time to resolution of the composite of 5 COVID-19 symptoms was significantly reduced with ensitrelvir 125 mg vs placebo (P=0.04 with a Peto-Prentice generalized Wilcoxon Test). A difference in median time to symptom resolution with ensitrelvir 125 mg vs placebo in the primary analysis population was –24.3 h.[6,7]
  - Most treatment-related adverse events (TRAEs) were mild; decreased high-density lipoprotein (HDL) was the most common TRAE. Two SAEs occurred (one in each arm), which were not considered related to the treatment.[6,7]

- **STRIVE** was an international Phase 3, randomized, double-blind, placebo-controlled trial evaluating ensitrelvir plus standard of care (SoC) vs placebo plus SoC in adults hospitalized with COVID-19 and lower respiratory tract involvement from 2023 to 2025. The mITT population included 589 participants (ensitrelvir, n=293; placebo, n=296).[8]

- No statistically significant difference was observed between treatment groups for the primary endpoint of Days to Recovery Scale through Day 60 (DRS-60). Median DRS-60 was 6 days (IQR, 3-15) with ensitrelvir vs 5.5 days (IQR, 3-12) with placebo (van Elteren *P*=0.19).[8]
- Ensitrelvir treatment was associated with lower detectable plasma viral antigen at Day 5 compared with placebo (13.4% vs 25.1%; *P*<0.001).
- The primary safety composite endpoint (death, SAEs, organ failure or serious infection, or grade 3 and 4 AEs) occurred in 28.0% (82/293) of participants receiving ensitrelvir and 27.7% (82/296) receiving placebo. Death through Day 60 occurred in 6.1% (18/293) and 4.4% (13/296) of participants, respectively; there was no statistical difference in time to death through Day 60 between the groups (log-rank *P*=0.28).[8]

- **PLATCOV** is a Phase 2, open-label, multicentre, randomized, controlled, pharmacometric platform trial conducted in Thailand, Brazil, Nepal, and Laos that evaluated the *in vivo* antiviral activity of potential COVID-19 treatments, including ensitrelvir, in low-risk adults with early symptomatic COVID-19.[9]
  - Ensitrelvir accelerated the oropharyngeal viral clearance rate (primary endpoint; assessed between Day 0 and Day 5) compared with no study drug, with a median estimated viral clearance half-life of 5.9 hours vs 11.6 hours, corresponding to an 82% faster viral clearance rate (95% CrI: 61-104). In a non-inferiority assessment of ensitrelvir vs ritonavir-boosted nirmatrelvir, viral clearance with ensitrelvir was 16% slower (95% CrI: 5-25), not meeting the prespecified 10% non-inferiority margin.[9]
  - Mean duration of fever and restricted mean symptom duration through Day 7 were numerically shorter with ensitrelvir compared with no study drug, with similar estimates to nirmatrelvir. Viral rebound occurred at similar frequencies across groups (ensitrelvir 5%, nirmatrelvir 7%, no study drug 7%). While no patients progressed to severe disease, hospital admission occurred in 7 patients overall (2/197 ensitrelvir; 3/201 ritonavir-boosted nirmatrelvir; 2/191 no study drug).[9]
  - No treatment-related SAEs were observed in the ensitrelvir arm; dysgeusia was reported less frequently with ensitrelvir (1%) vs nirmatrelvir (26%).[9]

Real World Evidence

In Japan, XOCOVA is approved for use in both PEP and treatment of COVID-19 from the (Ministry of Health, Labour, and Welfare (MHLW) and it is approved for treatment in Singapore based on the Special Access Route application. XOCOVA is not approved for treatment of COVID-19 in the United States.[10-12]

- **Japanese Postmarketing Surveillance Study**
  Hayashi et al. (2025) reported the final analysis of a multicenter, single-arm postmarketing surveillance (PMS) study conducted in Japan (November 2022 to December 2023) evaluating real-world safety and effectiveness of ensitrelvir in patients aged ≥12 years with COVID-19, including standard risk (SR) and high risk (HR) populations, with predominantly mild disease and no patients with severe disease.[13]
  - In the effectiveness analysis set (n=3638), the median time to resolution of fever was 36.0 hours, and the median time to resolution of all COVID-19 symptoms was 156.0 hours; in the SR and HR subgroups, the median time to resolution of fever was similar between the subgroups (36.0 hours) and the median time to resolution of all symptoms was 168.0 hours in SR subgroup and 144.0 hours in HR subgroup.[13]
  - In the safety analysis set (n=3760), the incidence of adverse drug reactions (ADRs) was 7.2%, with 379 ADRs reported, including 5 serious ADRs that resolved within 3-5 days; hospitalization occurred in 14 patients (0.4%), and 2 deaths (0.1%) were reported during follow-up, neither attributed to COVID-19 nor to ensitrelvir treatment.[13]

- **Prospective Registry-Based Cohort Study in COVID-19 Outpatients**
  Hibino et al. (2025) presented a pre-specified secondary/exploratory analysis (ANCHOR-02) of the ANCHOR study, a nationwide, multi-institutional, prospective COVID-19 registry-based cohort study conducted across 51 Tokushukai hospitals in Japan. The study included 8657 acute COVID-19 outpatients aged ≥12 years; 2447 received oral antiviral treatment and 6210 received no antiviral treatment. Among antiviral-treated patients, 1857 received ensitrelvir, 117 received nirmatrelvir, and 441 received molnupiravir.[14]
  - In the adjusted analysis, ensitrelvir was associated with a reduction in COVID-19-related re-consultation through Day 28 (secondary endpoint) compared with no antiviral treatment (adjusted RR 0.87; 95% CI: 0.77-0.98); *P*<0.05. The adjusted RR verses no antiviral was 0.92 (95% CI: 0.83-1.03) with any antiviral

treatment, 1.26 (95% CI: 0.91-1.73) with nirmatrelvir, and 1.07 (95% CI: 0.88-1.31) with molnupiravir.[14]
    - For exploratory outcomes:[14]
        - The adjusted risk of additional antibiotic prescriptions through Day 28 was numerically lower with ensitrelvir, higher with nirmatrelvir, and higher with molnupiravir compared with no antiviral treatment.
        - The risk of not returning to usual health at Day 28 was lower with any antiviral treatment vs no antiviral treatment, ensitrelvir, and molnupiravir.
        - Antiviral treatment was also associated with improvement in presenteeism, overall work impairment, and activity impairment, but not absenteeism.

- **Retrospective Cohort Study in Nonhospitalized High-Risk Patients**
  A retrospective database cohort study in Japan conducted by **Takazono et al (2024)** compared the outcomes of nonhospitalized patients with high risk of severe COVID-19 disease who received ensitrelvir to patients who received no antiviral treatment. High-risk patients treated with ensitrelvir had lower incidence of:[15]
    - All-cause hospitalization (0.494% vs 0.785%; RR, 0.629 [95% CI, 0.420 to 0.943]; risk difference [RD], −0.291 [95% CI, −0.494 to −0.088]).[15]
    - Respiratory and heart rate monitoring (0.143% vs 0.269%; RR, 0.531 [95% CI, 0.261 to 1.081]; RD, −0.126 [95% CI, −0.230 to −0.022]).[15]
    - Oxygen therapy (0.095% vs 0.149%; RR, 0.635 [95% CI, 0.258 to 1.563]; RD, −0.055 [95% CI, −0.141 to 0.032]).[15]

- **Retrospective Chart Review in Hospitalized Patients**
  A single-center, retrospective chart review by **Yamato et al (2024)** assessed the outcomes of hospitalized, predominantly elderly patients with a range of comorbidities who were treated with ensitrelvir (375 mg on Day 1 and 125 mg on Days 2 to 5) at Rinku General Medical Center in Japan.[16]
    - At final measurement, 78.1% (25/32) of patients had achieved viral clearance after 5 days of treatment, and 12.5% (4/32) experienced viral rebound without disease progression. All patients had clinical improvement at the end of ensitrelvir treatment. There was one death unrelated to COVID-19 or ensitrelvir use.[16]
    - In a subgroup analysis of patients (n=21) with persistent COVID-19 after ≥3 days of remdesivir treatment, 66.7% of patients had viral clearance after 5 days of ensitrelvir treatment and 9.5% experienced viral rebound without symptom rebound. All patients had clinical improvement at the end of ensitrelvir treatment.[16,17]

- **Retrospective Case Series of Ensitrelvir in Nonhospitalized Patients**
  Abe et al. (2024) conducted a retrospective case series in Japan evaluating real-world outcomes in 18 vaccinated outpatients (15 men; median age 39.5 years) with mild-to-moderate COVID-19 treated with a 5-day oral ensitrelvir regimen (375 mg loading dose, then 125 mg daily) between December 2022 and January 2023, with follow-up of up to 60 days; all patients were infected with the SARS-CoV-2 Omicron BA.5 variant, and symptom outcomes were descriptively compared with historical control data.[18]
    - Symptoms improved within 2 days in 33% of patients and within 3-6 days in an additional 33%; one patient had mild cough, and 5 patients had mild sore throat persisting beyond 6 days, with no symptom recurrence reported during follow-up.[18]
    - Mean SARS-CoV-2 Ct values increased from 21.82 at symptom onset to 37.65 by Day 6, with Ct values >35 reported within 6 days in 10 patients and undetectable viral RNA by Day 9 in most patients; greater increases in Ct values between Day 0 and Day 3 were observed among patients who initiated treatment within 48 hours of symptom onset.[18]
    - No increases in viral load based on Ct values, no newly emergent adverse events, no symptom recurrence, and no post-acute sequelae of COVID-19 were reported during the follow-up period.[18]

