XOCOVA - Use in Immunocompromised Patients

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1. SUMMARY

Clinical Trials

- **SCORPIO-PEP** (post-exposure prophylaxis) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of ensitrelvir vs placebo in preventing symptomatic COVID-19 in household contacts (HHCs) who were exposed to a person with SARS-CoV-2 infection. A 67% reduction in the risk of developing COVID-19 (risk ratio: 0.33; 95% CI: 0.22-0.49; *P*<0.0001) was observed with ensitrelvir vs placebo at Day 10 in the mITT population. TEAEs occurred in 15.1% (180/1190) of patients in the ensitrelvir group and 15.5% (184/1187) of patients in the placebo group.[1,2]
    - 2 (0.2%) patients in the ensitrelvir treatment group had immunocompromising conditions. Results based on immunosuppression are not currently available.[3]
- The global Phase 3 study **SCORPIO-HR** assessed the clinical and antiviral effects of ensitrelvir (oral once daily for 5 days) vs placebo in nonhospitalized patients with COVID-19 with or without high risk factors for severe COVID-19.
    - Patients were included if they had immunocompromising conditions or immunosuppressive treatments, but results based on immunosuppression are not currently available
    - There was no significant difference between ensitrelvir and placebo in restricted mean time to sustained resolution of symptoms (*P*=0.14) in the mITT population.[4]
- The **Phase 3 part of a Phase 2/3 (SCORPIO-SR)** clinical study conducted in Asia assessed efficacy and safety of ensitrelvir in a population of patients with mild-to-moderate COVID-19 and included patients who were taking corticosteroids or other immunosuppressive medications. Time to resolution of 5 COVID-19 symptoms was significantly reduced with ensitrelvir 125 mg vs placebo (*P*=0.04).
    - Results based on immunosuppression are not currently available.[5]
- **STRIVE** was an international Phase 3, randomized, double-blind, placebo-controlled trial in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) as part of the ACTIV public-private partnership program that evaluated 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).[6]
    - 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)
    - In subgroup analyses of days to recovery scale through Day 60 (DRS-60) in immunocompromised patients, the median DRS-60 was 16 vs 7 days with an odds ratio of 0.49 (95% CI: 0.23-1.04)

Retrospective Studies

- Retrospective studies have described outcomes of ensitrelvir treatment in immunocompromised patients:
  - A single-center, retrospective observational study (**Maruyama et al. 2025**) evaluated adult B-cell lymphoma patients diagnosed with SARS-CoV-2 infection who received B-cell depleting treatment with anti-CD20 antibodies in Japan between January 2022 and October 2024. After testing, subvariants were determined and monoclonal antibody drug regimens were provided followed prescribed antivirals (remdesivir, molnupiravir, nirmatrelvir/ritonavir, and ensitrelvir) either as monotherapy or in combination. Among 67 patients, 14 received ensitrelvir monotherapy and 7 received ensitrelvir in combination with another agent. Combination therapy (including with ensitrelvir) as the initial regimen significantly shortened the time to viral clearance (HR 0.36, 95% CI 0.20–0.65, $P<0.001$). Genome analysis was performed in 52 of the 67 patients and for monotherapy ensitrelvir, genome analysis showed rare amino acid substitutions in 9 cases of NSP5 (64%).[7]
  - A single-center chart review (**Yamato et al. 2025**) evaluated patient characteristics, outcomes and treatment patterns in patients receiving ensitrelvir or remdesivir in Japan between November 2022 and August 2024. In the ensitrelvir and remdesivir treatment groups, 19.9% (31/156) and 16% (54/337) of patients, respectively, had immunosuppressive conditions at baseline. In a subgroup analysis, the non-adjusted all-cause mortality at Day 28 in immunosuppressive conditions was 3.2% and 9.3% in the ensitrelvir and remdesivir groups, respectively (HR: 0.34; 95% CI 0.04-2.91). The IPTW-adjusted all-cause mortality in immunosuppressive conditions was 5.3% and 10.1% in the ensitrelvir and remdesivir groups, respectively (HR: 0.52; 95% CI 0.06-4.51).[8]
  - A chart review (**Yamato et al. 2024**) at a single center in Japan showed clinical improvement in patients after ensitrelvir treatment, including 10 patients receiving corticosteroids, 1 patient receiving immunosuppressants, and two patients who received rituximab prior to ensitrelvir.[9] The study included 2 patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, 1 patient with acute myeloid leukemia (AML), and 2 patients with hematopoietic stem cell transplantation (HSCT)[10]
  - A descriptive study (**Shimazu et al. 2023**) with no controls at a single center in Japan reported successful ensitrelvir treatment of 3 immunocompromised patients with persistent SARS-CoV-2 infection[11]

Case Presentations

- Several **case presentations** have described ensitrelvir treatment in immunocompromised patients. Ensitrelvir treatment led to resolution of COVID-19, including in patients with persistent COVID-19 and who had not responded to other COVID-19 therapeutics[12-14]

2. CLINICAL TRIALS

SCORPIO-PEP (Global Phase 3 Study)

Study Design

SCORPIO-PEP (NCT05897541) is a completed, global Phase 3 study that evaluated the safety and efficacy of ensitrelvir vs. placebo in the prevention of symptomatic SARS-CoV-2 infection in HHCs of people who tested positive for COVID-19 conducted from June 2023 to September 2024 (see **Appendix-SCORPIO-PEP** for more information on study design).[1,2,15]

HHC participants with a negative local screening test for SARS-CoV-2 infection and no symptoms who were exposed to a person living in their household with symptomatic COVID-19, were randomly assigned in a 1:1 ratio to receive ensitrelvir 125 mg (375 mg Day 1 and 125 mg Days 2-5) or placebo once daily for 5 days. Study participants began treatment within 3 days of when the household member with COVID-19 began showing symptoms.[1,2]

- The mITT population included all HHCs randomized that had CLC COVID-19 RT-PCR negative tests at baseline.
- The ITT population included all HHCs randomized, which included those that had CLC COVID-19 RT-PCR positive tests at baseline

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.[1,2,15]

Results

Efficacy

- 2 (0.2%) patients in the ensitrelvir treatment group had immunocompromising conditions. Results based on immunosuppression are not currently available.[1,2]
- **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% reduction in the risk of developing COVID-19 (risk ratio: 0.33; 95% CI: 0.22-0.49; $P < 0.0001$) in uninfected individuals (mITT population) treated after exposure.[1,2]

Safety

- TEAEs occurred in 15.1% (180/1190) of patients in the ensitrelvir group and 15.5% (184/1187) of patients in the placebo group, with 1 event in each group leading to discontinuation of treatment.[1]
- 2 serious TEAEs occurred in each group and they were considered to be unrelated to the study drug.[1]
- There were no AEs that led to hospitalization and no deaths were observed in either group.[1]
- Results based on immunosuppression are not currently available

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 (oral once daily for 5 days) vs placebo in nonhospitalized patients with COVID-19 with or

without high risk factors for severe COVID-19 (see **Appendix-SCORPIO-HR** for more information on study design).

