Xocova – Use in a Geriatric Population

SHIONOGI

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Overview

- XOCOVA (ensitrelvir) is indicated for post-exposure prophylaxis of COVID-19 in adults and adolescents aged ≥12 years following contact with an individual who has COVID-19.[1]
- The overall safety and efficacy assessment of ensitrelvir included data from clinical studies assessing subjects aged ≥65 years, for either post-exposure prophylaxis or treatment of COVID-19. Among these studies, the SCORPIO-PEP trial included 10% (114/1190) of ensitrelvir-treated subjects aged ≥65 years, and 3% (41/1190) aged ≥75 years. No overall differences in efficacy or safety were observed between the geriatric and younger patients; however, greater sensitivity in some older individuals cannot be ruled out.[1]

Clinical Studies

- In the Phase 3 **SCORPIO-PEP** study evaluating post-exposure prophylaxis in HHCs exposed to SARS-CoV-2 infection, ensitrelvir significantly reduced the risk of symptomatic COVID-19 vs placebo in the overall mITT population at Day 10 (primary endpoint: 2.9% [30/1030] vs 9% [91/1011]; RR 0.33, 95% CI: 0.22–0.49, *P*<0.0001). TEAEs occurred in 15.1% (180/1190) and 15.5% (184/1187) of patients in ensitrelvir and placebo groups, respectively.[2]
  - In a descriptive subgroup analysis of geriatric patients in the mITT population aged ≥65 years, symptomatic COVID-19 occurred in 3% (3/99) patients treated with ensitrelvir vs 12.2% (11/90) patients treated with placebo (RR 0.25, 95% CI: 0.08–0.82).
  - Safety outcomes were not stratified by age in the reported subgroup analysis.

- In the Phase 3 **SCORPIO-HR** study in nonhospitalized patients with COVID-19, the primary endpoint (time to sustained resolution of 15 common COVID-19-related symptoms) demonstrated a numerical but not statistically significant reduction with ensitrelvir vs placebo in the mITT population; from mITT, 99 patients were aged ≥65 years. AEs occurred in 61.5% (638/1037) of patients treated with ensitrelvir and in 60.6% (635/1048) of patients treated with placebo.[3,4]
  - In an exploratory analysis of patients aged ≥65 years, 100% (20/20) of patients treated with ensitrelvir had a negative SARS-CoV-2 viral culture on Day 4 vs 82.6% (19/23) in the placebo group.[5]
  - In the HR subgroup (mITT set), 1 (0.3%) geriatric patient in the placebo group died due to an SAE.[6]

- In the Phase 3 **SCORPIO-SR** study (part of Phase 2/3 study), ensitrelvir significantly reduced the time to resolution of 5 COVID-19 symptoms vs placebo in the ITT population (primary endpoint; *P*=0.04 with a Peto-Prentice generalized Wilcoxon test). Most TEAEs were mild in severity, and a decrease in HDL was the most commonly reported TEAE.[7]
  - Patients aged ≥65 years were comparable across groups and represented a small proportion of the study population; however, the efficacy outcomes were not stratified by age.[7,8]
  - Among geriatric patients with mild/moderate COVID-19, TEAEs were reported in 20% (1/5) of patients receiving ensitrelvir 125 mg, 28.6% (2/7) receiving ensitrelvir 250 mg, and 37.5% (3/8) receiving placebo; no deaths, SAEs, or discontinuations due to TEAEs were observed.[9]

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Clinical Studies (Cont.)

- In one part of the **Phase 1** study evaluating the PK, safety, and tolerability of ensitrelvir 375/125 mg (n=11) or placebo (n=5) in healthy elderly Japanese participants aged ≥65 years, the mean plasma concentration (C_{max}) was observed to be 19.7 µg/mL on Day 1 and 23.8 µg/mL on Day 5; AUC_{0-7} increased 1.4-fold (319.2 µg·h/mL on Day 1 to 446.1 µg·h/mL on Day 5). TEAEs occurred in 54.5% (6/11) of participants, most commonly observing reduced HDL cholesterol; no serious TEAEs or deaths were reported.[10]