2. CLINICAL STUDIES

Phase 3 Clinical Studies

SCORPIO-PEP

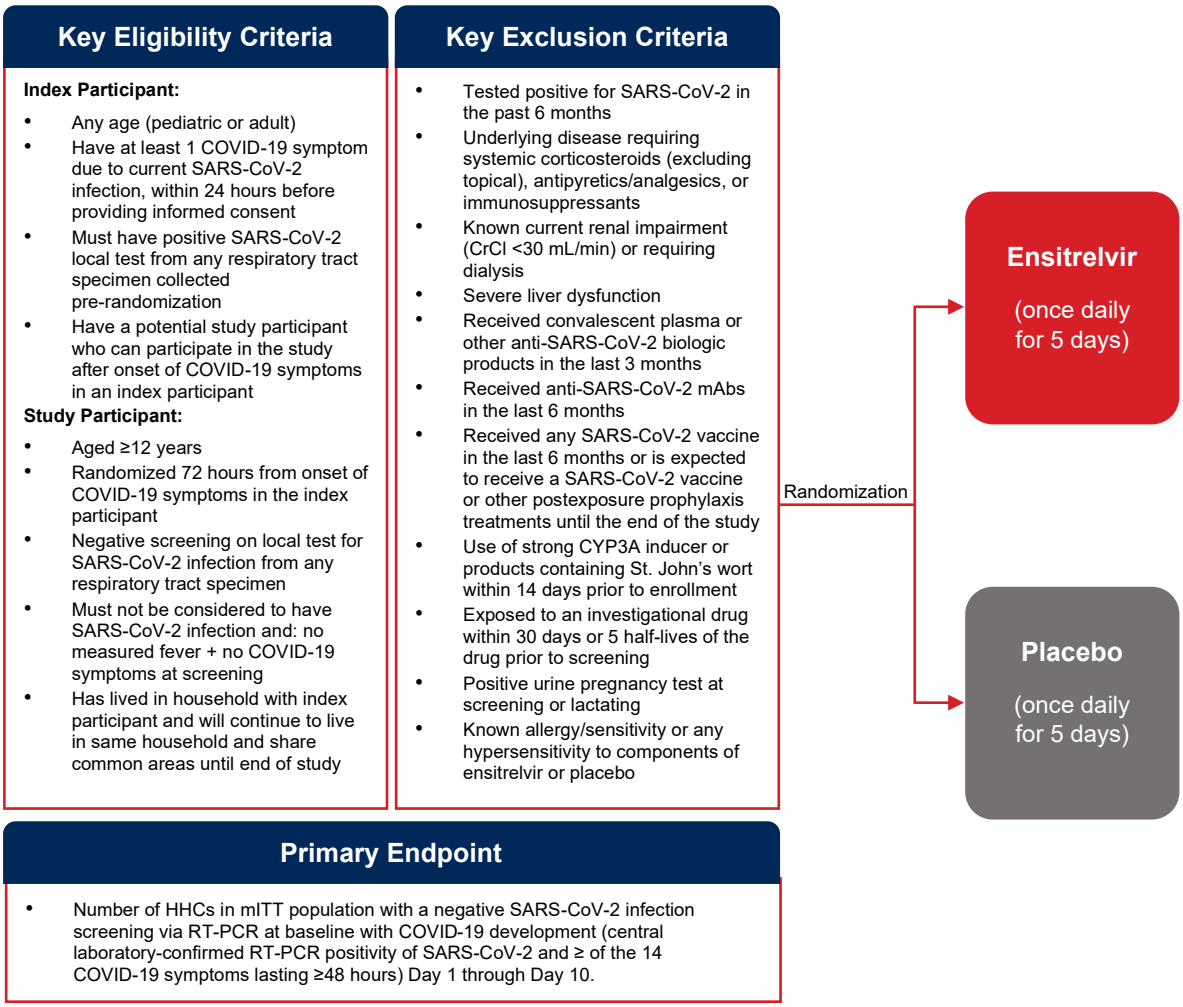
Study Design

SCORPIO-PEP (NCT05897541) is a completed Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical study that evaluated the safety and efficacy of ensitrelvir in the prevention of symptomatic COVID-19 in COVID-negative HHCs living with COVID-19-positive index patients, when compared to placebo (**Figure 1**).[2,19]

Ensitrelvir 375 mg was given orally once on Day 1 followed by ensitrelvir 125 mg orally once daily on Days 2-5 to HHCs in the active group while placebo was given to the control group.[2]

This study was conducted across the US, Japan, Vietnam, Argentina, and South America from June 2023 to September 2024.[2,19]

Figure 1. SCORPIO-PEP Study Design.[2,3,19]



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

Baseline characteristics were generally similar between treatment groups.[2]

Results

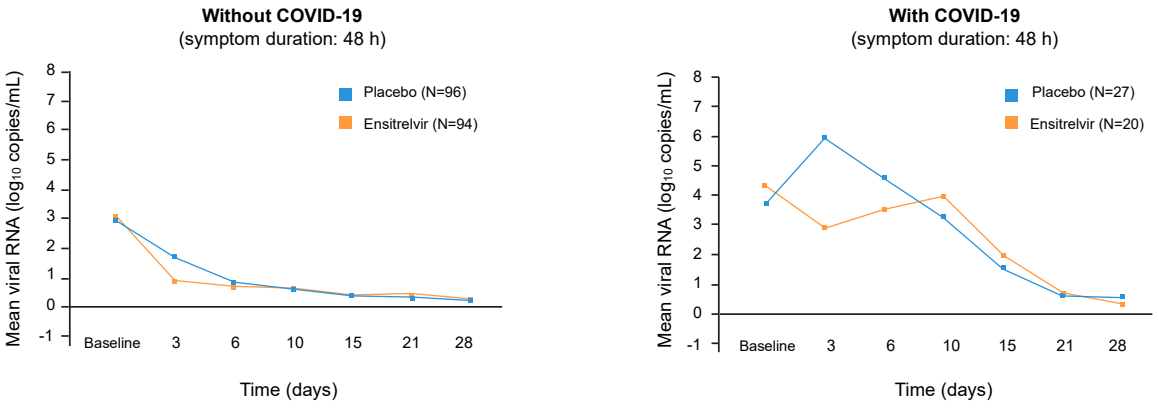
Efficacy

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

Post-hoc analysis

- A subset of participants were RT-PCR positive at baseline based on central testing (ITT baseline RT-PCR–positive population [ITT-BP]; n=114 ensitrelvir; n=123 placebo), continued with ensitrelvir treatment, and were evaluated in a post-hoc analysis.[2,3]
  - In the ITT-BP population, 17.5% (20/114) and 22% (27/123) of participants developed COVID-19 in the ensitrelvir and placebo groups, respectively (RR 0.75; 95% CI, 0.46–1.23). COVID-19 was defined as a central laboratory positive RT-PCR test and the occurrence (or worsening [increasing a symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.
  - Among those in the ITT-BP population, the ensitrelvir group showed numerically lower mean (SD) viral RNA levels (5.6 [2.0] vs 6.2 [1.8] $\log_{10}$ copies/mL) through day 10 vs placebo (**Figure 2**).
  - In the ensitrelvir group a numerically lower mean (SD) total symptom scores was seen (6.2 [6.7] vs 10.3 [4.5]) through day 10 relative to placebo for the ITT-BP population (**Figure 3**)

Figure 2. Mean Viral RNA Over Time in ITT-BP Population.[3]

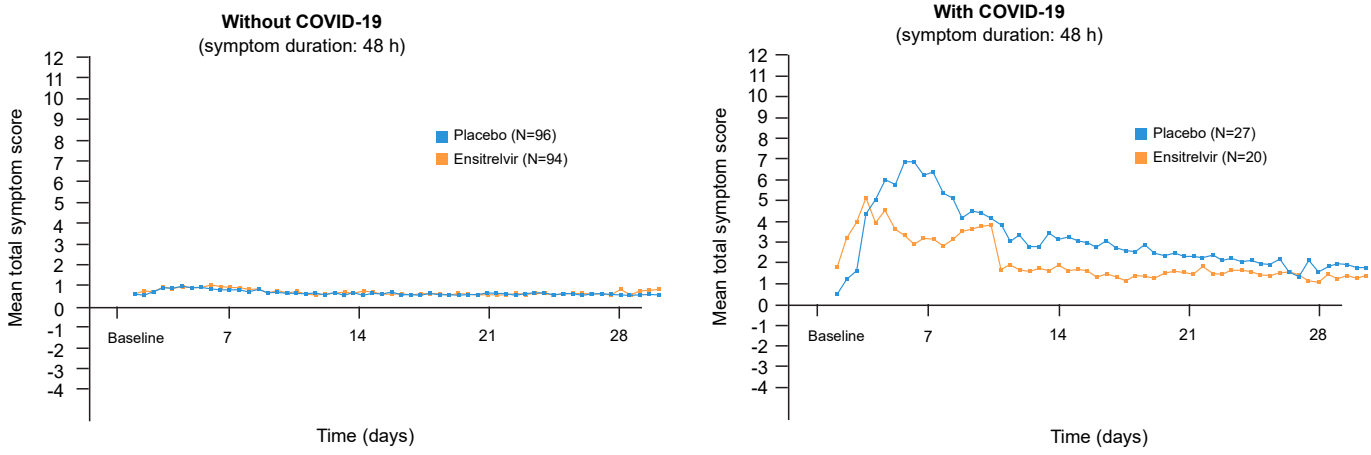


COVID-19 was defined as a central laboratory positive RT-PCR test and the occurrence (or worsening [increasing a symptom score from baseline] in the case of pre-existing COVID-19–like symptoms) of ≥1 of the 14 specified COVID-19 symptoms for ≥48 hours.

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

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

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



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

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

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

Post-hoc analyses were exploratory in nature and not controlled for multiplicity; therefore, no statistical or clinical conclusions can be made, and data should be interpreted with caution.

Primary Endpoint

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

Safety

AEs occurred in 15.1% of patients in the ensitrelvir group and 15.5% in the placebo group. Safety data are provided below in **Table 1**.[2]

Table 1. TEAEs in the safety analysis set[2]

Abbreviations: AE, adverse event; HHC, household contact; SAS, safety analysis set; TEAEs, treatment-emergent adverse events.

TEAEs, n (%)	Ensitrelvir (n=1,190)[a]	Placebo (n=1,187)[a]
Any TEAEs	180 (15.1)	184 (15.5)
TEAEs ≥1%		
Headache	35 (2.9)	30 (2.5)
Diarrhea	21 (1.8)	15 (1.3)
Nasopharyngitis	16 (1.3)	15 (1.3)
Cough	14 (1.2)	7 (0.6)
Influenza	13 (1.1)	19 (1.6)
Fatigue	13 (1.1)	12 (1)
Oropharyngeal pain	11 (0.9)	17 (1.4)
Any serious TEAEs	2 (0.2)	2 (0.2)
Any study drug-related TEAEs	19 (1.6)	21 (1.8)
Any study drug-related serious TEAEs	0	0
Any TEAEs leading to treatment discontinuation	1 (<0.1)	1 (<0.1)
Any TEAE leading to hospitalization	0	0
Any TEAEs leading to study discontinuation	0	1 (<0.1)
Deaths	0	0

[a]n represents the number of participating HHCs with each type of AE, and percentages are based on the number of participating HHCs in the SAS within each treatment group.

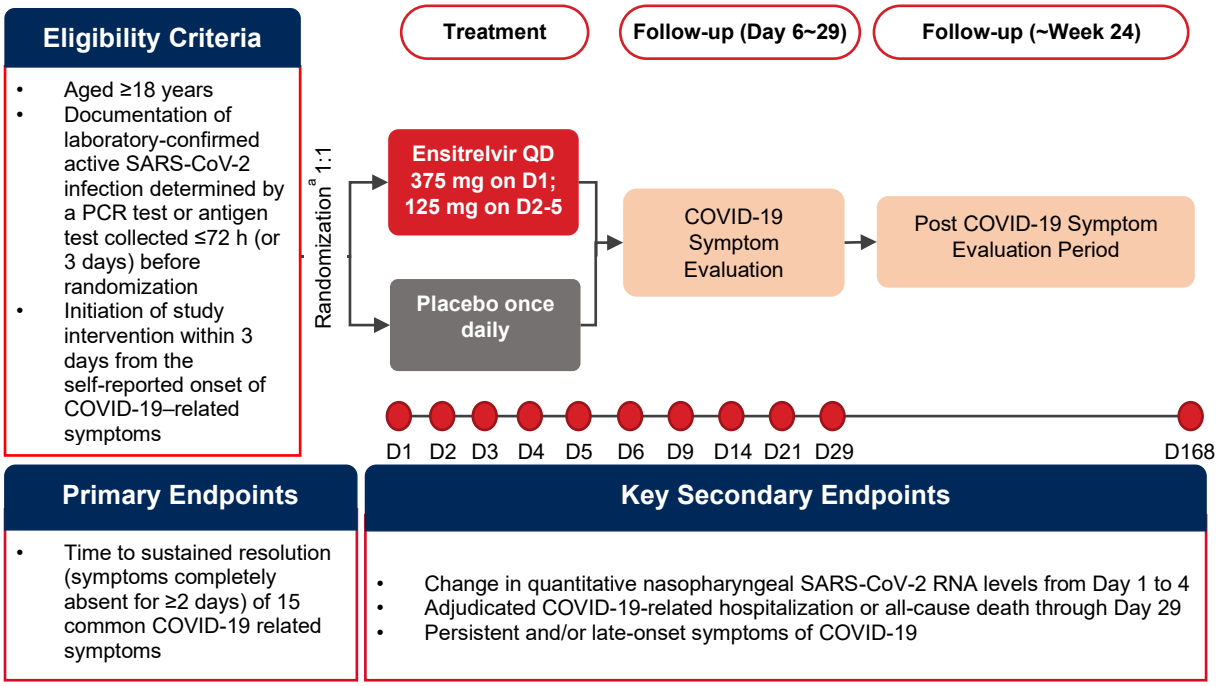
Table adapted from Hayden et al. *NEJM*. 2026.