- This study was conducted across North America, South America, Europe, Asia, and Africa.
- It is a part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-2 clinical trials portfolio, overseen by the AIDS Clinical Trials Group (ACTG) and supported by the National Institutes of Health (NIH).
- This study was conducted when Omicron variant infection was predominant and among a mostly vaccinated population.[4,16,17]

High risk patients were enrolled from throughout the world, excluding the US which only enrolled standard-risk patients. Patients were included if they had 1 of the following immunocompromising conditions or immunosuppressive treatments:[16]

- Receiving chemotherapy or other therapies for cancer
- Hematologic malignancy (active or in remission)
- History of a hematopoietic stem cell or a solid organ transplant
- HIV infection: not on antiretroviral therapy or with CD4+ cell count <200 cells/mm^3
- Combined primary immunodeficiency disorder
- Taking immunosuppressive medications

Results

Efficacy

Immunocompromised patients

- Results based on immunosuppression are not currently available. Patients receiving concomitant immunosuppressants and those with immunocompromising conditions are summarized in **Table 1** and **Table 2** below.[18]
- **Primary Endpoint:** In the modified intent-to-treat (mITT) population, the restricted mean time to sustained symptom resolution was not significantly different between the ensitrelvir (12.5 days) and placebo (13.1 days) groups (difference, -0.6 days; 95% CI: -1.38, 0.19; *P*=0.14).[4]

Table 1. Patients Taking Concomitant Corticosteroids or Other Immunosuppressive Medications in the mITT population[a18]

Medication	Ensitrelvir (N=945) n (%)	Placebo (N=943) n (%)
Methotrexate	2 (0.2)	0
Azathioprine	0	1 (0.1)
Hydroxychloroquine	0	1 (0.1)
Mycophenolate mofetil	1 (0.1)	0
Prednisone	7 (0.7)	6 (0.6)
Prednisolone	2 (0.2)	2 (0.2)
Dexamethasone	1 (0.1)	1 (0.1)
Hydrocortisone	0	2 (0.2)

Abbreviations: mITT, modified intent-to-treat.

[a]Concomitant medications are defined as any medication that started before the date of study Day 1 and ended on or after the date of study Day 1, or were ongoing at that time, or any medication that started on or after the date of study Day 1.

Table 2. Patients With Immunocompromising Conditions in the mITT population[18]

Condition	Ensitrelvir (N=945) n (%)	Placebo (N=943) n (%)
Hodgkin's disease	2 (0.2)	0
HIV[a]	8 (0.8)	18 (1.9)
Exogenous/endogenous immunosuppression	4 (0.4)	1 (0.1)

Abbreviations: HIV, Human Immunodeficiency Virus; mITT, modified intent-to-treat.
[a]CD4+ counts and HIV antiviral treatment status are not available.

Safety

- AEs occurred in 638 patients treated with ensitrelvir (61.5%; n=1037), and 635 patients treated with placebo (60.6%; n=1048).[4]
- TRAEs occurred in 86/1037 (8.3%) of patients treated with ensitrelvir and 74/1048 (7.1%) of patients that were given placebo.[4]
- Serious TEAE occurred in 5/1037 (0.5%) of the ensitrelvir-treated participants and 6/1048 (0.6%) of the patients given placebo.[4]
- 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.[4]

SCORPIO-SR (Phase 3 part of Phase 2/3 Study)

Study Design

The Phase 3 part of the Phase 2/3, multicenter, randomized, double-blind, placebo-controlled clinical study (SCORPIO-SR [**S**topping **CO**VID-19 p**R**ogression with early **P**rotease **I**nhibit**O**r-**S**tandard **R**isk]); jRCT2031210350) was conducted in Japan, Vietnam, and South Korea to evaluate the efficacy and safety of ensitrelvir (125 mg and 250 mg) given orally, once daily for 5 days vs placebo in patients aged 12 to <70 years with mild-to-moderate COVID-19 (see **Appendix-SCORPIO-SR** for more information on study design).[5,19]

Results

Efficacy

- In the intention-to-treat (ITT) population of patients randomized <72 h after disease onset, patients taking corticosteroids or other immunosuppressive medications made up 1.2% (4/347) of the ensitrelvir 125 mg arm (primary analysis population), 0.9% (3/340) of the ensitrelvir 250 mg arm, and 0.9% (3/343) of the placebo arm. In the ITT population of patients randomized within 120 h after disease onset, patients taking corticosteroids or other immunosuppressive medications comprised 0.8% (5/603) of the ensitrelvir 125 mg arm, 0.5% (3/595) of the ensitrelvir 250 mg arm, and 0.7% (4/600) of the placebo arm.[20]
- In the ITT population, 1 (0.2%) patient in the 125 mg arm had leukopenia. In the 250 mg arm, 1 (0.2%) patient had hemophagocytic lymphohistiocytosis and 1 (0.2%) had peripheral T-cell lymphoma.[5]
- Results based on immunosuppression are not currently available.

- **Primary Endpoint:** The time to resolution of 5 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 3**.[5]

Table 3. Phase 3 Part: Time to Resolution of 5 COVID-19 Symptoms[5,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 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.

Safety

- Most AEs were mild in severity, and a decrease in HDL was the most commonly reported AE and TRAE. There were 2 serious adverse events (SAE) reported in the study (1 in the ensitrelvir 125 mg arm and 1 in the placebo arm), both of which were judged as not treatment related.[5]

STRIVE

Study Design

STRIVE (**S**trategies and **T**reatments of **R**espiratory **I**nfections and **V**iral **E**mergencies; 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. This study was in collaboration with the NIAID as a part of the ACTIV public-private partnership program.[6]

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.[6]

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.[6]

The primary endpoint was “Days to Recovery Scale” through Day 60 (DRS-60).[6]

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). Overall, the 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. At baseline, 43 (14.7%) participants in the ensitrelvir group and 45 (15.2%) participants in the placebo group were immunocompromised.[6]

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).[6]
- In the subgroup analysis of participants with high-risk factors for severe disease, the median DRS-60 among immunocompromised participants was 16 days (IQR, 5-61) in the placebo group and 7 days (IQR, 4-61) in the ensitrelvir group (OR, 0.49; 95% CI, 0.23-1.04).[6]
    - Because the subgroup analyses were exploratory and did not account for multiple comparisons, the data are insufficient to determine whether concomitant treatments influenced the efficacy of ensitrelvir

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).[6]
- 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.[6]
- Grade 3 or 4 AEs were reported in 17.7% (52/293) and 16.9% (50/296) of participants receiving ensitrelvir and placebo respectively.[6]
- 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).[6]
- 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).[6]

3. RETROSPECTIVE STUDIES

RETROSPECTIVE CHART REVIEWS

Study Design

- Maruyama et al. 2025 conducted a single-center, retrospective, observational study at Kansai University Medical Center in Japan between January 2022 and October 2024 that evaluated adult B-cell lymphoma patients diagnosed with SARS-CoV-2 infection that had received B-cell depleting treatment with anti-CD20 antibodies. After determining the SARS-CoV-2 subvariant, patients

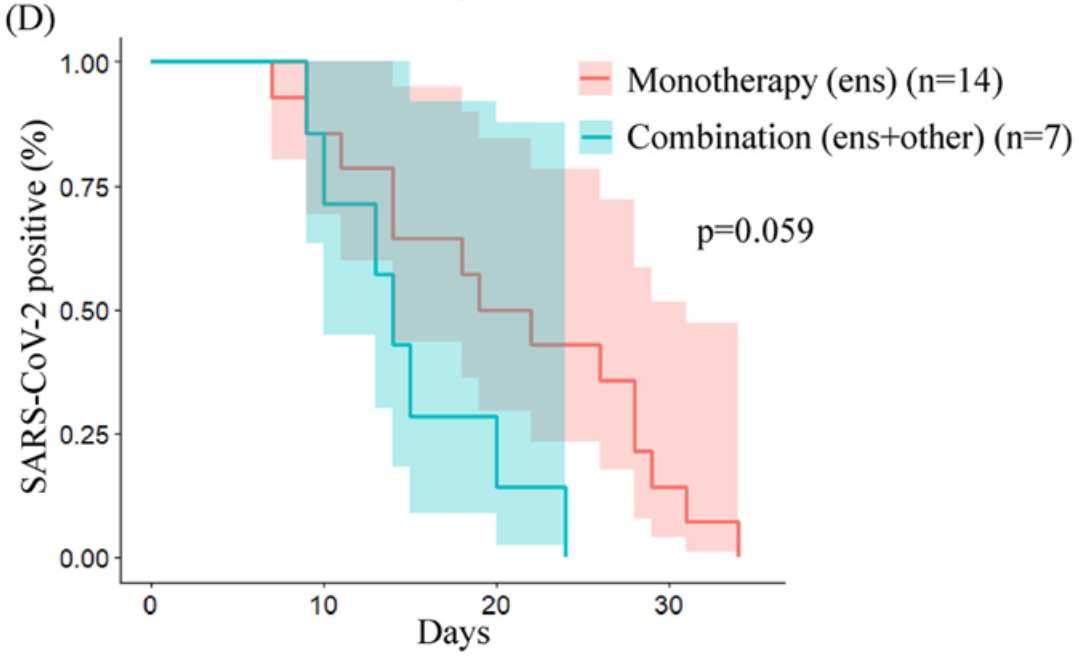
received targeted monoclonal antibodies and antivirals (ensitrelvir, molnupiravir, nirmatrelvir/ritonavir, or remdesivir) as monotherapy or in combination.[7]