Real-World Studies

- **Takazono et al (2024)** conducted a retrospective cohort study comparing ensitrelvir-treated nonhospitalized patients (n=5177) with patients who did not receive antiviral treatment (n=162,133). The primary analysis population included adults aged ≥18 years with ≥1 risk factor for severe COVID-19, including geriatric patients aged ≥65 years. Ensitrelvir treatment was associated with lower incidences of all-cause hospitalization (primary endpoint), respiratory and heart rate monitoring, and oxygen therapy. In a post-hoc analysis of HR patients aged ≥65 years, all-cause hospitalization was lower with ensitrelvir vs no antiviral treatment (0% [0/380] vs 1.298% [199/15,336]; *P*=0.0166). No safety-related subgroup analyses were reported separately for patients aged ≥65 years.[11]
- **Yoshida et al (2024)** conducted a retrospective observational study comparing remdesivir, molnupiravir, or ensitrelvir in hospitalized patients with COVID-19 (N=154). The mean age was 83.7 years, with many admitted for comorbidities including CV disease, diabetes, dyslipidemia, CKD, chronic liver disease, COPD, cancer, and stroke. Viral antigen levels, antigen-negative conversion rate after Day 10, and duration of hospitalization were all lower in the ensitrelvir group vs the remdesivir and molnupiravir groups. No significant differences were observed in fever resolution times between groups; no safety outcomes were reported.[12]
- **Yamato et al (2024)** conducted a retrospective chart review of 32 hospitalized patients treated with ensitrelvir in Japan. The mean age was 73.5 years, and 78.1% were aged ≥65 years. By Day 6, viral clearance was observed in 56.3% (18/32) of patients, increasing to 78.1% (25/32) at final assessment. No patients discontinued treatment, progressed to severe disease, or were admitted to the ICU, or experienced TRAEs or deaths.[13]
- **Tomita et al (2024)** conducted a retrospective chart review in 9 hospitalized female patients with mild COVID-19 and a mean age of 90.2 years. All received ensitrelvir within 2 days of symptom onset and completed the 5-day course without progression to severe disease. Fever resolved within 4 days in all febrile patients, and none required oxygen therapy or additional antivirals. No AEs, discontinuations, or deaths were reported during the 14-day follow-up.[14]

Surveillance Studies

- **Hayashi et al (2024)** conducted a post-marketing surveillance study evaluating ensitrelvir in Japanese clinical practice, including 452/3760 (12%) in the safety analysis set who were aged ≥65 years. The median time to resolution of all symptoms was 144 hours for HR patients, compared to 168 hours for SR patients. Among the geriatric subgroup, the median time to fever resolution was 24 hours, and the median time to resolution of all symptoms was 108 hours. The study reported that ensitrelvir was generally well tolerated, with no new identified safety concerns. A higher incidence of ADRs was reported in patients with comorbidities vs those without comorbidities (10.2% vs 6.4%, *P*=0.0002). No separate ADR analysis was reported for the geriatric subgroup.[15]

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Relevant Prescribing Information

Indications and Usage[1]

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.

Contraindications[1]

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

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.

Use in Specific Populations[1]

Geriatric Use

Clinical studies of XOCOVA included subjects 65 years of age and older, and their data contributes to the overall assessment of safety and efficacy. Among XOCOVA recipients in Trial SCORPIO-PEP, 114 (10%) were 65 years of age or older, and 41 (3%) were 75 years of age and older. No overall differences in efficacy and safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in safety between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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 FDA is not recommended.

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SCORPIO-PEP



Study Design

SCORPIO-PEP (NCT05897541) is a global Phase 3 trial that evaluated the safety and efficacy of ensitrelvir in preventing symptomatic SARS-CoV-2 infection in HHCs of people who tested positive for COVID-19, conducted from June 2023 to September 2024, across the US, Japan, Vietnam, Argentina, and South Africa.[2]

HHC participants aged ≥12 years with a negative local 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 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.[2]

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.[2]

