Xocova - Phase 2 and 3 (SCORPIO-SR) Studies

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Summary

- The phase 2/3 study of patients with mild-to-moderate or asymptomatic SARS-CoV-2 infection in Asia evaluated the phase 2a (N=69), phase 2b (N=428), phase 3 (N=1821), and 2b/3 (N=572; exploratory) parts, patients were randomized 1:1:1 to receive ensitrelvir 125 mg or 250 mg or placebo[1-6]
  - In part 2a, treatment with ensitrelvir resulted in greater reductions in viral titers at Day 4 (change in $\log_{10}$ 50% tissue culture infectious dose [$TCID_{50}$]/mL of −2.42, −2.81, and −1.54 for ensitrelvir 125 mg, ensitrelvir 250 mg, and placebo groups, respectively)[1]
  - In part 2b, the least squares (LS) mean change from baseline in SARS-CoV-2 viral titer ($\log_{10}$ $TCID_{50}$/mL) was significantly larger for both ensitrelvir doses than placebo on Day 4 (difference from placebo of -0.41 for both doses). The difference in the mean total score of 12 COVID-19 symptoms was not statistically significant between both ensitrelvir doses and placebo (time weighted average change from baseline up to 120 hours)[2]
  - In part 3, the time to resolution of 5 COVID-19 symptoms (primary endpoint) was significantly reduced with ensitrelvir 125 mg vs placebo (*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, ensitrelvir 250 mg, and placebo groups, respectively[3]
  - The TEAEs observed most commonly were decreased high-density lipoprotein (HDL), increased triglycerides, and increased bilirubin (31.1%, 8.1%, and 6%, respectively in part 3)[3]
  - In the phase 2b/3 exploratory analysis of the phase 2/3 study (N=572), a reduced proportion of patients with positive viral titers in patients with mild or asymptomatic infection was seen in those treated with ensitrelvir when compared to placebo[4]
  - In a post-hoc analysis in patients with post COVID-19 condition (PCC), treatment with ensitrelvir resulted in reduced risk of various COVID-19 and neurological symptoms compared to placebo at Days 85, 169, and 337[5]
  - In a post-hoc analysis, viral rebound was observed in 7.8% (46/590), 6.7% (38/570), and 4.7% (27/574) in the ensitrelvir 125 mg, ensitrelvir 250 mg, and placebo groups, respectively. Of these, one patient in the 250 mg group reported symptom recurrence[6]
- Shionogi has conducted two large-scale, global, phase 3 studies (SCORPIO-HR and SCORPIO-PEP) and is currently conducting additional phase 3 studies (including a Japanese pediatric study and STRIVE) to evaluate efficacy and safety of ensitrelvir in patients with COVID-19[7-10]

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PHASE 2/3 STUDY DESIGN

The phase 2/3, multicenter, randomized, double-blind, placebo-controlled clinical study (**jRCT2031210350**), conducted in Asia, evaluated the efficacy (clinical symptom improvement and antiviral effect) and safety of ensitrelvir administered orally, once daily for 5 days in patients with SARS-CoV-2 infection. The phase 2a part was conducted in Japan; phase 2b part, in Japan and South Korea; and phase 3 part (SCORPIO-SR [**S**topping **CO**VID-19 p**R**ogression with early **P**rotease **I**nhibit**O**r treatment - **S**tandard **R**isk]), in Japan, South Korea, and Vietnam.[1-3,6]

In the phase 2a part, patients with mild-to-moderate or asymptomatic SARS-CoV-2 infection (N=69) were randomized 1:1:1 to receive either oral ensitrelvir (375 mg on Day 1 followed by 125 mg daily, or 750 mg on Day 1 followed by 250 mg daily) or placebo[1]

- Patients underwent treatment with ensitrelvir or placebo for 5 days and were followed to Day 28[1]
- The primary outcome was change from baseline in the SARS-CoV-2 viral titer[1]
- Secondary outcomes were SARS-CoV-2 viral ribonucleic acid (RNA) level, proportion of patients with a positive viral titer, and time to infectious viral clearance defined as the first negative SARS-CoV-2 viral titer[1]
- Additional clinical outcomes included the total score of 12 COVID-19 symptoms, proportion of patients with anosmia following treatment, and those with dysgeusia following treatment[1]