- After testing, the subvariant was determined and the following drug regimens were provided; subvariant BA.1 received sotrovimab, subvariant BA.2 received imdevimab/casirivimab and subvariant BA.5 received wither imdevimab/casirivimab or tixagevimab/cilgavimab. Physicians then prescribed antivirals either as monotherapy or in combination which included ensitrelvir, molnupiravir, nirmatrelvir/ritonavir or remdesivir to target a viral load of <1 copy/μL/. Based on the viral loads determined, antiviral treatments were or either discontinued, changed or multiple agents were taken in combination. Steroids were given for pneumonia, and baricitinib for severe respiratory cases.[7]

Results

- Among 67 patients, 14 received ensitrelvir monotherapy and 7 received ensitrelvir in combination with another agent. Combination therapy (including with ensitrelvir) as the initial regimen significantly shortened the time to viral clearance (HR 0.36, 95% CI 0.20–0.65, P <0.001). Median antiviral treatment duration was 10 days (IQR 8–15), and median time from COVID-19 onset to viral clearance was 27 days (IQR 17–41).[7]
- Genome analysis showed drug-resistant NSP5 mutations (M49L, M49I, T25A, S144A) in 9 cases (64%) of patients after ensitrelvir monotherapy, but not after combination therapy.
- In a subgroup analysis of 40 patients who had a history of bendamustine treatment, a significantly shorter time to viral clearance occurred with combination treatment (*P*=0.044); ensitrelvir monotherapy (n=14) vs combination treatment of ensitrelvir and another agent (n=7), (*P*=0.059) as shown in **Figure 1**.[7]

Figure 1. Subgroup Analysis of SARS-CoV-2 Clearance in Patients Who Received Prior Bendamustine[7]



This table is adapted under a Creative Commons CC BY 4.0 International License specific to the article published by Elsevier Ltd: Maruyama et al. *J Infect Chemother*. 2025;31(7):102726.
Kaplan-Meier curves for SARS-Cov-2 clearance stratified by ensitrelvir monotherapy vs. ensitrelvir combination treatment with another drug.
Shaded area: 95% CI. P-values were calculated using the lob-rank test.

Study Design

- Yamato et al. 2025 conducted a single-center retrospective chart review (**Yamato et al. 2025**) evaluated patient characteristics, outcomes and treatment patterns in patients receiving ensitrelvir or remdesivir at Rinku General Medical Center in Japan between November 2022 and August 2024. Patients in the study received oral ensitrelvir 375 mg on Day 1 and 125 mg once a daily on Days 2-5 or IV remdesivir 200 mg on Day 1 and 100 mg once daily from Day 2 and up until Day 10.[8]
- All-cause mortality at Day 28, time to viral clearance up to Day 14 and time to discharge were endpoints assessed in this study. Subgroup analyses evaluated baseline COVID-19 severity, vaccination history and immunosuppressive conditions. Patients with immunosuppressive conditions were those patients with comorbidities including autoimmune disease and malignancies or patients taking concomitant drug therapy such as corticosteroids, methotrexate, rituximab and tacrolimus.[8]

Results

- There were 493 patients included in the analysis, 156 patients received ensitrelvir and 337 patients received remdesivir. Immunosuppressive conditions were present in 19.9% of the ensitrelvir group (31/156) and 16.0% of the remdesivir group (54/337). **Table 4** includes additional baseline characteristics pertaining to immunosuppression.[8]

Table 4. Baseline Immunosuppressive Characteristics[8]

Baseline Characteristic	Ensitrelvir n (%) (N=156)	Remdesivir n (%) (N=337)	Overall n (%) (N=493)
Chemotherapy	22 (14.1)	24 (7.1)	46 (9.3)
Immunosuppressive conditions	31 (19.9)	54 (16)	85 (17.2)

- All-cause mortality at Day 28 after IPTW modification was 3.8% and 5.7% for the ensitrelvir and remdesivir groups, respectively (HR: 0.66; 95% CI 0.19-2.29, E=2.4). In a subgroup analysis the non-adjusted all-cause mortality at Day 28 in immunosuppressive conditions was 3.2% (1/31) and 9.3% (3/54) in the ensitrelvir and remdesivir groups, respectively (HR: 0.34; 95% CI 0.04-2.91). The IPTW-adjusted all-cause mortality in immunosuppressive conditions was 5.3% (2.1/40) and 10.1% (4.5/44) in the ensitrelvir and remdesivir groups, respectively (HR: 0.52; 95% CI 0.06-4.51).[8] An analysis of patients taking chemotherapy was not provided.

Study Design

- A single-center, retrospective chart review (**Yamato et a. 2024**) assessed the outcomes of patients treated with ensitrelvir for SARS-CoV-2 infection in the Rinku General Medical Center (Izumisano, Japan) between November 2022 and April 2023.
- 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 (PCR) or antigen testing and investigator assessments of clinical improvement were used to assess effectiveness[9]

Results

- A total of 32 patients were included in the analysis, of which 10 (31.3%) patients were receiving corticosteroids, 1 (3.1%) patient was receiving immunosuppressants, and 2 (6.25%) patients received rituximab prior to ensitrelvir[9]
- The study included 2 patients with ANCA-associated vasculitis, 1 patient with AML, and 2 patients with HSCT (See **Table 5**)[10]

- Although Patient 9 (ANCA-associated vasculitis) and Patient 20 (AML) experienced viral rebound after end of ensitrelvir treatment, they were discharged from hospital on Day 11 and Day 9, respectively[9,10]
- All patients, including those who were immunocompromised, experienced clinical improvement as assessed by the investigator at the end of ensitrelvir treatment (Day 5)[9]
- No patients, including those who were immunocompromised, discontinued treatment, there were no TRAEs, no patients progressed to severe disease, none were admitted to the intensive care unit, and no treatment-related deaths occurred[9]
- Ensitrelvir treatment outcomes reported for individual immunocompromised patients are summarized in **Table 5**.[9,10]

Table 5. Virology Outcomes for Immunocompromised Patients in a Single-Center Chart Review[9,10]

Patient	Underlying Diseases	Prior SARS-CoV-2 Treatment	Days From Start of Ensitrelvir Administration															Treatment Outcome by Day 6[a]	Treatment Outcome at Final Measurement[a]	Viral Rebound
			Day -1 and Day 0	Day 1	Day 2	Day 3	Day 4	Day 5 (EOT)	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14			
			Quantitative Viral Antigen (pg/mL)																	
9[b,c]	AAV, CKD, DM, HTN	Remdesivir[d] Molnupiravir Tixagevimab/ cilgavimab	5000	5000		2587.88		4.77	1210.73		5000	5000	5000							Viral Rebound (at Day 6)
10[e]	Recurrent FL, post-HSCT, CKD, HTN, hemodialysis	Molnupiravir		1227.48		182.59	200.71													
20	Kidney stone disease, acute myelogenous leukemia, post-HSCT, kidney injury, HTN	None		5000[f]			5000	97.79		344.12	5000				4664.69					
24[b]	AAV, UTI, dyslipidemia, HTN	Remdesivir[d] Casirivimab/ imdevimab	5000	5000			223.72		2.37	8.01	5.99	41.02		1.23	0.01			Viral Clearance	Viral Clearance	

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Shading indicates days the patient was hospitalized.
Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; CKD, chronic kidney disease; DM, diabetes mellitus; EOT, end of treatment; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; HTN, hypertension; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 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 rituximab at Day -48. [d]Patient received ≥3 days of remdesivir.