Results

Baseline Characteristics

The total mITT population included 1030 HHCs treated with ensitrelvir and 1011 HHCs who received a placebo. The baseline demographics and characteristics of the HHCs in the ensitrelvir and placebo groups were similar, and the majority of participants were in the US (67.2% and 67.6%, respectively). A total of 99 (9.6%) geriatric patients (≥65 years) were included in the ensitrelvir group and 90 (8.9%) in the placebo group.[2]

Efficacy

- **Primary Endpoint**: 2.9% (30/1030) of HHCs in the ensitrelvir group developed symptomatic COVID-19 compared to 9% (91/1011) of HHC participants on placebo through Day 10, a 67% reduction in the risk of developing COVID-19 (RR 0.33, 95% CI: 0.22–0.49; $P<0.0001$) in uninfected individuals (mITT population) treated after exposure.[2]
- **Geriatric Patients**: In a subgroup analysis of geriatric patients in the mITT population aged ≥65 years, ensitrelvir significantly reduced the risk of developing COVID-19 compared with placebo (3% [3/99] vs 12.2% [11/90]; RR 0.25, 95% CI: 0.08–0.82). These results are descriptive and should be interpreted with caution.[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 in the SAS, with 1 event in each group leading to discontinuation of treatment.[2]
- 2 serious TEAEs occurred in each group, and they were considered to be unrelated to the study drug.[2]
- There were no AEs that led to hospitalization, and no deaths were observed in either group.[2]
- **Geriatric Patients**: Safety outcomes were not stratified by age in the reported subgroup analysis.

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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 (375 mg orally on Day 1 and 125 mg orally once daily on Days 2–5) vs placebo in nonhospitalized patients aged ≥18 years with COVID-19 with or without HR factors for severe COVID-19.[3,4,16]

This study was conducted across North America, South America, Europe, Asia, and Africa. It is a part of the ACTIV-2 clinical trials portfolio, overseen by the ACTG and supported by the NIH. This study was conducted when the Omicron variant infection was predominant among a mostly vaccinated population.[3,4,16]

The mITT population was the primary analysis population, and it was defined as all patients who were randomized and received ≥1 dose of treatment ≤3 days from when symptoms began. The study enrolled participants ≥18 years of age, including those ≥65 years of age.[3,4]

Results

Baseline Characteristics

In the mITT analysis set (N=1888), 99 patients (5.2%) were aged ≥65 years (5.2% [n=49] in the ensitrelvir group and 5.3% [n=50] in the placebo group).[6]

Efficacy

- **Primary Endpoint**: In the mITT population, the restricted mean time to sustained symptom resolution was not significantly different between the ensitrelvir (12.5 days) and placebo (13.1 days) groups (difference, 0.6 days; 95% CI: –1.38–0.19; *P*=0.14).[3]
- **Geriatric Patients**: In an exploratory analysis of patients aged ≥65 years 20/20 (100%) of participants treated with ensitrelvir had a negative SARS-CoV-2 viral culture on Day 4 vs 19/23 (82.6%) in the placebo arm.[5]

Safety

- AEs occurred in 638 patients treated with ensitrelvir (61.5%; n=1037), and 635 patients treated with placebo (60.6%; n=1048).[3]
- No serious TRAEs occurred in either group.[3]
- COVID-19-related hospitalization was observed in 3/1037 (0.3%) ensitrelvir-treated patients and 1/1048 (0.1%) placebo-treated participant.[3]
- No deaths were observed in either group.[3]
- **Geriatric Patients**: In the HR subgroup (mITT set), 1 (0.3%) geriatric patient in the placebo group died due to an SAE.[6]

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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 (jRCT2031210350) that evaluated the efficacy (clinical symptom improvement and antiviral effect) and safety of ensitrelvir administered orally, 375 mg on Day 1 and 125 mg once daily on Days 2–5, in patients aged 12–69 years with SARS-CoV-2 infection. SCORPIO-SR was conducted in Japan, South Korea, and Vietnam during when the Omicron BA.1 variant was dominant, between February to July 2022.[7]

The primary endpoint was time to resolution of the composite of 5 COVID-19 symptoms from the ITT population (all patients who tested positive for SARS-CoV-2 RNA at baseline).[7]