In the phase 2b part, patients (N=428) with mild-to-moderate COVID-19 were randomized 1:1:1 to orally receive 1 of 2 doses of ensitrelvir (375 mg on Day 1, 125 mg Days 2 through 5, or 750 mg on Day 1, 250 mg on Days 2 through 5), or matching placebo once daily without dose modification[2]

- Patients were followed to Day 28. Among the total sample, 341 patients were included in the intention-to-treat (ITT) population[2]
- Co-primary endpoints (virologic and clinical) were change from baseline at Day 4 in the SARS-CoV-2 viral titer and time-weighted average change from baseline up to 120 hours in total score of 12 COVID-19 symptoms[2]
- Secondary outcomes were absolute values and change from baseline in SARS-CoV-2 viral titer and viral RNA level up to Day 21, time to first negative SARS-CoV-2 viral titer, proportion of patients with positive viral titers, time to first improvement in COVID-19 symptoms, and subtotal scores of the 12 COVID-19 symptoms as self-recorded by patients[2]

The phase 3 part of the phase 2/3 study took place at 92 institutions in Japan, Vietnam, and South Korea. Eligible patients were aged 12 to <70 years, with mild-to-moderate COVID-19, within 120 hours of positive viral test at baseline[3]

- Patients were randomized 1:1:1 to receive 125 mg of once-daily ensitrelvir (375 mg on Day 1), 250 mg of once-daily ensitrelvir (750 mg on Day 1), or placebo for 5 days, with follow up to Day 28[3]
- The primary endpoint was time to resolution of the composite of 5 COVID-19 symptoms most commonly observed in the phase 2b part (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness)[3]
- Key secondary endpoints were change from baseline in SARS-CoV-2 RNA level on Day 4 and time to first negative SARS-CoV-2 titer[3]
- Additional secondary endpoints included time to resolution of 12 COVID-19 symptoms (the 5 previously noted symptoms plus shortness of breath, muscle or body aches, headache, chills or shivering, nausea, vomiting, and diarrhea), 14 COVID-19 symptoms (the 12 previously noted symptoms plus anosmia and dysgeusia), and SARS-CoV-2 RNA levels and titers up to Day 21[3]

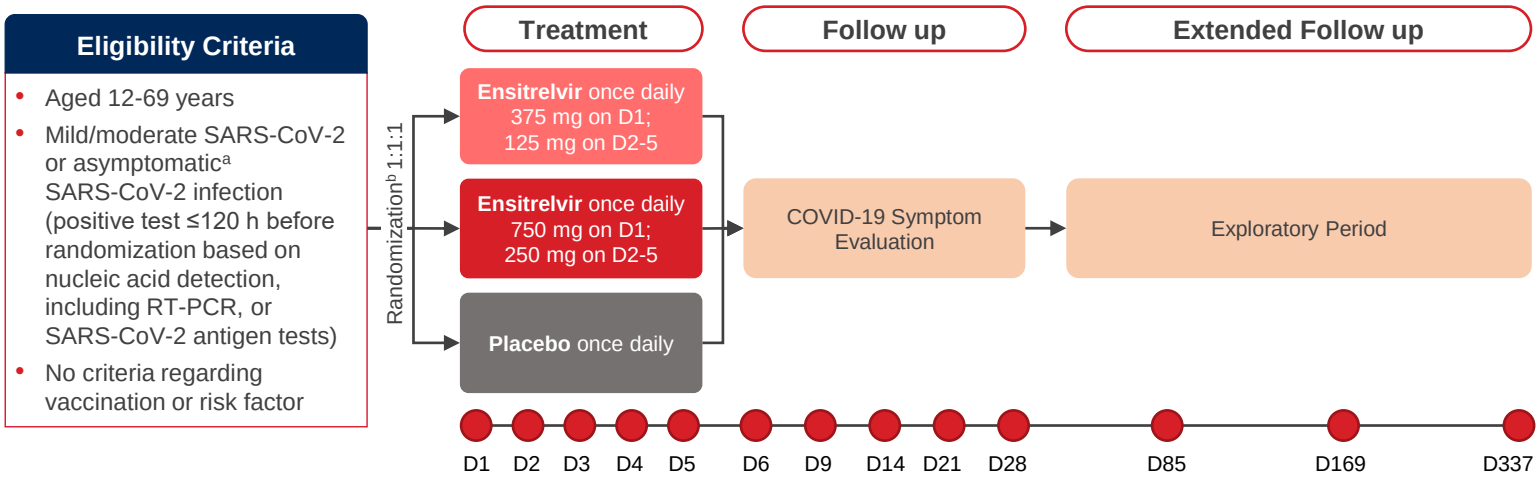
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PHASE 2/3 STUDY DESIGN