VIRAL GENOME ANALYSIS IN PATIENTS WITH PERSISTENT INFECTION

Study Design

- A single-center, retrospective descriptive study (**Shimazu et al. 2023**) with no controls reported the clinical courses of 17 B-cell immunocompromised patients over the age of 18 with persistent SARS-CoV-2 infection between January 2022 and January 2023; 11 patients started COVID-19 treatment at the Kansai Medical University General Medicine Center in Osaka, Japan, and 6 patients had initial COVID-19 treatment at other hospitals but were transferred to Kansai Medical University General Medicine Center because of persistent infection. Persistent infection was defined as immunocompromised patients in whom isolation was not ended after more than 2 weeks since the onset of disease due to viral load rebound or persistently high levels of virus[11]
- All patients in the study underwent SARS-CoV-2 genome analysis before the start of treatment and again because of persistent infection[11]
- SARS-CoV-2 subvariants were identified for each patient using single nucleotide polymorphism PCR and treatment with neutralizing antibodies was selected based on published reports for the subvariant[11]
- Antiviral treatment for persistent COVID-19 was selected by each physician from among remdesivir, molnupiravir, nirmatrelvir/ritonavir, and ensitrelvir; 3 patients were treated with ensitrelvir[11]
- Antiviral effect was assessed by monitoring viral load during treatment, and treatment was ended when spike-specific antibody levels were sufficiently increased or when virus levels could no longer be detected by PCR[11]

Results

- As measured by the end of isolation, COVID-19 treatment was successful in 16/17 patients, including the 3 patients treated with ensitrelvir; 1 out of the 17 patients died of sepsis due to *Candida albicans*[11]
- Ensitrelvir treatment outcomes reported for immunocompromised patients who were treated with ensitrelvir are summarized in **Table 6**[11]
- All patients treated with ensitrelvir were considered to have severe or critical COVID-19 severity[11]
- Patient 8 (follicular lymphoma) was successfully treated with remdesivir followed by ensitrelvir. Genomic analysis after COVID-19 treatment showed several mutations including M49L, which has been previously observed to be resistant to ensitrelvir[11]
- Patient 10 (multiple myeloma) was treated with ensitrelvir and molnupiravir for COVID-19 before genomic analysis and ended isolation following treatment[11]
- Patient 15 (mucosa-associated lymphoid tissue [MALT] lymphoma) was initially treated with remdesivir and casirivimab/imdevimab and developed persistent COVID-19. Genomic analysis after COVID-19 treatment detected a G446S mutation (associated with resistance to imdevimab) and V166A mutation (associated with resistance to remdesivir). Administration of ensitrelvir along with molnupiravir and tixagevimab/cilgavimab resulted in a steady decrease of viral levels and end of isolation[11]

Table 6. Summary of Treatment Outcomes in Immunocompromised Patients with Persistent Infection Who Were Treated with Ensitrelvir[11]

Patient (age, y/sex)	Comorbidities	Severity of COVID-19	Immuno-suppressive drug therapy	COVID-19 treatment before genomic analysis[a]	Drug-resistant mutations after COVID-19 treatment	COVID-19 treatment after genomic analysis	Clinical outcome	PANGOLIN	Viral load Initial genomic analysis (copy/μL) (days after onset)	Viral load Subsequent genomic analysis (copy/μL) (days after onset)
8 (78/M)	Follicular lymphoma	Critical	Polatuzumab vedotin, rituximab, bendamustine	Tixagevimab/ cilgavimab before COVID-19 onset; remdesivir/ ensitrelvir	M49L R346S N450D	Not specified	Ended isolation	BA.5.2.1	34647 (0)	165652 (18)
10 (80/M)	Multiple myeloma	Severe	Pomalidomide, ixazomib	Ensitrelvir/ molnupiravir	—	Not specified	Ended isolation	BA.5.2.46	22116 (0)	2049 (33) 32566 (46)
15 (81/M)	MALT lymphoma	Critical	Rituximab, bendamustine	Remdesivir, casirivimab/ imdevimab	G446S V166A	Ensitrelvir	Ended isolation on Day 188	BA.5.2.1	-	31406 (173)

Abbreviations: COVID-19, coronavirus disease 19; GA, genomic analysis; M, male; MALT, mucosa-associated lymphoid tissue; PANGOLIN, Phylogenetic Assignment of Named Global Outbreak Lineages; y, years.
[a]Drug resistance as noted in a previous paper or manufacturer's fact sheet.

4. CASE PRESENTATIONS

Several reports on ensitrelvir treatment have described outcomes in individual SARS-CoV-2–infected immunocompromised patients. Details of these cases are summarized in **Table 7**[12-14]

Table 7. Summary of Ensitrelvir Treatment Outcomes in Individual Immunocompromised Patients

Study	Age/Sex	Vaccination Status	Medical History	COVID-19 Treatment in Addition/Prior to Ensitrelvir	Ensitrelvir Treatment	Treatment Outcomes
Case 1 (Furuya et al 2024)[12]	76/M	5 COVID-19 vaccinations	Mantle cell lymphoma, diabetes mellitus, and cerebral infarction Treatment with rituximab and bendamustine 6 years before COVID-19 onset; ibrutinib at time of COVID-19 onset	Molnupiravir on Days 1 to 2 of COVID-19 onset; remdesivir on Days 2 to 6, Days 22 to 26, and Days 46 to 50; dexamethasone on Days 40 to 46; tocilizumab on Day 47; sotrovimab on Day 52	Ensitrelvir 375 mg on Day 60, 125 mg on Days 61 to 64	• RT-qPCR improvement on Day 66 and negative conversion on Day 73 • Discharged from hospital on Day 84; no recurrence as of Day 208
Case 2 (Furuya et al 2024)[12]	78/M	5 COVID-19 vaccinations	Diffuse large B-cell lymphoma, hypertension, and cerebral infarction Treatment with CHOP 12 days before COVID-19 onset (Day -12), rituximab on Day -8, intrathecal chemotherapy (methotrexate, cytarabine, prednisolone) on Day -3	Remdesivir on Days 0 to 4 and Days 9 to 24 of COVID-19 onset; immunoglobulin replacement on Days 10 to 12; sotrovimab on Day 31	Ensitrelvir 375 mg on Day 36, 125 mg on Days 37 to 40	• RT-qPCR negative conversion on Days 42 to 43 • General improvement in condition and discharged to a nursing home