Results

Baseline Characteristics

The proportion of patients aged ≥65 years were few and comparable across treatment groups.[8]

- Among patients randomized within 120 hours after disease onset, 4/603 (0.7%) patients in the ensitrelvir 125 mg group, 5/595 (0.8%) patients in the ensitrelvir 250 mg group, and 7/600 (1.2%) patients in the placebo group were aged ≥65 years.[8]
- Among patients randomized <72 hours after disease onset, 2/347 (0.6%) patients in the ensitrelvir 125 mg group, 2/340 (0.6%) patients in the ensitrelvir 250 mg group, and 2/343 (0.6%) patients in the placebo group were aged ≥65 years.[8]

Efficacy

- **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). Median time to symptom resolution was 167.9 hours, 171.2 hours, and 192.2 hours for ensitrelvir 125 mg (n=347), ensitrelvir 250 mg (n=340), and placebo (n=343) groups, respectively.[7]
- **Geriatric Patients**: Outcome analyses were not stratified by age; hence, geriatric-specific outcomes are not available.

Safety

- Most TEAEs were mild in severity, and a decrease in HDL was the most commonly reported TEAE.[7]
- TEAEs occurred in 44.2% (267/604) of patients in ensitrelvir 125 mg arm, with 24.5% being treatment-related, 53.6% (321/599) of patients in ensitrelvir 250 mg arm, with 36.2% being treatment-related, and 24.8% (150/605) in placebo arm, with 9.9% being treatment-related.[7]
- There were 2 SAEs 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.[7]
- **Geriatric Patients**: Among geriatric patients with mild/moderate COVID-19, TEAEs were reported in 1 of 5 (20%) patients receiving ensitrelvir 125 mg, 2 of 7 (28.6%) receiving ensitrelvir 250 mg, and 3 of 8 (37.5%) receiving placebo, with no deaths, SAEs, or discontinuations due to TEAEs observed.[9]

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Phase 1 PK Study

Study Design

This was a Phase 1, multicenter, double-blind, randomized, placebo-controlled study (jRCT2031210202) conducted to evaluate the safety, tolerability, and PK of ensitrelvir in healthy participants across diverse demographic populations. The study comprised several parts, including 1 conducted in:[10]

- Healthy Japanese **elderly participants** (≥65 years; 375/125 mg cohort only)

Participants received ensitrelvir 375 mg on Day 1, followed by 125 mg once daily on Days 2–5.[10]

Results

Baseline Characteristics

- A total of 16 healthy participants were enrolled, of whom 11 received ensitrelvir and 5 received placebo. The median age was 73 years, and the median BMI was 22.8 kg/m^2.[10]

PK Data

- Following multiple-dose administration of ensitrelvir 375/125 mg in elderly participants, C_{max} values were 19.7 µg/mL on Day 1 and 23.8 µg/mL on Day 5, while the $AUC_{0-\tau}$ increased from 319.2 µg·h/mL on Day 1 to 446.1 µg·h/mL on Day 5, representing a 1.4-fold increase.[10]
- The median time to reach C_{max} was 2 hours on Day 1 and 3 hours on Day 5.[10]
- $t_{1/2z}$ was 58.9 hours on Day 5.[10]
- C_{24} was 11.5 µg/mL on Day 1 and 17.1 µg/mL on Day 5.[10]

Safety

- TEAEs were reported in 6 of 11 (54.5%) participants receiving ensitrelvir.[10]
- The most common TEAEs included decreased HDL cholesterol (5 participants), nausea, headache, and mild transient increases in C-reactive protein and creatine phosphokinase (1 participant each).[10]
- No serious TEAEs or deaths were reported.[10]

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Retrospective Cohort Study in Nonhospitalized Patients

Takazono et al (2024) conducted a retrospective cohort study analyzing a large database of health insurance claims to assess the 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. Outpatient individuals were included if they were aged ≥18 years and could be tracked for 6 months before diagnosis with COVID-19, up to 1 month following that date.[11]