SCORPIO-HR

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 (oral once daily for five days) vs placebo in nonhospitalized patients with COVID-19 with or without high-risk factors for severe COVID-19 (**Figure 4**). 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.[4,5,20]

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



Abbreviations: COVID-19, coronavirus disease 19; D, day; h, hours; QD, once a 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.

Results

Efficacy

Primary Endpoint:
The primary endpoint of time to 2-day sustained resolution of 15 COVID-19 symptoms was not met (Table 2). The restricted mean time (days) to symptom resolution for 15 common COVID-19 related symptoms (symptoms completely absent for at least 2 days) for ensitrelvir vs placebo was 12.5 days vs 13.1 days, respectively. Although a numerical reduction in the time to symptom resolution was demonstrated, the difference was not statistically significant (P=0.14 [Peto-Prentice's Wilcoxon test P=0.07]).[4]

Pre-defined Analysis:
Prespecified and post hoc supportive analyses similarly demonstrated numerically shorter time to symptom resolution with ensitrelvir than with placebo (Table 2). An analysis of time to resolution of 6 symptoms (including cough, feeling feverish, fatigue, sore throat, and stuffy or runny nose) for at least 1 day in patients treated with ensitrelvir vs. placebo resulted in a restricted mean days to symptom resolution of 10.3 days vs 11 days, (unadjusted P=0.06 [Peto-Prentice's generalized Wilcox unadjusted P=0.02]), respectively. This analysis is similar to that used in SCORPIO-SR, but was not part of the statistical hierarchy, was not adjusted for multiplicity, and should be interpreted in an exploratory manner.[4]

Post-hoc supportive analysis:
An additional analysis of time to resolution of 15 symptoms for at least 1 day was shorter in patients treated with ensitrelvir vs. placebo (P=0.02 [Peto-Prentice's generalized Wilcox test]; Table 2). This analysis was not part of the statistical hierarchy, was not adjusted for multiplicity, and should be interpreted in an exploratory manner.[4]

Table 2. Time to Resolution of COVID-19 Symptoms Through Day 29[4]

Analysis	Number of COVID-19 symptoms evaluated[a]	Analysis population	Symptom resolution definition	Restricted mean days to symptom resolution				Median (IQR) from KM Estimate		Peto-Prentice's generalized Wilcoxon test (*P* value)
				Ensitrelvir	Placebo	Difference (95% CI)	*P* value	Ensitrelvir	Placebo	
Primary analysis	15	mITT (N=1888)	≥ 2 consecutive days	12.5	13.1	-0.6 (-1.38, 0.19)	0.14	9 (5, 2)	10 (6, 22)	0.07
Prespecified supportive analyses[b]	15	mITT2[c] (N=1535)	≥ 2 consecutive days	12.3	13.	-0.7 (-1.56, 0.16)	0.11	-	-	-
	15	mITT (N=1888)	≥ 1 day	11.4	12.2	-0.8 (-1.54, 0.01)	0.05	-	-	-
	6	mITT (N=1888)	≥ 1 day	10.3	11	-0.7 (-1.48, 0.02)	0.06	7 (4, 14)	7. (5, 15)	0.02
Post hoc supportive analyses[b]	15	mITT (N=1888)	≥ 1 day	-	-	-	-	8 (5, 16)	9 (5, 18)	0.02
	15	mITT2[c] (N=1535)	≥ 2 consecutive days	-	-	-	-	9 (6, 19)	10 (6, 21)	0.08

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 19; IQR, interquartile range; KM, Kaplan-Meier; LoD, limit of detection; mITT, modified intention-to-treat; PCR, polymerase chain reaction.
Peto-Prentice's generalized Wilcoxon test is employed to compare the entire KM curve of time to symptom resolution between treatment groups. This test is often selected to increase the sensitivity of detecting a group difference in survival distributions in situations where the group difference in the KM curve is large during the early time points but decreases toward the end of a period.
[a]15 COVID-19 symptoms: stuffy nose, runny nose, sore throat, cough, 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. The 6 targeted COVID-19 symptoms for the prespecified supportive analysis were stuffy nose, runny nose, sore throat, cough, low energy or tiredness, and feeling hot or feverish.
[b]Supportive analyses were not part of the statistical hierarchy, were not adjusted for multiplicity, and should be interpreted in an exploratory manner.
[c]The mITT2 population included all randomized participants who took ≥1 dose of ensitrelvir or placebo and who started intervention within 3 days of symptom onset with positive PCR results (above limit of detection) on Day 1.
Table adapted from Luetkemeyer et al. *Clin Infect Dis*. 2025

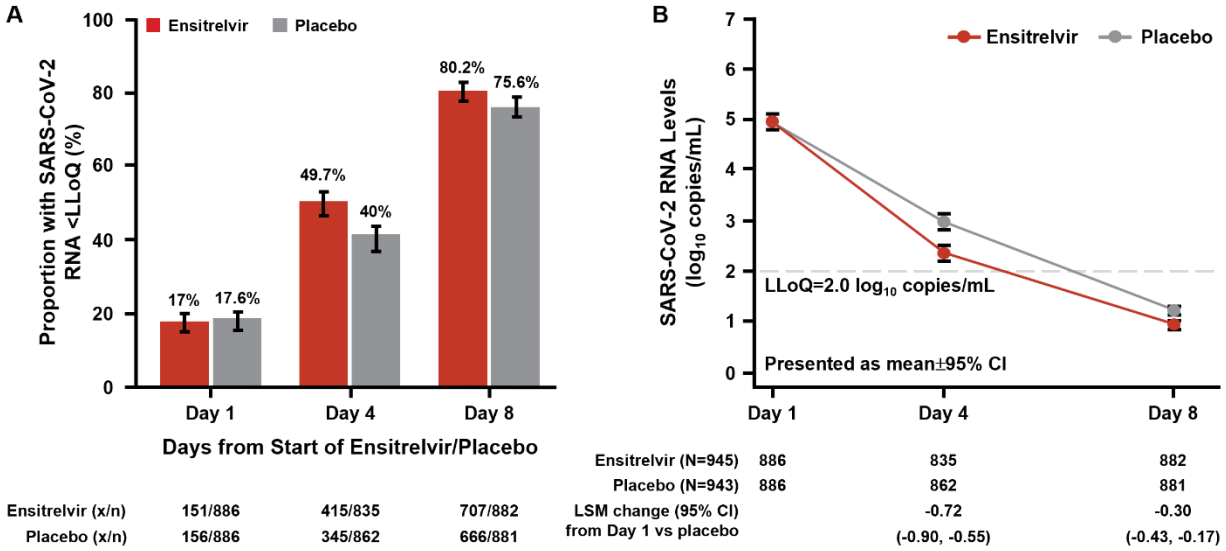
Secondary Endpoints:

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.[4]

Key Secondary Endpoint: The change in quantitative SARS-CoV-2 RNA level at Day 4 showed a 0.72 $\log_{10}$ copies/mL greater reduction in least squares mean RNA with ensitrelvir vs placebo (**Figure 5**).[4]

At Day 4, the proportion of patients (mITT population) in the ensitrelvir arm vs placebo arm with a SARS-CoV-2 RNA less than the LLoQ is 50% (415/835) vs 40% (345/862), respectively, copies/mL greater reduction in least squares mean RNA with ensitrelvir vs placebo (**Figure 5**).[4]

Figure 5. Antiviral Efficacy as Assessed by (A) Proportion of Participants with SARS-CoV-2 RNA level <LLoQ (mITT population), and (B) Change in Quantitative SARS-CoV-2 RNA Level on D4 and D8 (mITT population)[4]



Ensitrelvir (x/n)	151/886	415/835	707/882
Placebo (x/n)	156/886	345/862	666/881

Ensitrelvir (N=945)	886	835	882
Placebo (N=943)	886	862	881
LSM change (95% CI) from Day 1 vs placebo		-0.72 (-0.90, -0.55)	-0.30 (-0.43, -0.17)

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LLoQ, lower limit of quantification; LSM, least-squares mean; mITT, modified intention-to-treat; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ULoQ, upper limit of quantification.

A, The proportion of participants with SARS-CoV-2 RNA levels below the LLoQ in the mITT population. Data are presented as percentage (%) ± 95% CI.

B, The adjusted mean change in SARS-CoV-2 viral RNA from D 1 in the mITT population.

ANCOVA was used to obtain the estimate of difference in mean and associated 95% CI adjusted for D1. Participants who were alive and not hospitalized on D4 or D8 but who had missing RNA values (including due to loss to follow-up, samples not obtained, lost samples, and laboratory issues) on D4 or D8, respectively, were excluded. As the primary efficacy endpoint was not statistically significant, secondary endpoint results are descriptive. For quantitative analyses of $\log_{10}$ SARS-CoV-2 RNA, D1, D4, and D8 values were imputed. D1, D4, and D8 values that were detected and were <LLoQ were imputed as 1.7 $\log_{10}$ SARS-CoV-2 RNA; undetected values were imputed as 0.0; and values above ULoQ = 8.0 were imputed as 8.3 $\log_{10}$ SARS-CoV-2 RNA.