Study	Age/Sex	Vaccination Status	Medical History	COVID-19 Treatment in Addition/Prior to Ensitrelvir	Ensitrelvir Treatment	Treatment Outcomes
Case 3 (Jung et al 2023)[13]	59/F	3 COVID-19 vaccinations	Follicular lymphoma Treatment with obinutuzumab/ bendamustine 5 to 8 months before COVID-19 onset Receiving antimicrobial prophylaxis with levofloxacin, acyclovir, and atovaquone	Prophylactic tixagevimab/ cilgavimab 3 months before COVID-19 onset; molnupiravir on Day 1 of COVID-19 onset, later discontinued due to severe anorexia development; remdesivir on Days 2 to 6 and Days 32 to 34 due to persistent COVID-19	Dual antiviral therapy consisting of: • Ensitrelvir 375 mg on Day 32, tapered to 125 mg on Days 33 to 36 • Remdesivir 200 mg on Day 34, tapered to 100 mg on Days 35 to 36	• Clinical improvement on Day 36 • RT-qPCR negative conversion on Day 38 • Discharged from hospital on Day 38 with no adverse events reported
Case 4 (Sakamaki et al 2024)[14]	75/F	3 COVID-19 vaccinations	Grade 2, Stage IV follicular lymphoma Treatment with obinutuzumab/ bendamustine 1 year before SARS-CoV-2 infection, followed by obinutuzumab maintenance therapy	Prophylactic tixagevimab/ cilgavimab 2 weeks before SARS-CoV-2 infection	Ensitrelvir 375 mg on Day 1, 125 mg on Days 2 to 5 starting 7 weeks after SARS-CoV-2 infection detected	• Sharp decrease in viral load during ensitrelvir treatment • RT-PCR negative 1 week after initiation of ensitrelvir • Obinutuzumab maintenance therapy for lymphoma restarted due to low risk of SARS-CoV-2 recurrence • RT-PCR negative 6 months after ensitrelvir treatment
Case 5 (Haino et al 2026)[21]	67/M	4 COVID-19 vaccinations	• The patient had grade 2, stage IV follicular lymphoma and was treated with R-CHOP 8 years before SARS-CoV-2 infection. • Four years before infection, the patient started GB therapy followed by obinutuzumab maintenance therapy, which continued until 17 months before infection • Developed COVID-19 pneumonia 3 months prior current presentation treated with 10-day course of remdesivir and dexamethasone	Remdesivir 200 mg on Day 1, then 100 mg every day for 5 days and dexamethasone 6 mg QD for 10 days and oxygen at 2 L/min via a nasal cannula. Intravenous immunoglobulin 5000 mg administered on Days 12, 19, and 27. By Day 16 SARS-CoV-2 antigen levels rose to 3719 pg/mL, CRP levels increased from 1.8 to 4.1mg/dL, and there was no improvement in clinical symptoms, therefore dual antiviral therapy was started consisting of ensitrelvir and remdesivir.	Dual antiviral therapy consisting of: • Ensitrelvir 375 mg on Day 20, then 125 mg on Days 21 to 24 • Remdesivir 200 mg on Day 20, then 100 mg/day on Days 21 to 24	• Day 21: Oxygen supplementation was no longer required • Day 26: SARS-CoV-2 antigen level decreased from 3719 to 66.71 pg/mL and CRP improved to <1 mg/dL • Day 28: Chest CT showed significant improvement of pneumonia and CRP had normalized • Day 29: SARS-CoV-2 antigen level was <1.00 pg/mL[a] and patient was discharged

Study	Age/Sex	Vaccination Status	Medical History	COVID-19 Treatment in Addition/Prior to Ensitrelvir	Ensitrelvir Treatment	Treatment Outcomes
Case 6 (Sueda et al 2024)[22]	68/F	3 COVID-19 vaccinations	Follicular lymphoma in complete remission; received 6 cycles of GB induction chemotherapy (March–August 2021) followed by 8 cycles of obinutuzumab maintenance therapy through January 2023; impaired humoral immunity with B-cell depletion and hypogammaglobulinemia	• Due to persistent SARS-CoV-2 infection, the patient received multiple antiviral therapies, including an initial course of molnupiravir at COVID-19 diagnosis and a subsequent 5-day course of molnupiravir (800 mg twice daily) on day 81. Because of ongoing symptoms and recurrent fever, remdesivir was administered on day 96, followed by ensitrelvir on day 133 (375 mg on first day, then 250 mg daily for 4 days), which resulted in temporary virologic improvement; however, fever and respiratory symptoms recurred approximately 1 week after treatment completion. A second 10-day course of remdesivir was initiated on day 153, followed by additional 5-day courses of ensitrelvir on days 173 and 219 for recurrent pulmonary findings and symptoms.		• Although COVID-19 treatment was associated with transient clinical improvement and temporary viral suppression, the persistent infection ultimately resolved only after recovery of peripheral B cells approximately 15 months after COVID-19 onset
Case 7 (Seki et al 2024)[23]	85/F	1 dose	Patient hospitalized in the hematology ward with underlying Non-Hodgkin Lymphoma and had received anti-CD20+ B-cell depletion therapy	Initial treatment with remdesivir before recurrence; no additional concomitant therapy specified for this patient; Patient also received neutralizing antibody therapy	Ensitrelvir administered as the second treatment following COVID-19 recurrence after 9 days.	SARS-CoV-2 antigen level decreased from 867 IU before ensitrelvir treatment to 0.71 IU after ensitrelvir treatment; survived with no further relapse reported.
Case 8 (Seki et al 2024)[23]	88/F	4 doses	Patient hospitalized in the hematology ward with underlying Non-Hodgkin Lymphoma and had received anti-CD20+ B-cell depletion therapy	Initial treatment with remdesivir before recurrence; no additional concomitant therapy specified for this patient; Patient also received neutralizing antibody therapy	Ensitrelvir administered as the second treatment following COVID-19 recurrence after 9 days.	SARS-CoV-2 antigen level decreased from 661 IU before ensitrelvir treatment to 8.76 IU after treatment; survived with no further relapse reported

Abbreviations: BAL, bronchoalveolar lavage; BID, twice a day; CHOP, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine sulfate (Oncovin), and prednisone; COVID-19, coronavirus disease 19; CRP, C-Reactive Protein; F, female; GB, bendamustine and Obinutuzumab; HSC, hematopoietic stem cell; IL, interleukin; M, male; QD, once daily; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, real-time quantitative polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Below the detection limit

5. RELEVANT PPRESCRIBING 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.[24]

Contraindications

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[24]

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.[24]

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

- Hayashi N, Tsukimura E, Ogura E. Ensitrelvir for the treatment of COVID-19: Final analysis of a post-marketing surveillance from Japan. J Infect Chemother. Mar 2025;31(3):102574. doi:10.1016/j.jiac.2024.12.003
- Miyata Y, Yamaguchi R, Yamamoto T, et al. Drug-drug interaction between ensitrelvir and tacrolimus in a patient underoing treatment for COVID-19; a case report. J Pharm Health Care Sci. 2025;11(1):3. doi: 10.1186/s40780-025-00411-y.
- Ikeuchi K, Saito M, Okushin K, et al. Comparative effectiveness of antiviral treatment on household transmission of SARS-CoV-2: a retrospective cohort study using administrative data. BMC Infect Dis. 2025;25(1):1213. doi:10.1186/s12879-025-11651-6.
- Maruyama S, Wada D, Kanayama S, et al. The evaluation of risk factors for prolonged viral shedding during anti-SARS-CoV-2 monoclonal antibodies and long-term administration of antivirals in COVID-19 patients with B-cell lymphoma treated by anti-CD20 antibody. *BMC Infect Dis*. 2024;24(1):715. Doi: 10.1186/s12879-024-09631-3
- Naganawa H, Katada Y, Nakagawa S, et al. Influence of ensitrelvir or nirmatrelvir/ritonavir on tacrolimus clearance in kidney transplant recipients: a single-center case series. *J Pharm Health Care Sci*. 2024;10(1):37. doi: 10.1186/s40780-024-00361-x
- Ogura E, Nakagawa N, Hayashi N, Takashima S. Real-world safety and effectiveness of ensitrelvir in COVID-19 patients with risk factor a post-marketing surveillance in Japan. Poster presented at: IDWeek 2024; October 16-19, 2024; Los Angeles, CA.
- Omori K, Kitagawa H, Takamori A, et al. Antiviral combination therapy in severely immunocompromised patients with persistent or recurrent COVID-19. *J Infect Chemother.* 2025;31(10):102802. doi: 10.1016/j.jiac.2025.102802.
- Seki M, Kubosawa C, Ono M, Kamoshita F, Shimizu A, Mitsutake K. Clinical features of patients with COVID-19 recurrence during hospitalization in the omicron variant surge. *Infect Drug Resist*. 2024;17:5011-5015. doi: 10.2147/IDR.S485976.
- Takazono T, Fujita S, Komeda T, et al. Real-world effectiveness of ensitrelvir in reducing severe outcomes in outpatients at high risk for COVID-19. *Infect Dis Ther*. 2024;13(8):1821-1833. doi: 10.1007/s40121-024-01010-4