The primary analysis target population consisted of patients with ≥1 risk factor for severe COVID-19 disease according to MHLW COVID-19 guidelines. Risk factors for severe disease included age ≥65 years, malignancy, chronic pulmonary disease, diabetes, chronic renal disease, hypertensive disease, CV disease, dyslipidemia, cerebrovascular disease, morbid obesity, immunosuppressive disorders, and HIV/AIDS.[11]

The primary endpoint was all-cause hospitalization (starting on Days 2–28), and secondary endpoints included respiratory and heart rate monitoring, oxygen therapy, ventilator use, ICU admission, each starting on Days 2–28 and all-cause death, within the following month.[11]

Results

Baseline Characteristics

- Baseline demographic and clinical characteristics in the HR population were similar for ensitrelvir-treated patients and those patients who did not receive antiviral treatment.[11]
- A total of 167,310 eligible HR 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. **Patients ≥65 years of age** were enrolled.[11]

Study Results

- After IPTW adjustment, the incidence of all-cause hospitalization (primary endpoint) was significantly lower in HR 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]).[11]
  - In a post-hoc analysis of **HR 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).[11]
- Incidence of respiratory and heart rate monitoring (secondary endpoint) was lower in HR patients who received ensitrelvir compared with no antiviral treatment (0.143% vs 0.269%; RR, 0.531 [95% CI: 0.26–11.081]; RD, −0.126 [95% CI: −0.230 to −0.022]).[11]
- Incidence of oxygen therapy (secondary endpoint) was lower in HR 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: −0.141–0.032]).[11]
- Due to the small number of unadjusted incidences (0–2 cases), it was difficult to assess other secondary endpoint events, including ventilator use, ICU admission, and all-cause death.[11]
- The incidence of all-cause hospitalization was suppressed in ensitrelvir-treated patients, and the 95% CI of each group had no overlap from Day 2 to Day 12.[11]
  - No safety-related subgroup analyses were reported separately for **patients aged ≥65 years**.

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Retrospective Observational Comparative Study in Hospitalized Patients

Yoshida et al (2024) conducted a retrospective observational study using real-world data from electronic health records and patient follow-ups to compare the effectiveness of 3 antiviral drugs in patients who were diagnosed with COVID-19 and required hospitalization. Remdesivir, molnupiravir, or ensitrelvir were selected by the attending physician and administered to patients, post-admission to Yoshida Hospital in Asahikawa City, Japan, between July 1, 2022, and September 15, 2023. Outcomes were assessed by measuring SARS-CoV-2 antigen levels, duration of hospitalization, and time to fever resolution.[12]

Results

Baseline Characteristics

- Overall, baseline demographic and clinical characteristics were generally similar across the remdesivir, molnupiravir, and ensitrelvir groups, although some differences were observed in age distribution, CKD prevalence, and prior hospitalization rates.[12]
- The study included 154 patients, 85 received remdesivir, 44 received molnupiravir, and 25 received ensitrelvir:[12]
  - Due to many of the patients being referred from chronic care facilities and nursing homes, the average age of the study population was 83.7 (range, 53–104) years.[12]
    - Of the 25 patients receiving ensitrelvir, 24 (96%) were **aged ≥60 years**; specifically, 7 in their 70s, 10 in their 80s, and 4 in their 90s.[12]

Efficacy

- On Day 10 of antiviral treatment, viral antigen levels were lower in patients treated with ensitrelvir (antigen level not reported) compared with remdesivir (3383±770.7 pg/mL; *P*=0.0662) or molnupiravir (2587±884.4 pg/mL; *P*=0.1275), although the differences did not reach statistical significance (*P*=0.5240).[12]
- Antigen-negative conversion rate after 10 days of antiviral treatment was highest for patients treated with ensitrelvir (40%; 10/25) compared to remdesivir (20%; 17/85) and molnupiravir (4.54%; 2/44).[12]
- Viral antigen levels surged from admission to Day 10 of treatment in all treatment groups; resurgence rates were lowest for patients treated with ensitrelvir (8%; 2/25) compared to remdesivir (22.3%; 19/85) and molnupiravir (20.4%; 9/44).[12]
- Duration of hospitalization was significantly shorter in patients treated with ensitrelvir compared to molnupiravir (11.04±0.212 vs 12.7±0.354 days; *P*=0.0013). No significant differences in hospitalization duration were observed between ensitrelvir and remdesivir (11.04±0.212 vs 12.11±0.369; *P*=0.1264) or remdesivir and molnupiravir (*P*=0.2982).[12]
- Patients were classified into 2 categories based on whether viral antigen levels decreased from admission to Day 10 after treatment (Down group; n=124) or levels increased (Up group; n=30). The average duration of hospitalization was significantly shorter in the Down group compared to the Up group (11.57 days vs 14.3 days, respectively; *P*<0.0001).[12]
- Fever exceeding 37°C was present at admission in 78.8% (67/85), 80.4% (37/46), and 68% (17/25) of patients treated with remdesivir, molnupiravir, and ensitrelvir, respectively. Mean±SEM time for fever at admission to decrease to below 37°C was not statistically different between patients treated with remdesivir (3.493±0.1784 days), molnupiravir (3.432±0.1958 days), and ensitrelvir (2.882±0.3417 days).[12]