Figure adapted from Luetkemeyer et al. *Clin Infect Dis*. 2025

Key Secondary Endpoint: Ensitrelvir did not demonstrate a statistically significant reduction in the proportion of participants with post COVID-19 symptoms (Long COVID-19) at three months. There was a tendency for a higher proportion of participants to report "having returned to pre-COVID health" and "felt no fatigue" compared to placebo. Further detailed analysis is planned, including additional analysis of the long COVID-19 endpoints at 24 weeks.[20]

Safety

AEs occurred in 638 patients treated with ensitrelvir (61.5%; n=1037), and 635 patients treated with placebo (60.6%; n=1048) (Table 3). TRAEs occurred in 86 (8.3%) of patients treated with ensitrelvir and 74 (7.1%) of patients that were given placebo. Serious TEAEs occurred in 5 (0.5%) of the ensitrelvir-treated participants and 6 (0.6%) of the patients given placebo. No serious TRAEs occurred in either group.[4]

COVID-19–related hospitalization was observed in 3 (0.3%) ensitrelvir-treated patients and 1 (0.1%) placebo-treated participant.[4]

No deaths were observed in either group.[4]

Table 3. SCORPIO-HR: Summary of AEs in the Safety Analysis Population through Day 29[4,a]

n (%)	Total (n=2085)	Ensitrelvir 125 mg (n=1037)	Placebo (n=1048)
TEAEs	1273 (61.1)	638 (61.5)	635 (60.6)
Serious TEAEs other than death[b]	11 (0.5)	5 (0.5)	6 (0.6)
Maximum event Grade 3 or 4	267 (12.8)	116 (11.2)	151 (14.4)
TEAEs leading to permanent discontinuation	11 (0.5)	6 (0.6)	5 (0.5)
TRAEs	160 (7.7)	86 (8.3)	74 (7.1)
Serious TEAEs other than death[b]	0	0	0
TEAEs leading to permanent discontinuation	4 (0.2)	2 (0.2)	2 (0.2)
Event leading to treatment interruption	3 (0.1)	2 (0.2)	1 (0.1)
COVID-19–related hospitalizations	4 (0.2)	3 (0.3)	1 (0.1)
Death	0	0	0

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; COVID-19, coronavirus disease 19; SAEs, serious adverse event.TEAE, treatment-emergent adverse event; TRAE, treatment related adverse event

[a]The safety analysis population included participants who received at least 1 dose of ensitrelvir or placebo and were analyzed according to the study intervention that the participants received rather than the intervention to which they were randomized to. The severity of adverse events was graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) [26].

[b] Overall, 11 (0.5%) participants reported 14 SAEs: increased alanine aminotransferase, increased aspartate aminotransferase. increased hepatic enzyme, decreased lymphocyte count, acute myocardial infarction, pericarditis, appendicitis, lower respiratory tract infection, cerebral atrophy, migraine, abdominal pain, pyrexia, dyslipidemia, and myalgia.

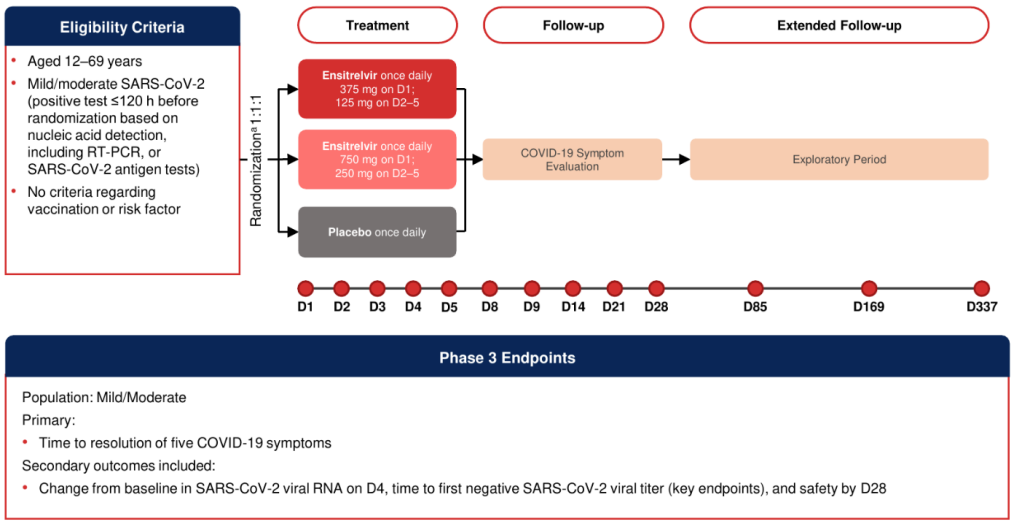
Table adapted from Luetkemeyer et al. *Clin Infect Dis*. 2025.

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 (Figure 6). 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]

Figure 6. SCORPIO-SR Study Design[6,7]



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

Results

Efficacy

Primary Endpoint:

- The time to resolution of 5 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).[6]
- A difference in median time to symptom resolution with ensitrelvir 125 mg vs placebo in the primary analysis population was –24.3 h as depicted in **Table 4**.[6]

Table 4. Primary Endpoint: Time to Resolution of 5 COVID-19 Symptoms[6,21,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]5 COVID-19 symptoms were runny or stuffy nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness. [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.
Table adopted from Uehara et al. Oral Presentation; CROI 2023.

Key Secondary Endpoints:

- Compared with placebo, ensitrelvir 125 mg significantly shortened the median time to first confirmed negative SARS-CoV-2 viral titer by 29 h as depicted in **Table 5**.[6]

Table 5. Key Secondary Endpoint: Time to First Confirmed Negative SARS-CoV-2 Viral Titer[6,21]

	Ensitrelvir 125 mg (n=199)	**Ensitrelvir 250 mg (n=183)**	**Placebo (n=211)**
Kaplan-Meier estimator (h)			
Median (95% CI)	36.2 (23.4, 43.2)	22.7 (21.2, 37.9)	65.3 (62, 66.8)
Difference vs placebo (95% CI)	−29.1 (−42.3, −21.1)	−42.6 (−44.6, −27.4)	-
Stratified log-rank test[a]			
Two-sided *P*-value	< 0.001	< 0.0001	-

Abbreviations: CI, confidence interval; h, hours; mITT, modified intention-to-treat; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Note: Analysis in the mITT population (all pretreatment RT-PCR–positive patients with detectable SARS-CoV-2 viral titers at baseline). The efficacy analysis group comprised of the ensitrelvir 125 mg treatment arm and placebo arm.
[a]Adjusted for SARS-CoV-2 vaccination status.
Table adopted from Uehara et al. Oral Presentation; CROI 2023.

- Ensitrelvir 125 mg reduced viral RNA by 2.48 $\log_{10}$ copies/mL on Day 4, a difference from placebo of -1.47 $\log_{10}$ copies/mL ($P < 0.001$ [CI -1.63 to -1.31]). Please see **Table 6** for additional efficacy data[6]

Table 6. Change from Baseline to Day 4 in SARS-CoV-2 RNA Levels (Key Secondary Endpoint)[6a]

	Ensitrelvir 125 mg (n=347)[b]	**Ensitrelvir 250 mg (n=340)**	**Placebo (n=343)**
Change from baseline to Day 4 in SARS-CoV-2 RNA level			
Patients, number	340	333	337
LS mean (SE), $\log_{10}$ copies/mL[c]	-2.48 (0.08)	-2.49 (0.08)	-1.01 (0.08)
Difference vs placebo, LS mean (SE) [95% CI], $\log_{10}$ copies/mL[c]	-1.47 (0.08) [-1.63 to -1.31]	-1.48 (0.08) [-1.64 to -1.32]	NA
P value[c]	< 0.001	< 0.001	NA

Abbreviations: CI, confidence interval; ITT, intention-to-treat; LS, least-squares; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Results are for the ITT population of patients randomized in < 72 hours of disease onset. [b]Primary analysis population. [c]Analysis of covariance using baseline SARS-CoV-2 RNA and SARS-CoV-2 vaccination history (yes or no) as covariates.
Table adapted from Yotsuyanagi et al. *JAMA Netw Open*. 2024

A fixed-sequence hierarchical testing procedure was applied to control type 1 errors for the primary endpoint and two key secondary endpoints.[6]

Safety

Ensitrelvir therapy was well-tolerated. The most common TEAEs in the ensitrelvir 125 mg group were decreased HDL (31.1%), increased TG (8.1%), and increased bilirubin (6%). There as one report of a serious TEAE in the ensitrelvir 125 mg group (heavy menstrual bleeding), and 1 serious TEAE in the placebo group (acute cholecystitis) – neither was deemed treatment-related, and there were no deaths in either group. The safety profile is summarized in **Table 7**.[6]

Table 7. Safety Profile in the Safety Analysis Population[6a]

n (%)	COVID-19 Onset to Randomization ≤120 hours		
	Ensitrelvir 125 mg (n=604)	**Ensitrelvir 250 mg (n=599)**	**Placebo (n=605)**
TEAEs	267 (44.2)	321 (53.6)	150 (24.8)
TRAEs	148 (24.5)	217 (36.2)	60 (9.9)
Serious TEAEs other than death[b]	1 (0.2)	0	1 (0.2)
Death	0	0	0
TEAEs leading to discontinuation[c]	4 (0.7)	6 (1)	2 (0.3)
TEAEs occurring in ≥2% of patients in either group			
Aspartate aminotransferase level increased	4 (0.7)	9 (1.5)	12 (2)
Bilirubin conjugated increased	15 (2.5)	20 (3.3)	3 (0.5)
Blood bilirubin increased	36 (6)	56 (9.3)	6 (1)
Blood cholesterol decreased	20 (3.3)	28 (4.7)	3 (0.5)
Blood creatinine phosphokinase increased	14 (2.3)	8 (1.3)	11 (1.8)
Blood lactate dehydrogenase increased	6 (1)	15 (2.5)	6 (1)
Blood triglycerides increased	49 (8.1)	74 (12.4)	32 (5.3)
Diarrhea	6 (1)	9 (1.5)	12 (2)
Headache	13 (2.2)	20 (3.3)	14 (2.3)
High-density lipoprotein decreased	188 (31.1)	231 (38.6)	23 (3.8)
TRAEs in ≥2% of patients in either group			
Blood bilirubin increased	17 (2.8)	35 (5.8)	3 (0.5)
Blood cholesterol decreased	8 (1.3)	12 (2)	1 (0.2)
Blood triglycerides increased	16 (2.6)	37 (6.2)	17 (2.8)
Headache	4 (0.7)	13 (2.2)	2 (0.3)
High-density lipoprotein decreased	111 (18.4)	157 (26.2)	9 (1.5)

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 19; TEAE, treatment-emergent adverse event; TRAE, treatment related adverse events
[a]Data for all patients who received ≤1 ensitrelvir or placebo dose. [b]Both Serious TEAEs were judged as not treatment-related, and patients recovered with appropriate intervention. [c]Among the adverse events leading to treatment discontinuation, 1 patient in each arm experienced a treatment-related TEAE. All treatment-related TEAEs leading to discontinuation were deemed to be resolving or resolved after study discontinuation.
Table adapted from Yotsuyanagi et al. *JAMA Netw Open*. 2024.