- Takikawa K, Sota M, Imai Y, et al. Efficacy of oral antivirals and combination therapy with remdesivir in hematological patients with COVID-19. *J Infect Chemother.* 2025;31(10):102805. doi: 10.1016/j.jiac.2025.102805.

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

AAV	ANCA-associated vasculitis	IPTW	inverse probability of treatment weighting
ACTG	AIDS Clinical Trials Group	IQR	interquartile range
ACTIV-2	Accelerating COVID-19 Therapeutic Interventions and Vaccines-2	ITT	intention-to-treat
AE	adverse event	IVIG	intravenous immunoglobulin
AML	acute myeloid leukemia	M	male
ANCA	anti-neutrophil cytoplasmic antibody	MALT	mucosa-associated lymphoid tissue
CHOP	cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine sulfate (Oncovin), and prednisone	mITT	modified intention to treat
CI	confidence interval	NIAID	National Institute of Allergy and Infectious Diseases
CKD	chronic kidney disease	NIH	National Institutes of Health
COVID-19	Coronavirus disease 19	OR	Odds ratio
CrCl	creatinine clearance	PANGOLIN	Phylogenetic Assignment of Named Global Outbreak Lineages
CYP3A	Cytochrome P450 3A	PCR	polymerase chain reaction
DM	diabetes mellitus	RNA	ribonucleic acid
DRS-60	Days to Recovery Scale through Day 60	RT-PCR	reverse transcription polymerase chain reaction
EOT	end of treatment	RT-qPCR	real-time quantitative polymerase chain reaction
F	female	SAE	serious adverse event
FDA	Food and Drug Administration	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
FL	follicular lymphoma	SCORPIO-HR	Stopping COVID-19 pRogression with early Protease InhibitOr-High Risk
GA	genomic analysis	SCORPIO-PEP	Stopping COVID-19 pRogression with early Protease InhibitOr- Post Exposure Prophylaxis
h	hours	SCORPIO-SR	Stopping COVID-19 pRogression with early Protease InhibitOr-Standard Risk
HDL	high-density lipoprotein	SoC	Standard of care
HHC	household contact	TEAE	treatment emergent adverse event
HIV	human immunodeficiency virus	RNA	ribonucleic acid
HR	hazard ratio	TRAE	treatment-related adverse event
HSC	hematopoietic stem cell	UTI	urinary tract infection
HSCT	hematopoietic stem cell transplant	y	years

REFERENCES

1. Hayden FG, Shinkai M, Clark TW, et al. Ensitrelvir to Prevent COVID-19 in Households: SCORPIO-PEP Phase III Placebo-Controlled Trial Results. Oral presentation presented at: CROI; March 9 - 12, 2025; San Francisco, CA.

2. Hayden FG, Ohmagari N, Clark TW, et al. Ensitrelvir for the prevention of COVID-19 among household contacts: key subgroup analyses of SCORPIO-PEP phase 3 study. Oral presentation presented at: ESCMID 2025; April 11 - 15, 2025; Vienna, Austria.
3. Ensitrelvir Data on File 5. Shionogi Inc.
4. Luetkemeyer AF, Chew KW, Lacey S, et al. Ensitrelvir for the treatment of nonhospitalized adults with COVID-19: results from the SCORPIO-HR, phase 3, randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2025;doi:/10.1093/cid/ciaf029/8017725
5. Yotsuyanagi H, Ohmagari N, Doi Y, et al. Efficacy and safety of 5-day oral ensitrelvir for patients with mild to moderate COVID-19 the SCORPIO-SR randomized clinical trial. *JAMA Netw Open*. 2024;7(2):e2354991. doi:10.1001/jamanetworkopen.2023.54991.
6. Baker JV, Siegel L, Losso M, et al. Ensitrelvir for the treatment of hospitalized adults with COVID-19: an international phase 3 randomized placebo-controlled trial. *Clin Infect Dis*. Apr 22 2026;doi:10.1093/cid/ciag272
7. Maruyama S, Wada D, Inoue A, et al. Efficacy of initial combination therapy with anti-SARS-CoV-2 antivirals targeting viral clearance in COVID-19 patients with B-cell lymphoma treated with anti-CD20 antibodies: A retrospective single-centre study in Japan. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*. 2025;31(7):102726. doi:10.1016/j.jiac.2025.102726
8. Yamato M, Kinoshita M, Yoshida Y, Yamamoto Y, Izuhara R, Sonoyama T. Ensitrelvir in hospitalised patients with SARS-CoV-2 during the omicron epidemic: a single-center observational study. Poster presented at: ESCMID 2025; April 11 - 15, 2025; Vienna, Austria.
9. Yamato M, Kinoshita M, Miyazawa S, Seki M, Mizuno T, Sonoyama T. Ensitrelvir in patients with SARS-CoV-2: A retrospective chart review. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*. 2024;doi:10.1016/j.jiac.2024.02.015
10. Yamato M, Kinoshita M, Miyazawa S, Seki M, Mizuno T, Sonoyama T. Ensitrelvir in patients with SARS-CoV-2: A retrospective chart review. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*. 2024;(Suppl)doi:10.1016/j.jiac.2024.02.015
11. Shimazu H, Wada D, Maruyama S, et al. Clinical experience of treatment of immunocompromised individuals with persistent SARS-CoV-2 infection based on drug resistance mutations determined by genomic analysis: a descriptive study. *BMC infectious diseases*. 2023;23(1):780. doi:10.1186/s12879-023-08797-6
12. Furuya C, Yasuda H, Hiki M, et al. Case report: Ensitrelvir for treatment of persistent COVID-19 in lymphoma patients: a report of two cases. *Front Immunol*. 2024;15:1287300. doi:10.3389/fimmu.2024.1287300
13. Jung S, Yagi Y, Fukushima K, et al. Successful dual antiviral therapy with remdesivir and ensitrelvir in a case of prolonged COVID-19 following B-cell depleting immunotherapy for malignant lymphoma. *IDCases*. 2023;34:e01890. doi:10.1016/j.idcr.2023.e01890
14. Sakamaki I, Negoro E, Iwasaki H, Yamauchi T. Ensitrelvir eradicates persistent SARS-CoV-2 infection in a follicular lymphoma patient treated with anti-CD20 antibodies. *J Infect Chemother*. 2024;30(2):147-149. doi:10.1016/j.jiac.2023.09.008
15. Phase 3 study of S-217622 in prevention of symptomatic SARS-CoV-2 infection (SCORPIO-PEP). NLM Identifier: NCT05897541. Last accessed June 18, 2025. https://clinicaltrials.gov/study/NCT05897541?term=scorpio-pep&rank=1.
16. Luetkemeyer AF, Chew KW, Lacey S, et al. Ensitrelvir for the treatment of nonhospitalized adults with COVID-19: results from the SCORPIO-HR, phase 3, randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. Feb 17 2025;doi:10.1093/cid/ciaf029
17. A study to compare S-217622 with placebo in non-hospitalized participants with COVID-19 (SCORPIO-HR). Accessed March 6, 2023. https://clinicaltrials.gov/ct2/show/NCT05305547?term=nCT05305547&draw=2&rank=1
18. Ensitrelvir Data on File 9. Shionogi Inc.