Safety

- No safety outcomes or AEs were reported for any of the antiviral groups.

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Retrospective Chart Review in Hospitalized Patients

Yamato et al (2024) conducted a single-center, retrospective chart review assessing the outcomes of hospitalized patients treated with ensitrelvir in a real-world setting in the 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. Patients received daily oral treatment with ensitrelvir over 5 days with a 375 mg loading dose on Day 1 and a 125 mg maintenance dose on Days 2–5. Antiviral activity, as indicated by PCR or antigen testing and investigator assessments of clinical improvement, was used to assess effectiveness.[13]

Results

Baseline Characteristics

- A total of 32 patients were included in the analysis, all receiving 5 days of ensitrelvir treatment.[13]
  - Average age of the study population was 73.5 years, and most patients (78.1%; n=25) were **aged ≥65 years**, including 16 patients (50%) **aged ≥75 years**.[13]
    - Within the disease-severity subgroups, **geriatric patients** were represented across all categories:[13]
      - Mild disease (n=21): included 6 patients aged 65–74 years; 13 patients aged ≥75 years.
      - Moderate I disease (n=4): included 2 patients aged 65–74 years; 1 patient aged ≥75 years.
      - Moderate II disease (n=7): included 1 patient aged 65–74 years and 2 patients aged ≥75 years.
- Comorbidities in the overall population included HTN in 78.1% (25/32), CKD in 25% (8/32), hemodialysis in 22.6% (7/32), and malignant tumors in 28.1% (9/32) of patients.[13]
- Antiviral treatment had previously been administered to 93.8% (30/32) of patients; the most common was remdesivir in 87.5% (28/32) of patients.[13]
- Outcomes were not stratified by age and **geriatric-specific efficacy results are not available**.

Efficacy

- 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 an antigen level below the LLoQ of <1.34 pg/mL. At final measurement, 78.1% (25/32) of patients had achieved viral clearance.[13]
- Viral rebound occurred in 12.5% (4/32) of patients after the completion of ensitrelvir treatment, and no disease progression occurred in these patients.[13]
- Clinical improvement occurred in all 32 patients, as assessed by the investigator at the end of ensitrelvir treatment (Day 5).[13]

Safety

- No patients discontinued treatment, had TRAEs, progressed to severe disease, or were admitted to the ICU, and no treatment-related deaths occurred.[13]
- By Day 14, a total of 16 patients were discharged from the hospital, and by Day 15, 15 patients were discharged (range, Day 15–78).[13]
- 1 patient death (Day 55) occurred due to anti-neutrophil cytoplasmic antibody-associated vasculitis and was determined to be unrelated to COVID-19 or ensitrelvir.[13]

Xocova – Use in a Geriatric Population

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Retrospective Chart Review in Hospitalized Patients

Tomita et al (2024) conducted a retrospective chart review to evaluate the real-world clinical outcomes of ensitrelvir in hospitalized **patients of very advanced age** with laboratory-confirmed COVID-19 at Tomita Hospital, Wakayama, Japan, between November 2022 and April 2023. Ensitrelvir was given orally with a loading dose of 375 mg on Day 1 and 125 mg once daily on Days 2–5.[14]