STRIVE

Study Design

STRIVE (Strategies and Treatments of Respiratory Infections and Viral Emergencies; NCT05605093) was an international Phase 3, randomized, double-blind, placebo-controlled trial evaluating ensitrelvir plus SoC versus placebo plus SoC in adults hospitalized with COVID-19 and lower respiratory tract involvement. Adults aged ≥18

years with signs and/or symptoms of lower respiratory tract infection, documented SARS-CoV-2 infection, and symptom onset within 14 days were enrolled across 89 sites in 18 countries between February 2023 and August 2025.[8]

Participants were randomized 1:1 to receive ensitrelvir (375 mg on Day 0 followed by 125 mg once daily on Days 1-4) or matched placebo plus SoC. Concomitant treatment with remdesivir and/or corticosteroids was permitted within SoC; however, nirmatrelvir/ritonavir was prohibited.[8]

The primary endpoint was "Days to Recovery Scale" through Day 60 (DRS-60).[8]

Results

A total of 602 participants were enrolled; 589 participants who received ≥1 dose of study drug comprised the mITT population (ensitrelvir, n=293 versus placebo, n=296). Median age was 69 years, 49.1% were female, and the median time from symptom onset to enrollment was 5 days. Prior to randomization, 61.0% (359/589) of participants received remdesivir, 57.6% (339/589) received corticosteroids, and 4.4% (26/589) received nirmatrelvir/ritonavir or molnupiravir.[8]

Efficacy

Primary Endpoint:
Among 566 participants with known DRS-60 status, no statistically significant difference was observed between the treatment groups. Median DRS-60 was 6 days (IQR, 3-15) with ensitrelvir versus 5.5 days (IQR, 3-12) with placebo (van Elteren P=0.19); the odds ratio for a better (lower) recovery category with ensitrelvir versus placebo was 0.82 (95% CI: 0.62-1.09).[8]

Secondary Endpoints:
- **Time to sustained recovery and discharge from index hospitalization**
  Time to sustained recovery (sHR, 0.99; 95% CI: 0.84-1.16) and time to discharge from index hospitalization (sHR, 1.00; 95% CI: 0.86-1.16) did not differ between groups.[8]

- **Virologic assessments through Day 5**
  - Positive plasma nucleocapsid antigen (NC-Ag) at Day 5 was reported in 13.4% (33/247) of participants receiving ensitrelvir versus 25.1% (61/243) receiving placebo (P<0.001).[8]
  - Positive nasal cavity viral RNA at Day 5 was reported in 43.3% (100/231) of participants receiving ensitrelvir versus 52.4% (120/229) receiving placebo (P=0.052).[8]

Safety

- The primary safety composite endpoint (death, SAEs, organ failure or serious infection, or grade 3 and 4 AEs) occurred in 28.0% (82/293) of participants receiving ensitrelvir and 27.7% (82/296) receiving placebo (HR, 1.02; 95% CI: 0.75-1.38; P=0.91).[8]
- Death through Day 60 occurred in 6.1% (18/293) of patients receiving ensitrelvir and 4.4% (13/296) receiving placebo which was not a statistical difference between groups; HR (95% CI) 1.48 (0.72, 3.02, log-rank P=0.28.[8]
- Grade 3 or 4 AEs were reported in 17.7% (52/293) and 16.9% (50/296), of patients receiving ensitrelvir and placebo, respectively.[8]
- The most common selected clinical event categories were infections, reported in 8.5% (25/293) of participants receiving ensitrelvir and 9.8% (29/296) receiving placebo (P=0.60), respiratory failure, reported in 7.8% (23/293) and 7.4% (22/296) of participants, respectively (P=0.85) and nervous system disorders, reported in 4.8% (14/293) and 5.1% (15/296) of participants, respectively (P=0.87).[8]
- Hemorrhagic events occurred more frequently in the ensitrelvir group compared with the placebo group (3.4% [10/293] vs 0.3% [1/296], P=0.006).[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. Low-risk was defined by the absence of hypoxia, pneumonia, or chronic medical conditions requiring ongoing treatment. 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.

The primary endpoint was the oropharyngeal SARS-CoV-2 viral clearance rate between Day 0 and Day 5.[9]

Results

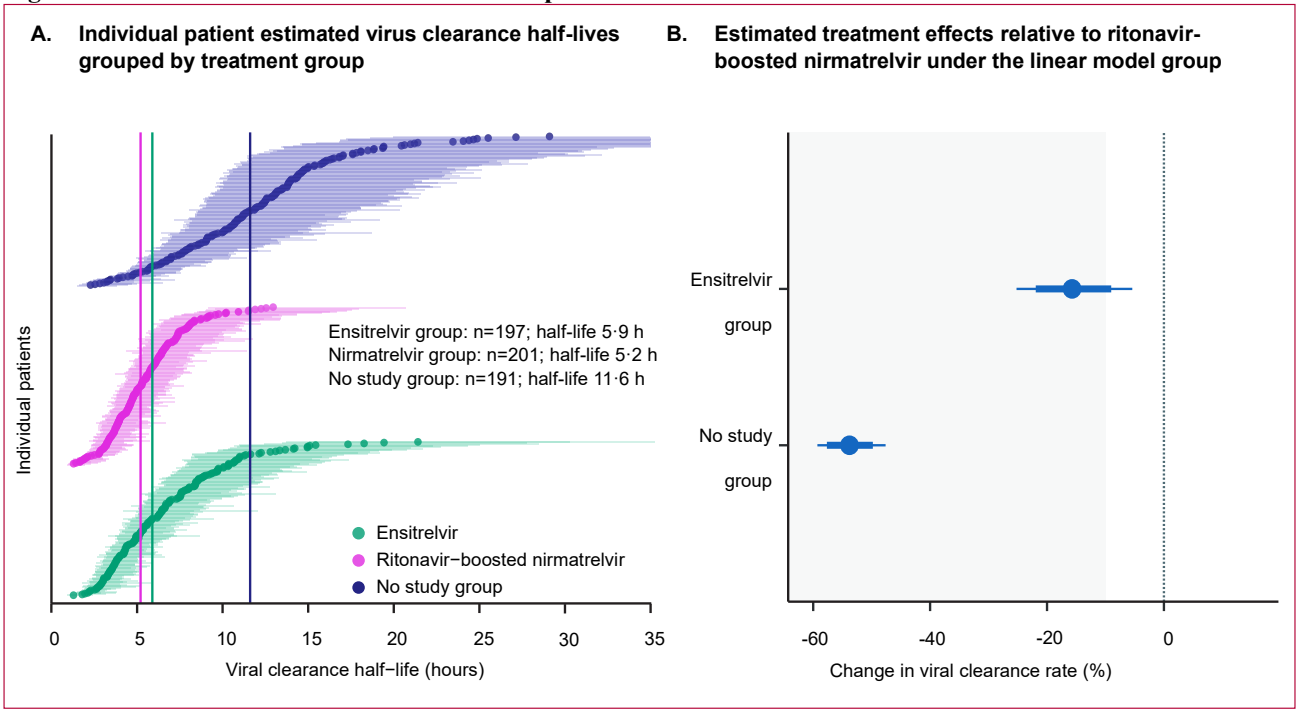
Among the 589 patients in the mITT population (defined as participants with more than two days of follow-up data), 545 (93%) patients had received at least one COVID-19 vaccine dose. The majority of participants (98%) were enrolled in Thailand, with the remaining 2% enrolled in Laos. The mean interval 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 $\log_{10}$ genomes/mL lower than in the ritonavir-boosted nirmatrelvir group and the no study drug group.[9]

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 $\log_{10}$ 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, 5.2 hours (IQR 3.8-6.6) for nirmatrelvir, and 11.6 hours (IQR 8.1-14.5) for the no study drug group (see **Figure 7A**).[9]
- 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 of being below the non-inferiority margin of 10%). (see **Figure 7B**).[9]

Figure 7. Viral Clearance Rates in the mITT Population[9]



Abbreviations: h, hours; mITT, modified intention-to-treat.
Figure (A): Point estimates and 80% credible intervals are shown. The vertical lines show the median half-lives in each group. Figure (B): The grey zone shows the inferiority zone relative to nirmatrelvir. Thick and thin error bars indicate the 80% and thick error bars the 95% credible intervals. Figure adapted from Schilling et al. *Lancet Infect Dis.* 2025.

Secondary Endpoints:

- **Time to fever and symptom resolution through Day 7**
  Time to fever resolution was defined as an axillary temperature of ≤37°C for at least 24 hours. The mean duration of fever was 1.2 days (95% CI: 0.9-1.6) in both the ensitrelvir and nirmatrelvir groups versus 1.4 days (95% CI: 1.2-1.7) in the no study drug group (*P*=0.36). The restricted mean symptom duration was 5.4 days (95% CI: 5.2-5.7) in the ensitrelvir group, 5.4 days (95% CI: 5.1-5.6) for nirmatrelvir group, and 5.9 days (95% CI: 5.6-6.1) in the no study drug group, corresponding to a 32% faster symptom resolution with ensitrelvir (95% CI: –3 to 78) and a 38% faster resolution with ritonavir-boosted nirmatrelvir (95% CI: 3–86) compared with no study drug.[9]

- **Viral rebound**
  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. 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 for the ensitrelvir group, 9.9 days for the nirmatrelvir group, and 6.9 days for the no study drug group.[9]

- **All-cause hospitalization for clinical deterioration through Day 28**
  Seven patients were admitted to hospital during follow-up (ensitrelvir: 2/197; ritonavir-boosted nirmatrelvir: 3/201; no study drug: 2/191). No patients developed severe COVID-19, and hospitalizations were considered unrelated to disease progression or study treatment.[9]

Safety

- No severe COVID-19 cases were observed.[9]
- Fatigue related to COVID-19 was reported by 1 patient each in the nirmatrelvir group and the no study drug group (none in the ensitrelvir group).[9]

- One patient experienced a likely drug–drug interaction in the nirmatrelvir group, and two patients in the nirmatrelvir group discontinued treatment due to concomitant medication interaction.[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]

Platform-wide Meta-analysis

A pooled individual-patient meta-analysis of 1157 patients across PLATCOV antiviral evaluations demonstrated that of all the tested antiviral agents, ensitrelvir and nirmatrelvir were the most potent antiviral agents. Relative to no study drug, ensitrelvir accelerated viral clearance by 87% (95% CrI: 68-111), and nirmatrelvir by 126% (95% CrI: 105-151).[9]

3. REAL WORLD EVIDENCE STUDIES

Japanese Postmarketing Surveillance Study

Study Design

Hayashi et al. (2025) reported the final analysis of a multicenter, single-arm, observational postmarketing surveillance study conducted in Japan to evaluate the safety and effectiveness of ensitrelvir in real-world clinical practice. The survey was conducted from November 2022 to December 2023, with a 28-day observation period following initiation of ensitrelvir. Patients aged ≥12 years with COVID-19 who received ensitrelvir for the first time were eligible. Both SR and HR patients were included, with the majority (97.5%) presenting with mild COVID-19. A small proportion of patients had moderate disease or were asymptomatic at baseline. No patients with severe disease were included. A total of 73.4% of patients had previously received the COVID-19 vaccination. The study assessed ADRs, hospitalization and mortality, and time to resolution of COVID-19 symptoms based on patient-reported questionnaires.[13]

A total of 3760 patients were included in the safety analysis set and 3638 patients in the effectiveness analysis set. High-risk factors for progression to severe COVID-19 were present in 25.0% (939/3760) of patients in the safety analysis set and 24.8% (903/3638) of patients in the effectiveness analysis set.[13]

Results

Efficacy

- In the effectiveness analysis set, the median time to resolution of fever (defined as the first time when body temperature of <37°C was maintained for ≥24 hours) was 36.0 hours, and the median time to resolution of all symptoms (defined as the first time when none of fever, systemic, respiratory, and gastrointestinal symptoms persisted for ≥24 hours) was 156.0 hours.[13]
- Median time to resolution of systemic, respiratory, and gastrointestinal symptoms was 60.0, 132.0, and 48.0 hours, respectively.[13]
- Median time to resolution of fever was similar between SR (n=1645) and HR (n=547) subgroups (36.0 hours). Median time to resolution of all symptoms was 168.0 hours in SR patients (n=2424) and 144.0 hours in HR patients (n=854).[13]