19. A phase 2/3 study of S-217622 in participants with SARS-CoV-2 infection. Accessed March 11, 2024. https://jrct.niph.go.jp/en-latest-detail/jRCT2031210350.
20. Yotsuyanagi H, Ohmagari N, Doi Y, et al. Efficacy and safety of 5-day oral ensitrelvir for patients with mild to moderate COVID-19 the SCORPIO-SR randomized clinical trial. *JAMA Netw Open*. 2024;7(2)(Suppl):e2354991. doi:10.1001/jamanetworkopen.2023.54991.
21. Haino Y, Kenzaka T, Hayashi T, Yakushijin K. Successful Treatment of Persistent and Relapsing COVID-19 with Ensitrelvir in a Patient with Obinutuzumab-Induced Long-Term B-Cell Depletion: A Case Report. *Reports (MDPI)*. Mar 18 2026;9(1)doi:10.3390/reports9010089
22. Sueda Y, Tokuyasu H, Atsuta M, et al. Persistent SARS-CoV-2 infection resolved after B-cell recovery in a patient with follicular lymphoma treated with B-cell depletion therapy. *Respir Med Case Rep*. 2024;52:102131. doi:10.1016/j.rmcr.2024.102131
23. Seki M, Kubosawa C, Ono M, Kamoshita F, Shimizu A, Mitsutake K. Clinical features of patients with COVID-19 recurrence during hospitalization in the omicron variant surge. *Infect Drug Resist*. 2024;17:5011-5015. doi:10.2147/idr.S485976
24. XOCOVA® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.
25. Hayden FG, Shinkai M, Clark TW, et al. Ensitrelvir for Covid-19 postexposure prophylaxis in household contacts. *New England Journal of Medicine*. 2026;394(19):1905-1915. doi:10.1056/NEJMoa2509306.

ENCLOSURE

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

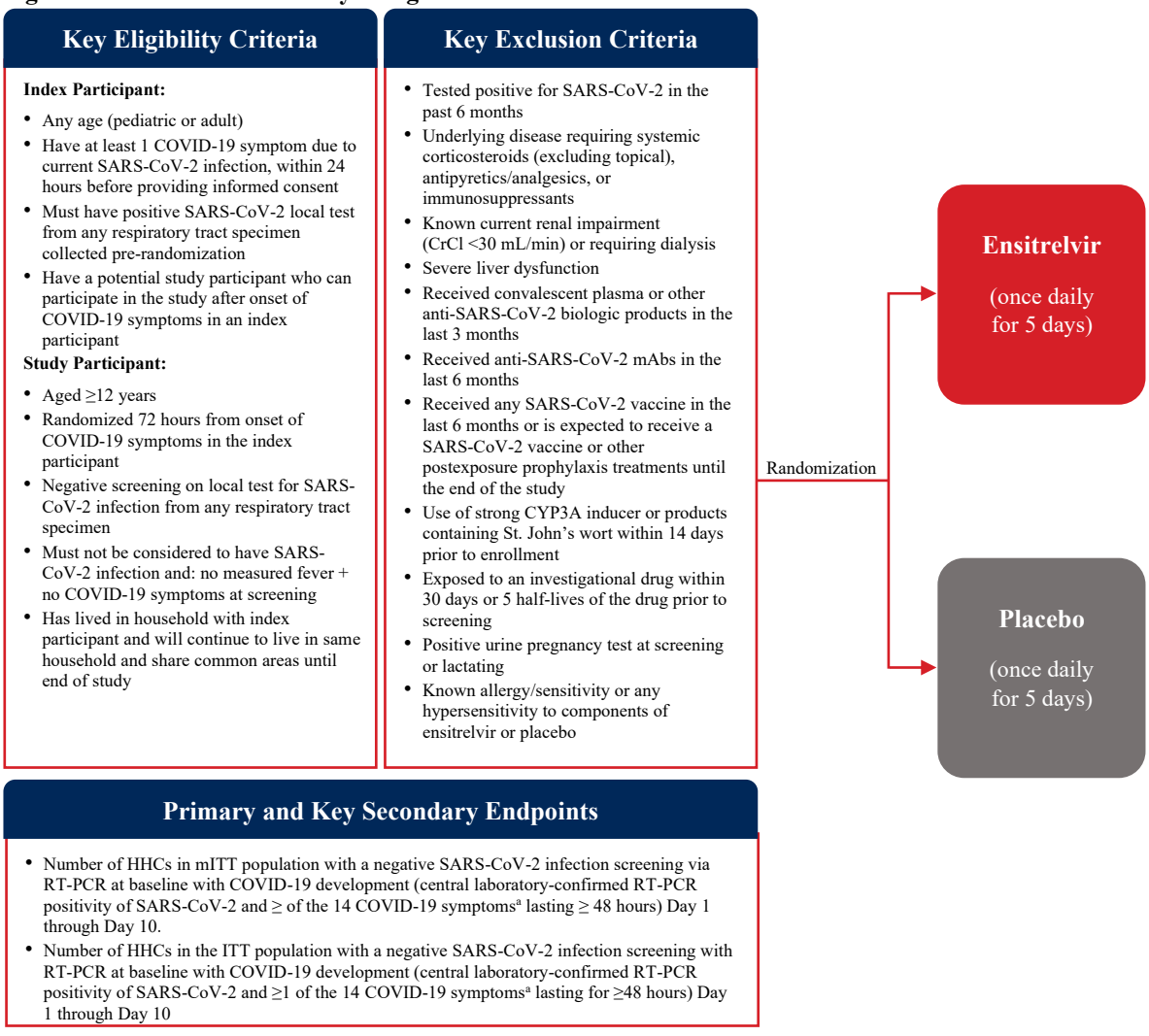
APPENDIX

SCORPIO-PEP (Global Phase 3 Study)

HHC participants with a negative screening test for SARS-CoV-2 infection and no symptoms (mITT population), who were exposed to a person living in their household with symptomatic COVID-19, were randomly assigned in a 1:1 ratio to receive ensitrelvir 125 mg (375 mg on Day 1 and 125 mg on Days 2-5) or placebo once daily for 5 days. Study participants began treatment within 3 days of when the household member with COVID-19 began showing symptoms.[25]

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.[15,25]

Figure 1. SCORPIO-PEP Study Design[15,25]



Abbreviations: COVID-19, coronavirus disease 19; CYP3A, cytochrome P450 enzyme 3A4; mITT, modified Intention-to-Treat; RT-PCR, Reverse transcriptase polymerase chain reaction SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Note: mITT population included all randomized HHCs with a central laboratory-confirmed SARS-CoV-2 negative result by RT-PCR at baseline. Patients with local (-) and central (+) were excluded from mITT population.
[a]14 COVID-19 symptoms: Stuffy nose, runny nose, cough, sore throat, low energy or tiredness, feeling hot or feverish, shortness of breath or difficulty breathing, chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, loss of taste and loss of smell