Results

Baseline Characteristics

- A total of 9 female patients with symptomatic COVID-19 were included, with a **mean age of 90.2±5.5 years**; 5 patients were 80–89 years and 4 were 90–99 years old. All patients had mild disease at initiation and received ensitrelvir within 2 days of symptom onset. Comorbidities included disuse syndrome (88.9%), chronic heart failure (55.6%), and HTN (55.6%), among others. 8 of the 9 patients had received ≥2 COVID-19 vaccine doses prior to infection.[14]

Efficacy

- All 9 patients completed the 5-day ensitrelvir course and recovered without progression to severe COVID-19.[14]
- At baseline, 7 of 9 patients had fever ≥37.5°C; all achieved fever resolution (<37°C) within 4 days of starting ensitrelvir, with 5 experiencing transient fever recurrence.[14]
- None required supplementary oxygen therapy or additional antiviral agents. All patients maintained oxygen saturation ≥93% throughout the 14-day observation period.[14]

Safety

- No AEs related to ensitrelvir were reported.[14]
- No patients discontinued therapy.[14]
- No treatment-related deaths were observed during the follow-up until Day 14.[14]

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Post-Marketing Surveillance Study

Hayashi et al (2025) conducted a post-marketing surveillance study across multiple facilities in Japan from November 2022 to December 2023 to evaluate the safety and efficacy of ensitrelvir in real-world clinical practice. The study included patients who tested positive for COVID-19 and were taking ensitrelvir for the first time. Using a continuous survey method, the observation period lasted 28 days from the initial dose of ensitrelvir. The reported outcomes included patient characteristics, the time to resolution of COVID-19 symptoms, and ADRs.[15]

Results

Baseline Characteristics

- The study included 3760 patients in the SAS and 3638 patients in the effectiveness analysis set.[15]
- In the SAS, 452/3760 (12%) patients were **aged ≥65 years** and 8.5% of patients were >70 years.[15]

Efficacy

- The median time to resolution of symptoms in the overall population: all symptoms, 156 hours; fever, 36 hours; systemic symptoms, 60 hours; respiratory symptoms, 132 hours, and GI symptoms, 48 hours.[15]
- In the **geriatric subgroup** (≥65 years), the median time to resolution of fever was 24 hours, and all symptoms was 108 hours.[15]

Safety

- In the SAS, there were 379 incidences of AEs, of which 5 were SAEs.[15]
- A higher incidence of ADRs occurred in patients with comorbidities (10.2% vs 6.4%, *P*=0.0002).[15]
- The occurrence of ADRs in the SR and HR groups was 7.1% and 7.6%, respectively (*P*=0.6284).[15]
- Common ADRs included diarrhea (n=91), nausea (n=43), and headache (n=42).[15]
  - There were 14 patients hospitalized for worsening COVID-19 or other reasons and 2 deaths, which were determined to be unrelated to ensitrelvir or COVID-19.[15]
    - No separate ADR analysis was reported for the **geriatric subgroup**.

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Literature Search

May 2026

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 use of ensitrelvir in geriatric patients. For your review, these references are listed in the bibliography that follows:

- Kawai N, Bando T, Goto T, et al. Durations of fever and other symptoms among COVID-19 outpatients administered ensitrelvir during the 2023 Japanese XBB epidemic period. *J Infect Chemother*. 2025;31(12):102852. [Web Link]
- Hirai J, Hanai Y. Comparative study of ensitrelvir and symptomatic therapy in healthcare workers with mild COVID-19: a single center retrospective analysis in Chiba, Japan. *J Infect Chemother*. 2025;31(4):102668. [Web Link]
- 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. [Web Link]
- Seki M. Differences in treatment patterns and patient characteristics between COVID-19 patients treated with nirmatrelvir/ritonavir and ensitrelvir in Japan. *Int J Gen Med*. 2024;17:3621-3624. [Web Link]
- 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. [Web Link]
- Hibino M, Shintani A, Murayama H, et al. Real-world impact of early outpatient COVID-19 antiviral treatment on post-COVID-19 condition: the ANCHOR-01 study. Poster presented at: ISRV-AVG/IMRP; September 17-20, 2025; Singapore.
- 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.