Safety

- In the safety analysis set, the incidence of ADRs was 7.2%. A total of 379 ADRs were reported, including 5 serious ADRs and 374 non-serious ADRs.[13]
- The 5 serious ADRs reported in 3 patients (generalized edema, headache, nausea, cold sweat, and vomiting) resolved within 3-5 days.[13]
- Most ADRs (n=348) occurred within 5 days of initiating ensitrelvir, with the highest number occurring on Day 2 (n=138).[13]
- The most frequently reported ADRs were diarrhea (n=91), nausea (n=43), headache (n=42), vomiting (n=24), and rash (n=20).[13]
- The incidence of ADRs was 7.1% in SR subgroup and 7.6% in HR subgroup (P=0.6284).[13]

- Outcomes of ADRs were recovered (including remission; n=344), not recovered (n=10), and unknown (n=25); no ADRs resulted in sequelae or death.[13]
- During the observation period, hospitalization occurred in 14 patients (0.4%), including hospitalizations due to COVID-19 exacerbation (n=10) and other causes (n=6).[13]
- Two patients (0.1%) died during the observation period; neither death was attributed to COVID-19 nor to ensitrelvir treatment.[13]

Prospective Registry-Based Cohort Study in COVID-19 Outpatients

Study Design

Hibino et al. (2025) presented a pre-specified secondary/exploratory analysis (ANCHOR-02) of the ANCHOR study, a nationwide, multi-institutional, prospective COVID-19 registry-based cohort study conducted across 51 Tokushukai hospitals in Japan. ANCHOR-02 evaluated the impact of acute-phase oral antiviral treatment on COVID-19-related re-consultation through Day 28 as the secondary endpoint, and return to usual health, work productivity and activity impairment, and additional antibiotic use through Day 28 as exploratory endpoints among mixed-risk outpatients with COVID-19.[14]

Patients were enrolled from February to October 2024 and followed until February 2025. Eligible patients were outpatients aged ≥12 years with symptom onset of SARS-CoV-2 infection ≤5 days before consent. Patients were excluded if they had received anti-SARS-CoV-2 treatment ≤30 days before enrollment or were using or planning to use other antiviral agents, including remdesivir, casirivimab/imdevimab, sotrovimab, tixagevimab/cilgavimab, dexamethasone, baricitinib, or tocilizumab at study entry.[14]

Treatment options included supportive care only or oral antiviral treatment with ensitrelvir, nirmatrelvir, or molnupiravir for a 5-day regimen, in accordance with the MHLW COVID-19 management guidelines in Japan. Data were collected from the Tokushukai Medical Database (TMD) and patient-reported electronic questionnaires (ePRO) on Days 28 and 84. The analyses compared oral antivirals with no antiviral treatment and were adjusted for demographics, comorbidities, symptoms, vaccination status, and timing.[14]

Results

Of 9014 participants enrolled in the ANCHOR study, 8657 acute COVID-19 outpatients were included in the ANCHOR-02 study. Overall, 2447 patients received antiviral treatment, and 6210 received no antiviral treatment; baseline characteristics were summarized for 2415 and 6164 patients, respectively. Among antiviral-treated patients, 1857 received ensitrelvir, 117 received nirmatrelvir, and 441 received molnupiravir. Patients in the antiviral group were generally older and had a higher prevalence of comorbidities, including hypertension, diabetes, dyslipidemia, chronic kidney disease on dialysis, malignant tumor, cardiovascular disease, respiratory disease, liver disorders, genetic disorders, mental disorders, or immunodeficiency than those in the no-antiviral group.[14]

Efficacy

Efficacy outcomes through Day 28 are presented in **Table 8**.

Secondary Analysis:[14]
- In the adjusted analysis, ensitrelvir was associated with a reduction in COVID-19- related re-consultation through Day 28 compared with no antiviral treatment (adjusted RR 0.87; 95% CI: 0.77-0.98; $P<0.05$).
- The adjusted RR vs. placebo was 0.92 (95% CI: 0.83-1.03) with any antiviral treatment, 1.26 (95% CI: 0.91-1.73) with nirmatrelvir, and 1.07 (95% CI: 0.88-1.31) with molnupiravir.

Work productivity and activity impairment were assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire at Day 28. Antiviral treatment was associated with improvement in presenteeism, overall work impairment, and activity impairment, but not absenteeism (see **Figure 8**).[14]

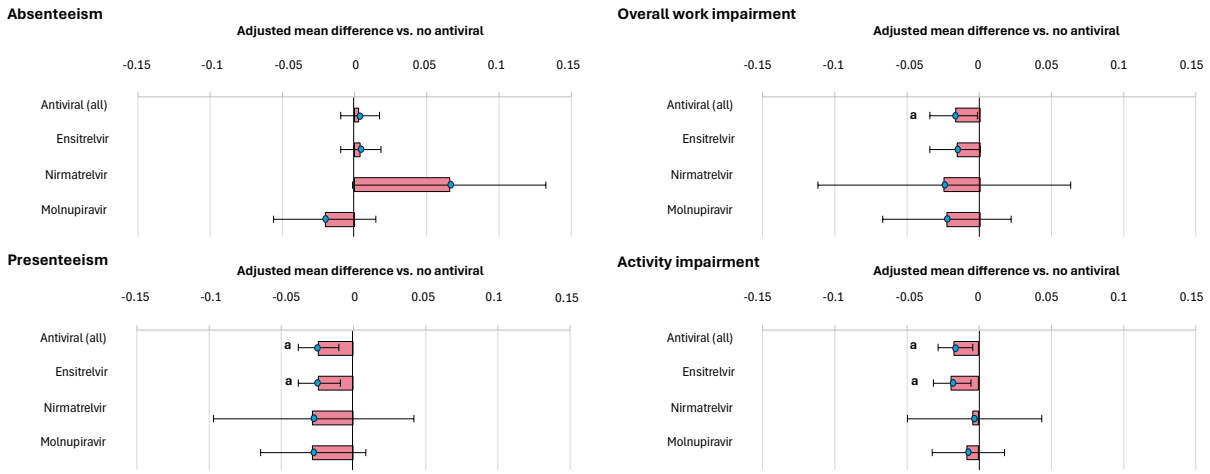
Safety results are not yet available.

Table 8. Efficacy Outcomes Through Day 28 Outcomes in ANCHOR-02.[14]

Outcome	No antiviral treatment	Any antiviral	Ensitrelvir	Nirmatrelvir	Molnupiravir
COVID-19-related re-consultation through Day 28 (Secondary Outcome)					
n/N	1045/5794	419/2282	297/1771	28/103	94/408
Unadjusted rate, %	18.0	18.4	16.8	27.2	23.0
Adjusted rate, %	17.8	16.4	15.5	22.3	19.1
Adjusted RR (95% CI)	Reference	0.92 (0.83-1.03)	0.87[a] (0.77-0.98)	1.26 (0.91-1.73)	1.07 (0.88-1.31)
Additional antibiotic prescriptions through Day 28 (Exploratory Analysis)					
n/N	193/5776	93/2278	58/1768	7/103	28/407
Unadjusted rate, %	3.3	4.1	3.3	6.8	6.9
Adjusted rate, %	3.3	3.5	3.0	5.7	5.7
Adjusted RR (95% CI)	Reference	1.06 (0.81-1.37)	0.91 (0.68-1.22)	1.74 (0.84-3.61)	1.75[a] (1.13-2.71)
Not returning to usual health at Day 28 (Exploratory Analysis)					
n/N	2031/5768	614/2271	474/1764	30/102	110/405
Unadjusted rate, %	35.2	27.0	26.9	29.4	27.2
Adjusted rate, %	33.7	25.6	25.2	29.7	25.2
Adjusted RR (95% CI)	Reference	0.76[a] (0.70-0.82)	0.75[a] (0.68-0.81)	0.88 (0.65-1.19)	0.78[a] (0.66-0.93)

Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio.
Table adapted from Hibino. APCCMI. 2025.
Participants with missing values in outcome measures or baseline covariates were excluded prior to the analysis. RR values were calculated using modified Poisson regression. Covariates included in the model-multivariate regressions were BMI, sex, smoking history, medical history (hypertension, diabetes mellitus, dyslipidemia, malignancy, cardiovascular disease, respiratory disease, and liver disease), maximum temperature from onset to Day 1, severity of Day 1 COVID-19 symptom score, presence of pneumonia on Day 1, time-to-taking from onset of COVID-19, date of last SARS-CoV-2 vaccination, and number of SARS-CoV-2 vaccinations.
[a]*P*<0.05 vs. no antiviral.

Figure 8. Changes in WPAI Domain Scores at Day 28.[14]



Abbreviations: BMI, body mass index; WPAI, Work Productivity and Activity Impairment.
Table adapted from Hibino. APCCMI. 2025.
SARS -CoV-2 antiviral drug-weighted mean was calculated using the generalized estimation equation for the weighted mean vs. no treatment for ensitrelvir, nirmatrelvir, and molnupiravir. Covariates included in the model-multivariate regressions were BMI, sex, smoking history, medical history (hypertension, diabetes mellitus, dyslipidemia, malignancy, cardiovascular disease, respiratory disease, and liver disease), maximum temperature from onset to Day 1, severity of Day 1 COVID-19 symptom score, presence of pneumonia on Day 1, time-to-taking from onset of COVID-19, date of last SARS-CoV-2 vaccination, and number of SARS-CoV-2 vaccinations.
[a]*P*<0.05 vs. no antiviral.

Retrospective Cohort Study in Nonhospitalized High-Risk Patients

Study Design

Takazono et al. (2024) conducted a retrospective cohort study analyzing a large database of health insurance claims to assess real-world effectiveness of ensitrelvir in nonhospitalized patients in Japan. The outcomes of patients who received ensitrelvir between November 2022 and July 2023 (B.1.1.529 [Omicron] dominant period) were compared with patients who received no antiviral treatment. The primary analysis target population consisted of patients who were aged ≥18 years and had at least one risk factor for severe COVID-19 disease according to MHLW guidelines who could be tracked for 6 months before diagnosis with COVID-19 up to 1 month following that date. Risk factors for severe disease included age ≥65 years, malignancy, chronic pulmonary disease, chronic renal disease, diabetes, hypertensive disease, dyslipidemia, cardiovascular disease, cerebrovascular disease, morbid obesity, immunosuppressive disorders, and HIV/AIDS.[15]

The primary endpoint was all-cause hospitalization (starting on Days 2-28). Secondary endpoints included:[15]

- Respiratory and heart rate monitoring (starting on Days 2-28)
- Oxygen therapy (starting on Days 2-28)
- Ventilator use (starting on Days 2-28)
- Intensive care unit (ICU) admission (starting on Days 2-28)
- All-cause death (within the following month)