Results

Efficacy

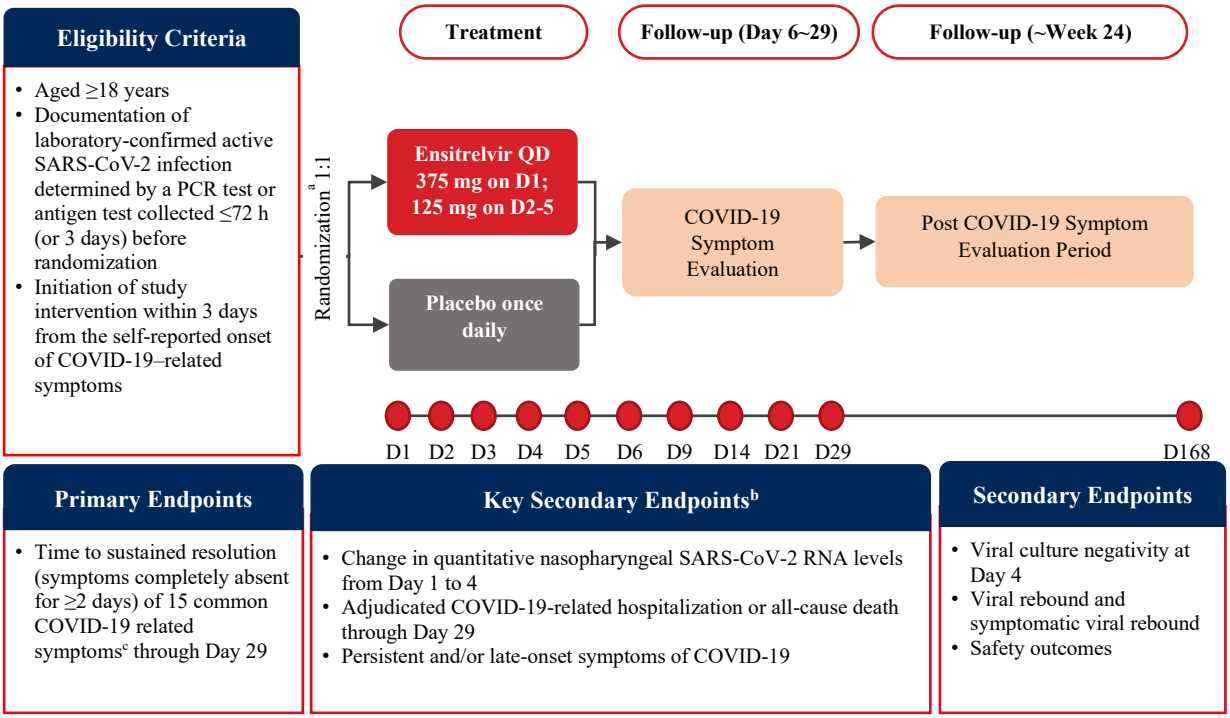
- **Primary Endpoint**: 2.9% (30/1030) of HHCs in the ensitrelvir group developed symptomatic COVID-19 compared to 9.0% (91/1011) of HHC participants on placebo through Day 10, a 67% reduction in the risk of developing COVID-19 (risk ratio: 0.33; 95% CI: 0.22-0.49; $P < 0.0001$) in uninfected individuals (mITT population) treated after exposure[25]

Safety

- TEAEs occurred in 15.1% (180/1190) of patients in the ensitrelvir group and 15.5% (184/1187) of patients in the placebo group, with 1 event in each group leading to discontinuation of treatment[25]
- 2 serious TEAEs occurred in each group and they were considered to be unrelated to the study drug[25]
- There were no AEs that led to hospitalization and no deaths were observed in either group[25]

SCORPIO-HR (Global Phase 3 Study)

Figure 2. SCORPIO-HR Study Design[4,17]



Abbreviations: COVID-19, coronavirus disease; D, day; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]N=~2000; ~1000 patients in each treatment arm
[b]Primary and key secondary endpoints were tested using a fixed-sequence hierarchical approach at two-sided significance level of 0.05.
[c]15 COVID-19 symptoms: stuffy nose, runny nose, cough, sore throat, low energy or tiredness, feeling hot or feverish, shortness of breath or difficulty breathing, chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, loss of taste and loss of smell.

Results

Efficacy

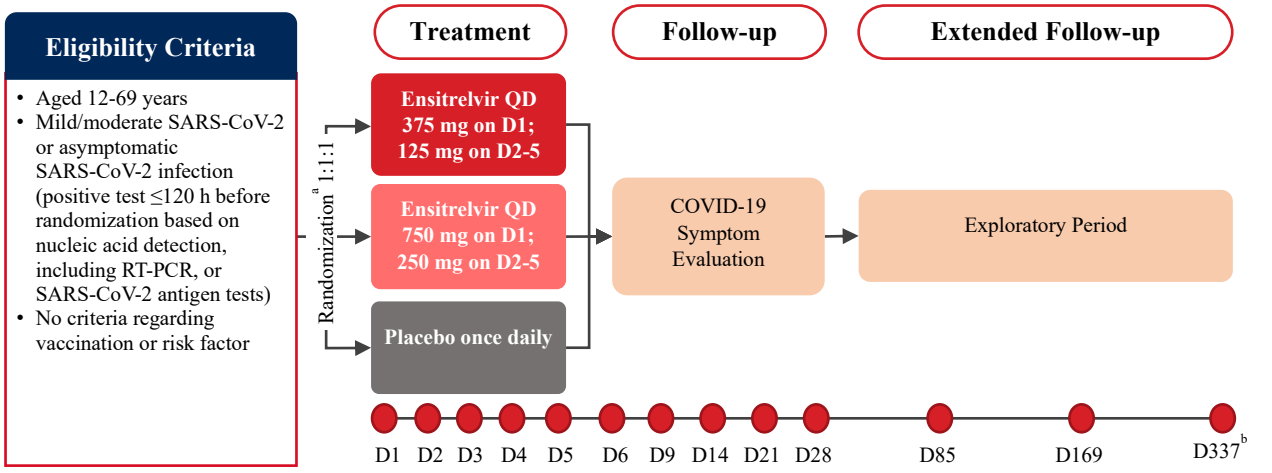
- **Primary Endpoint:** In the modified intent-to-treat (mITT) population, the restricted mean time to sustained symptom resolution was not significantly different between the ensitrelvir (12.5 days) and placebo (13.1 days) groups (difference, -0.6 days; 95% CI: -1.38, 0.19; *P*=0.14).[4]

Safety

- AEs occurred in 638 patients treated with ensitrelvir (61.5%; n=1037), and 635 patients treated with placebo (60.6%; n=1048).[4]
- TRAEs occurred in 86/1037 (8.3%) of patients treated with ensitrelvir and 74/1048 (7.1%) of patients that were given placebo.[4]
- Serious TEAE occurred in 5/1037 (0.5%) of the ensitrelvir-treated participants and 6/1048 (0.6%) of the patients given placebo.[4]
- 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.[4]

SCORPIO-SR (Phase 3 Study)

Figure 3. Phase 2/3 Study, Phase 3 Part[5,20]



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

Results

- **Primary Endpoint:** The time to resolution of 5 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 8.**[5]
- Most adverse events (AEs) were mild in severity, and a decrease in high-density lipoprotein (HDL) was the most commonly reported AE and treatment-related adverse event (TRAE). There were 2 serious adverse events (SAE) reported in the study (1 in the ensitrelvir 125 mg arm and 1 in the placebo arm), both of which were judged as not treatment related.[5]

Table 8. Phase 3 Part: Time to Resolution of 5 COVID-19 Symptoms[5,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 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.