Please keep in mind that medical literature databases, while considered a major source of biomedical information, are selective in their sources, and the information derived from them should not be considered all-inclusive.

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Abbreviations

3CL	3-chymotrypsin-like	ITT	intention-to-treat
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines	IQR	interquartile range
ACTG	AIDS Clinical Trials Group	LLoQ	lower limit of quantification
ADR	adverse drug reactions	MHLW	Ministry of Health, Labour and Welfare
AE	adverse event	mITT	modified intention-to-treat
$AUC_{0-\tau}$	area under the concentration-time curve over the dosing interval	NIH	National Institutes of Health
BMI	body mass index	NHC	nucleotide analogue, β-D-N4-hydroxycytidine
C_{24}	plasma concentration at 24 hours post-dose	PK	pharmacokinetic
CI	confidence interval	RD	risk difference
CKD	chronic kidney disease	RNA	ribonucleic acid
C_{max}	geometric mean maximum plasma concentrations	RR	risk ratio
COPD	chronic obstructive pulmonary disease	RT-PCR	reverse transcription polymerase chain reaction
COVID-19	coronavirus disease 19	SAE	serious adverse event
CV	cardiovascular	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
GI	gastrointestinal	SAS	safety analysis set
HDL	high-density lipoprotein	SD	standard deviation
HHC	healthy household contacts	SR	standard-risk
HIV/AIDS	human immunodeficiency virus/ acquired immunodeficiency syndrome	$t_{1/2z}$	geometric mean terminal elimination half-life
HR	high-risk	TEAE	treatment-emergent adverse event
ICU	intensive care unit	TRAE	treatment-related adverse event
HTN	hypertension	US	United States
IPTW	inverse probability of treatment weighting		

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1. XOCOVA® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.
2. Hayden FG, Shinkai M, Clark TW, et al. Ensitrelvir for COVID-19 postexposure prophylaxis in household contacts. *N Engl J Med*. 2026;394(19):1905-1915. [Web Link]
3. 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;80(6):1235-1244. [Web Link]
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 (Supplementary Appendix). *Clin Infect Dis*. 2025;80(6):1235-1244. [Web Link]
5. Draica F, Luetkemeyer A, Chew KW, et al. Clearance of infectious virus in COVID-19 patients treated with ensitrelvir across vaccination status, age, and risk subgroups: exploratory analyses from the SCORPIO-HR study. Poster presented at: IDWeek; October 19-22, 2025; Atlanta, GA.
6. Ensitrelvir Data on File 9. Shionogi Inc.
7. Yotsuyanagi H, Ohmagari N, Doi Y, et al. Efficacy and safety of 5-day oral ensitrelvir for patients with mild to moderate COVID-19: the SCORPIO-SR randomized clinical trial. *JAMA Netw Open*. 2024;7(2):e2354991. [Web Link]
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9. Ensitrelvir Data on File 5. Shionogi Inc.
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11. 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. [Web Link]
12. Yoshida R, Sasaki T, Ohsaki Y. Real-world efficacy of ensitrelvir in hospitalized patients with COVID-19 in Japan: a retrospective observational study. *Cureus*. 2024;16(5):e61048. [Web Link]
13. Yamato M, Kinoshita M, Miyazawa S, Seki M, Mizuno T, Sonoyama T. Ensitrelvir in patients with SARS-CoV-2: a retrospective chart review. *J Infect Chemother.* 2024;30(9):946-950. [Web Link]
14. Tomita T, Miyazawa S, Sonoyama T. Treatment with ensitrelvir for COVID-19 in hospitalized patients of very advanced age: case series. *Medicine (Baltimore).* 2024;103(30):e39080. [Web Link]
15. 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*. 2025;31(3):102574. [Web Link]
16. ClinicalTrials.gov [Website]. A study to compare S-217622 with placebo in non-hospitalized participants with COVID-19 (SCORPIO-HR). NLM Identifier: NCT05305547. Last accessed September 17, 2026. Available at: [Web Link]

Enclosure

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