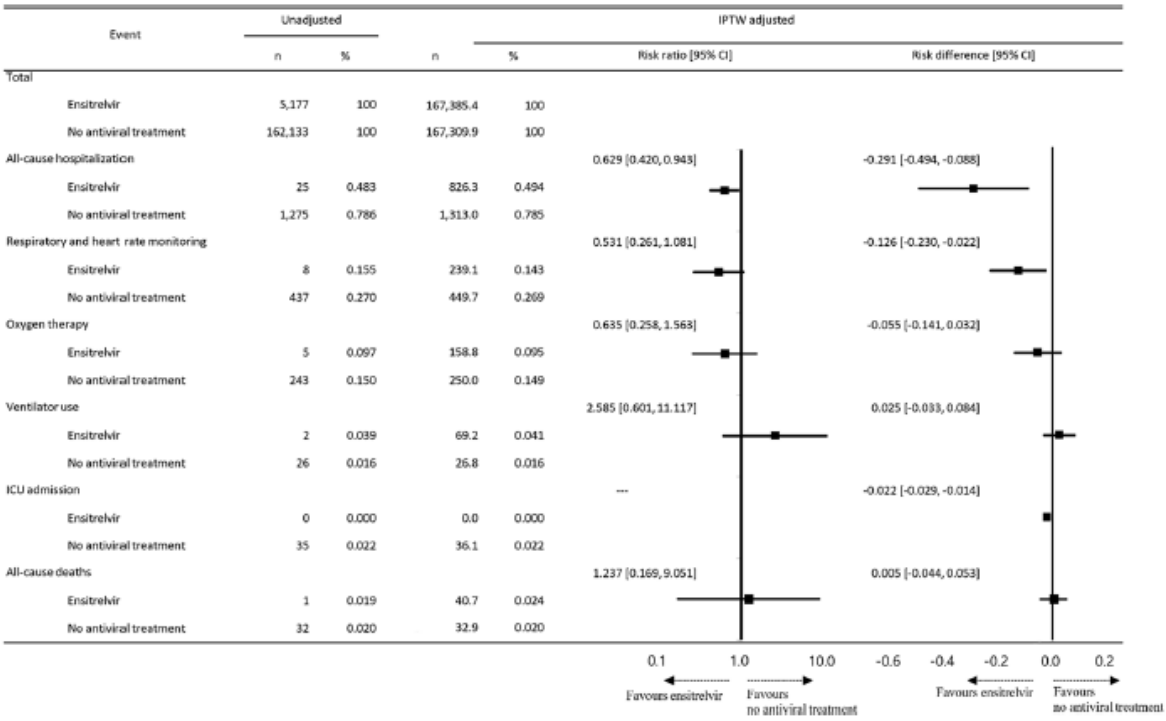
Baseline demographic and clinical characteristics between the treatment groups were standardized by employing a propensity score, calculated through a logistic regression analysis in which covariates were selected based on their relevance to COVID-19 disease severity, and applying the inverse probability of treatment weighting (IPTW) method.[15]

Results

- A total of 167,310 eligible high-risk patients were included in the analysis, of which 5177 (3.1%) were treated with ensitrelvir and 162,133 (96.9%) did not receive antiviral treatment.[15]
- Incidence of all-cause hospitalization (primary endpoint) was significantly lower in high-risk patients who received ensitrelvir compared with no antiviral treatment (0.494% vs 0.785%; RR, 0.629 [95% CI, 0.420-0.943]; RD, −0.291 [95% CI, −0.494 to −0.088]) (**Figure 9**)[15]
    - In the overall (N=666,865 [ensitrelvir n=20,735; no antiviral treatment n=646,130]) population, which included patients not at risk of severe COVID-19 disease, incidence of all-cause hospitalization was significantly lower in patients who received ensitrelvir compared with no antiviral treatment (0.287% vs 0.413%; RR, 0.696 [95% CI, 0.537-0.903]; RD, −0.125 [95% CI, −0.201 to −0.050])
    - In a post-hoc analysis in high-risk patients aged ≥65 years, incidence of all-cause hospitalization was lower in patients who received ensitrelvir compared with no antiviral treatment (0% [0/380] vs 1.298% [199/15,336]; P=0.0166 using Fisher's exact test)
- Incidence of respiratory and heart rate monitoring (secondary endpoint) was lower in high-risk patients who received ensitrelvir compared with no antiviral treatment (0.143% vs 0.269%; RR, 0.531 [95% CI, 0.261-1.081]; RD, −0.126 [95% CI, −0.230 to −0.022]) (**Figure 9**)[15]
- Incidence of oxygen therapy (secondary endpoint) was lower in high-risk patients who received ensitrelvir compared with no antiviral treatment (0.095% vs 0.149%; RR, 0.635 [95% CI, 0.258-1.563]; RD, −0.055 [95% CI, −0.141 to 0.032]) (**Figure 9**)[15]
- Other secondary endpoint events (ie, ventilator use, ICU admission, and all-cause death) were difficult to assess due to the limited number of unadjusted incidences (0-2 cases) (**Figure 9**)[15]

- Cumulative incidence of all-cause hospitalization was suppressed up to Day 28 in high-risk patients who received ensitrelvir compared with no antiviral treatment; the 95% CIs of each group did not overlap from Day 2 to Day 12 (**Figure 10**)[15]

Figure 9. Incidence and Risk of Events[a] in High-Risk Patients who Received Ensitrelvir Compared with no Antiviral Treatment.[15]

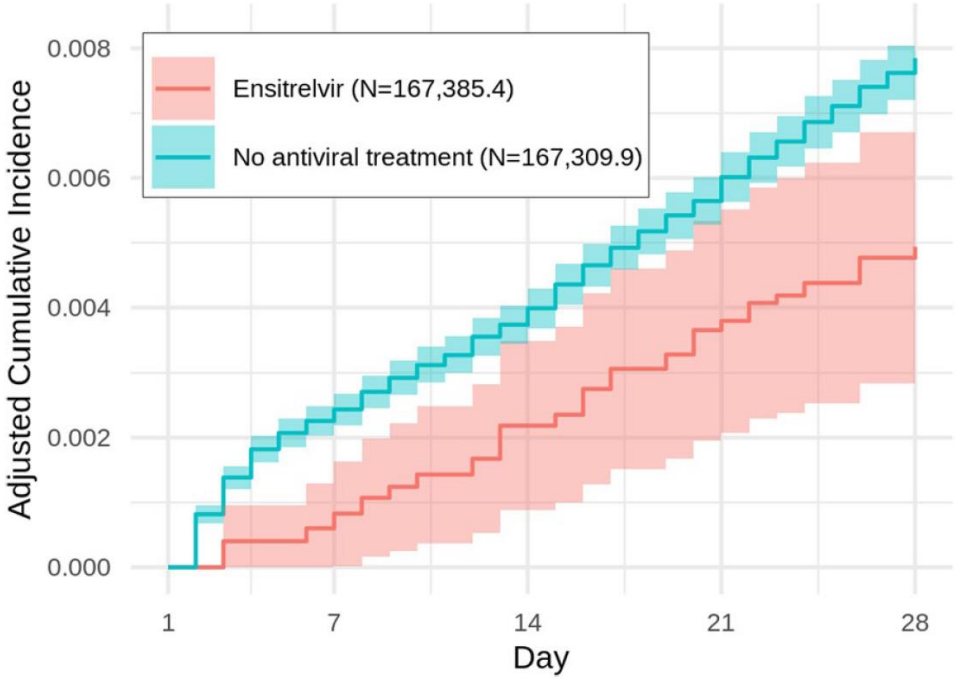


This image is used under a Creative Commons CC BY-NC 4.0 International License specific to the article published by Springer Nature: Takazono T et al. *Infect Dis Ther*. 2024;13(8):1821-1833. doi: 10.1007/s40121-024-01010-4

Abbreviations: CI, confidence interval; ICU, intensive care unit; IPTW, inverse probability of treatment weighting.

[a]Incidence, risk ratio, and risk difference were adjusted by inverse probability of treatment weighting.

Figure 10. Cumulative Incidence[a] of All-Cause Hospitalization in High-Risk Patients Who Received Ensitrelvir Compared With No Antiviral Treatment.[15]



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[a]Incidence was adjusted by inverse probability of treatment weighting.

Retrospective Chart Review in Hospitalized Patients

Study Design

Yamato et al. (2024) conducted a single-center, retrospective chart review to assess outcomes among hospitalized patients treated with ensitrelvir in a real-world setting in Rinku General Medical Center in Izumisano, Japan, between November 2022 and April 2023. Severity of COVID-19 disease prior to ensitrelvir treatment was classified according to MHLW guidelines in Japan.[16]

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 as indicated by polymerase chain reaction or antigen testing and investigator assessments of clinical improvement were used to assess effectiveness.[16]

Results

- A total of 32 patients were included in the analysis, all of whom received 5 days of ensitrelvir treatment[16]
  - Average age of the study population was 73.5 years and most patients (78.1%; 25/32) were aged ≥65 years
  - Comorbidities included hypertension in 78.1% (25/32), chronic kidney disease in 25% (8/32), hemodialysis in 22.6% (7/32), and malignant tumors in 28.1% (9/32) of patients
  - Severity of COVID-19 disease at the start of treatment was mild in 65.6% (21/32), moderate I in 12.5% (4/32), and moderate II in 21.9% (7/32) of patients
- Antiviral treatment had previously been administered to 93.8% (30/32) of patients, the most common of which was remdesivir in 87.5% (28/32) of patients[16]
  - Remdesivir monotherapy was given to 21.9% (7/32) of patients, and remdesivir with casirivimab/imdevimab was given to 56.3% (18/32) of patients
  - Remdesivir therapy was administered for ≥3 days in 75% (21/28) of patients (mean, 6.6 days; range, 3-22 days)

- By Day 6, 56.3% (18/32) of patients had viral clearance (defined as an antigen level of <89.73 pg/mL) and 15.6% (5/32) of patients had antigen level below the lower limit of quantification (LLoQ, <1.34 pg/mL). At final measurement, 78.1% (25/32) of patients had achieved viral clearance[16]
- Viral rebound occurred in 12.5% (4/32) of patients; none of these patients had disease progression[16]
- Virology outcome data are presented in **Table 9**.[16]
- All patients experienced clinical improvement as assessed by the investigator at the end of ensitrelvir treatment (Day 5). No patients discontinued treatment, there were no treatment-related adverse events (TRAEs), no patients progressed to severe disease, none were admitted to the ICU, and no treatment-related deaths occurred. A total of 16 patients were discharged from hospital by Day 14, and 15 patients were discharged from Day 15 (range, Day 15-78)[16]
    - One patient death (Day 55) occurred due to anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis and was determined to be unrelated to COVID-19

Subgroup Analysis of Patients with Persistent COVID-19 After Remdesivir Treatment

- A subgroup analysis was performed in 21 patients who were administered remdesivir for ≥3 days before switching to ensitrelvir[16,17]
    - Comorbidities included malignant tumors in 33.3% (7/21), diabetes mellitus in 28.6% (6/21), and renal failure in 19% (4/21) of patients[17]
    - Severity of COVID-19 disease in this subgroup of patients was mild in 81% (17/21), moderate I in 9.5% (2/21), and moderate II in 9.5% (2/21) of patients (COVID-19 disease severity criteria is according to Japanese guidelines and takes into account blood oxygen saturation and clinical condition)[17]
- By Day 5, 66.7% of patients had viral clearance[17]
- Viral rebound occurred in 9.5% (2/21) of patients; neither of these patients had rebound of symptoms or received additional antiviral therapy[17]

Virology outcome data for all study patients, including those in the subgroup analysis, are presented in **Table 9**. All patients experienced clinical improvement as assessed by the investigator at the end of ensitrelvir treatment (Day 5). There were no TRAEs, no patients progressed to severe disease or were admitted to the ICU through Day 28, and no treatment-related deaths occurred. A total of 20 patients were discharged from hospital by Day 77[16,17]

Table 9. Virology Outcomes in a Single-Center Chart Review in Hospitalized Patients.[16,17]

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)																	
1[b]	Esophageal cancer, HTN	Remdesivir[c]	5000	5000		571.44			21.75	18.67	9.43	2.81	0.06	4.79	0.01	0.10		Viral Clearance	Viral Clearance	
2[b]	T2D, chronic atrial fibrillation, chronic subdural hematoma, hydrocephalus, HTN	Remdesivir[c] Molnupiravir	206.25	3429.86	235.08	10.35	1.06	0.95										Viral Clearance	Viral Clearance	
3	DM, HTN	Remdesivir	5000		5000			113.88		0.01									Viral Clearance	
4[b]	Exertional angina pectoris, lung cancer, cerebral infarction, dyslipidemia, HTN	Remdesivir[c]	255.09	5000			36.55		25.72	1.61	0.30	0.01						Viral Clearance	Viral Clearance	
5[b]	Unstable angina pectoris, organizing pneumonia, CHF, CKD, hypothyroidism, DM	Remdesivir[c] Casirivimab/ imdevimab	5000	5000		5000	5000	5000				1233.07	494.52		254.76	8.67	44.64		Viral Clearance	
6[b]	Traumatic subarachnoid hemorrhage, heart failure, asymptomatic myocardial ischemia, cerebral contusion, HTN	Remdesivir[c]	5000	5000		1394.43		39.12	43.49	46.30		28.65	0.83	0.89				Viral Clearance	Viral Clearance	
7[b]	Liver metastasis from cancer of the sigmoid colon, breast cancer	Remdesivir[c] Casirivimab/ imdevimab		5000		1676.19					27.73								Viral Clearance	
8[b]	Osteoarthritis	Remdesivir[c] Casirivimab/ imdevimab	5000	2728.74	3736.13	142.46		13.50	0.30									Viral Clearance	Viral Clearance	
9[b,d]	AAV, CKD, DM, HTN	Remdesivir[c] Molnupiravir Tixagevimab/	5000	5000		2587.88		4.77	1210.73		5000	5000	5000							Viral Rebound (at Day 6)

		cilgavimab																		
10[c]	Recurrent FL, post-HSCT, CKD, HTN, hemodialysis	Molnupiravir		1227.48		182.59	200.71													
11[b]	Asthma, cerebral infarction, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000	5000	5000		1086.83	4091.46			16.27	11.83	3.76	1.73	0.01				Viral Clearance	
12[b]	atrial fibrillation, malignant melanoma, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000			1.04	0.11											Viral Clearance	Viral Clearance	
13	Bronchiectasis, previous history of TB, HTN	Remdesivir	5000		5000			0.75										Viral Clearance	Viral Clearance	
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)
15	CKD, abdominal aortic aneurysm, HTN	None		5000			5000		665.36		352.02			8.56	1.30	4.21	0.01		Viral Clearance	
16[b]	Valve disorders, gastric ulceration, dyslipidemia, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000	5000		53.22			2.10	0.62								Viral Clearance	Viral Clearance	
17[b]	CHF, DM, cerebral infarction, pyelonephritis, ischemic heart disease	Remdesivir[c] Casirivimab/ imdevimab	5000	5000			537.86		84.40	7.89	43.06	3.56	2.08	0.01	0.06			Viral Clearance	Viral Clearance	
18[b]	Depression, upper gastrointestinal bleeding, HTN	Remdesivir[c] Casirivimab/ imdevimab	4328.71	5000		5000			2468.05		5000		3637.23			114.93	12.95		Viral Clearance	
19	CKD, DM, HTN, hemodialysis	Remdesivir	5000			344.33														
20	Kidney stone disease, acute myelogenous leukemia, post-HSCT, kidney injury, HTN	None		5000[f]			5000	97.79		344.12	5000				4664.69					
21[b]	Candidemia, asthma, colorectal cancer, peritoneal metastases, dyslipidemia, HTN	Remdesivir[c] Casirivimab/ imdevimab	1727.71	2393.09		1354.45			2.51	1.61	1.05	2.59	1.03	0.01				Viral Clearance	Viral Clearance	
22[b]	Asthma, bronchitis, liver failure, cerebral infarction, renal failure	Remdesivir[c]	5000		5000			7.42	8.09	1.97	4.39	0.71	2.78	0.67	1.72	0.08	0.24	Viral Clearance	Viral Clearance	
23	IgAN, congestive heart failure, CKD, HTN, hemodialysis	Remdesivir Molnupiravir		88.50	2.89	0.09												Viral Clearance	Viral Clearance	
24[b]	AAV, UTI, dyslipidemia, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000	5000			223.72		2.37	8.01	5.99	41.02		1.23	0.01			Viral Clearance	Viral Clearance	
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)
26[b]	Benign prostatic hyperplasia, gastric cancer, cholelithiasis, cerebral infarction, RA	Remdesivir[c] Casirivimab/ imdevimab	1305.00	5000			1021.42				19.95	1.89	0.57	0.24					Viral Clearance	
27[b]	Atrial fibrillation, chronic hepatitis B, CHF, chronic renal failure, pyelonephritis, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000			1767.49	274.52	245.85	147.76	111.48			3.44	6.81	1.92	1.15	0.56		Viral Clearance	
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[g] (at Day 12)
29	Post-CABG, CKD, DM, dyslipidemia, HTN, hemodialysis	Remdesivir Casirivimab/ imdevimab	1635.16		115.32		1463.78		41.1									Viral Clearance	Viral Clearance	
30	Lacunar infarction, CKD, DM, HTM, hemodialysis	Remdesivir Casirivimab/ imdevimab	5000		1125.20															
31[b]	Organizing pneumonia, chronic obstructive, pulmonary disease, cerebral infarction, HTN, T2D	Remdesivir[c] Casirivimab/ imdevimab	5000	5000		5000		1330.12												
32[b]	Dyslipidemia, cerebral infarction, HTN	Remdesivir[c] Casirivimab/ imdevimab	5000	5000		1292.38			63.29		9.86	11.31	1.56	0.01				Viral Clearance	Viral Clearance	

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Shading indicates days the patient was hospitalized.
Abbreviations: AAV, ANCA-associated vasculitis; BSI, bloodstream infection; ANCA, anti-neutrophil cytoplasmic antibody; CABG, coronary artery bypass graft; CHF, chronic heart failure; CKD, chronic kidney disease; Ct, cycle threshold; DM, diabetes mellitus; EOT, end of treatment; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; HTN, hypertension; IgAN, immunoglobulin A nephropathy; PCR, polymerase chain reaction; RA, rheumatoid arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T2D, Type 2 diabetes; TB, tuberculosis; UTI, urinary tract infection.
[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]Patient received rituximab at Day -15. [f]PCR positive at Day 1. [g]Viral clearance documented on Day 15 and Day 16.

Retrospective Case Series of Ensitrelvir in Nonhospitalized Patients

Study Design

Abe et al. (2024) conducted a retrospective case series in Japan evaluating real-world outcomes in symptomatic, vaccinated, outpatients with mild-to-moderate COVID-19 treated with ensitrelvir between December 1, 2022, and January 31, 2023. The study population comprised 18 patients with a median age of 39.5 years (range: 26-56 years) who were treated with a 5-day oral regimen of ensitrelvir consisting of 3 tablets (each tablet 125 mg) every 8 hours on Day 1, followed by 1 tablet daily from Day 2-5.[18]

Sore throat was the most commonly reported presenting symptom, and mild fever was reported by most patients. Underlying conditions were reported in a small number of patients, including chronic sinusitis, allergic rhinitis, and bronchial asthma. All patients were infected with the SARS-CoV-2 Omicron BA.5 variant, as confirmed through Sanger sequencing. Patients were followed for up to 60 days after treatment initiation to assess symptom course, virologic outcomes, adverse events, and post-acute sequelae of COVID-19 (PASC); symptom outcomes were descriptively compared with historical control data.[18]

Results

Efficacy

- Clinical Outcomes:
  - Symptoms such as sore throat and mild fever improved after initiation of ensitrelvir treatment. Symptoms improved within 2 days in 33% of patients, and between 3 and 6 days in an additional 33% of patients.[18]
  - One patient had mild cough, and 5 patients had mild sore throat persisting beyond 6 days.[18]

- Virologic Outcomes:
  - Mean cycle threshold (Ct) values increased from 21.82 at symptom onset to 37.65 by Day 6.[18]
  - Ten patients had Ct values >35 within 6 days of treatment initiation.[18]
  - SARS-CoV-2 RNA became undetectable by Day 9 in most patients.[18]
  - Greater increases in Ct values between Day 0 and Day 3 were observed in patients who initiated treatment within 48 hours of symptom onset.[18]

- Symptom outcomes were descriptively compared with historical control data. In untreated outpatients with mild symptomatic Omicron variant infection, the median time to symptom resolution was reported as 8.5 days (95% CI: 6-11 days; data not shown). In the ensitrelvir-treated cohort, the majority of patients (>66%) had symptom resolution reported within a median of 1.4 days (95% CI: 1-6 days).[18]

Safety

- No increases in viral load, as assessed by Ct values, were observed during follow-up.[18]
- No patients experienced symptom recurrence or newly emergent adverse events.[18]
- No signs or symptoms of post-acute sequelae of COVID-19 were reported during the follow-up period.[18]

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 May 2026, a computerized search of the published medical literature using internal and external databases (eg, PubMed®) has identified additional relevant references regarding the efficacy of ensitrelvir for the treatment of COVID-19. For your review, these references are listed in the bibliography that follows:

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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	mITT	Modified-intention-to-treat
$3CL^{pro}$	3-chymotrypsin-like protease	NA	Not applicable
ACTG	AIDS Clinical Trials Group	NIH	National Institutes of Health
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines	nsps	Nonstructural proteins
AE	Adverse event	PCR	Polymerase chain reaction
AIDS	Acquired immunodeficiency syndrome	PEP	Post-exposure prophylaxis
ANCOVA	Analysis of covariance	PK	Pharmacokinetics
CI	Confidence interval	pp1a/pp1ab	Polyproteins 1a/1ab
COVID-19	Coronavirus disease 2019	QD	Once a day
CrCl	Creatinine clearance	RNA	Ribonucleic acid
CYP3A4	cytochrome P450 3A4	RoW	Rest of world
D1, 2, 3,...	Day 1, 2, 3, ...	RR	Relative risk
GEE	Generalized estimatin equation	RTC	Replicase-transcriptase complex
h	hours	RT-PCR	replicase-transcriptase polymerase chain reaction
HDL	High-density lipoprotein	SAE	Serious adverse event
HHC	Household contact	SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
HR	High-risk	SAS	Safety analysis set
IQR	Interquartile ration	SD	Standard deviation
ITT	Intention to treat	SE	Standard error
KM	Kaplan-Meier	$TCID_{50}$	50% tissue culture infectious dose
LoD	Limit of detection	TEAE	Treatment-emergent adverse event
LLoQ	Lower limit of quantification	TG	Triglyceride
LS	Least square	TRAE	Treatment related adverse event
mAbs	Monoclonal antibodies	ULoQ	Upper limit of quantification
MHLW	Ministry of Health, Labor and Welfare	US	United States

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ENCLOSURE

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