The study design and follow-up timeline for the phase 2/3 study are shown in **Figure 1**.

Figure 1. Phase 2/3 Study Design[1-3,11]



Abbreviations: COVID-19, coronavirus disease 19; D, day; h, hours; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Asymptomatic patients were included in the 2a and 2b/3 parts. [b]Patients were stratified based on their vaccination status and time from onset to allocation (<72 h, ≥72 h).

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PHASE 2/3 STUDY RESULTS

Phase 2a Part

- Of 70 patients screened, 69 were randomized. The ITT population included a total of 47 patients, including 16 in the ensitrelvir 125 mg group, 14 in the ensitrelvir 250 mg group, and 17 in the placebo group (modified ITT [mITT] population included 43 patients after exclusion of those with a negative reverse transcription polymerase chain reaction [RT-PCR] test at baseline)[1]
- The majority of patients were vaccinated for SARS-CoV-2, were infected by the Delta variant, and had mild-to-moderate COVID-19 (7 were asymptomatic)[1]

No prespecified statistical hypothesis was set because this phase 2a part was conducted in an exploratory manner.

Efficacy

- Primary Endpoint:
  - A decrease in the SARS-CoV-2 viral titer was observed with ensitrelvir up to Day 4 and remained stable at a level below viral detection (0.8 $\log_{10}$ 50% tissue culture infectious dose [$TCID_{50}$]/mL) up to Day 21. Reduction in viral titer from baseline to Day 4 was greater with ensitrelvir vs placebo (**Figure 2** and **Table 1**)[1]

Figure 2. SARS-CoV-2 Viral Titer as (A) Absolute Values and (B) Change From Baseline (mITT Population)[1]

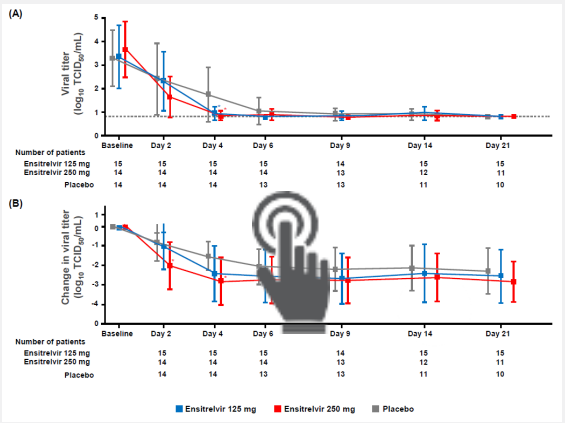


Table 1. Change in SARS-CoV-2 Viral Titer From Baseline on Day 4[1]

Change in log_{10} 50% tissue culture infectious dose ($TCID_{50}$)/mL	Ensitrelvir 125 mg	Ensitrelvir 250 mg	Placebo
Mean (SD)	−2.42 (1.43)	−2.81 (1.21)	−1.54 (0.74)
Difference from placebo	−0.88	−1.27	–
P value	0.0712	0.0083	–

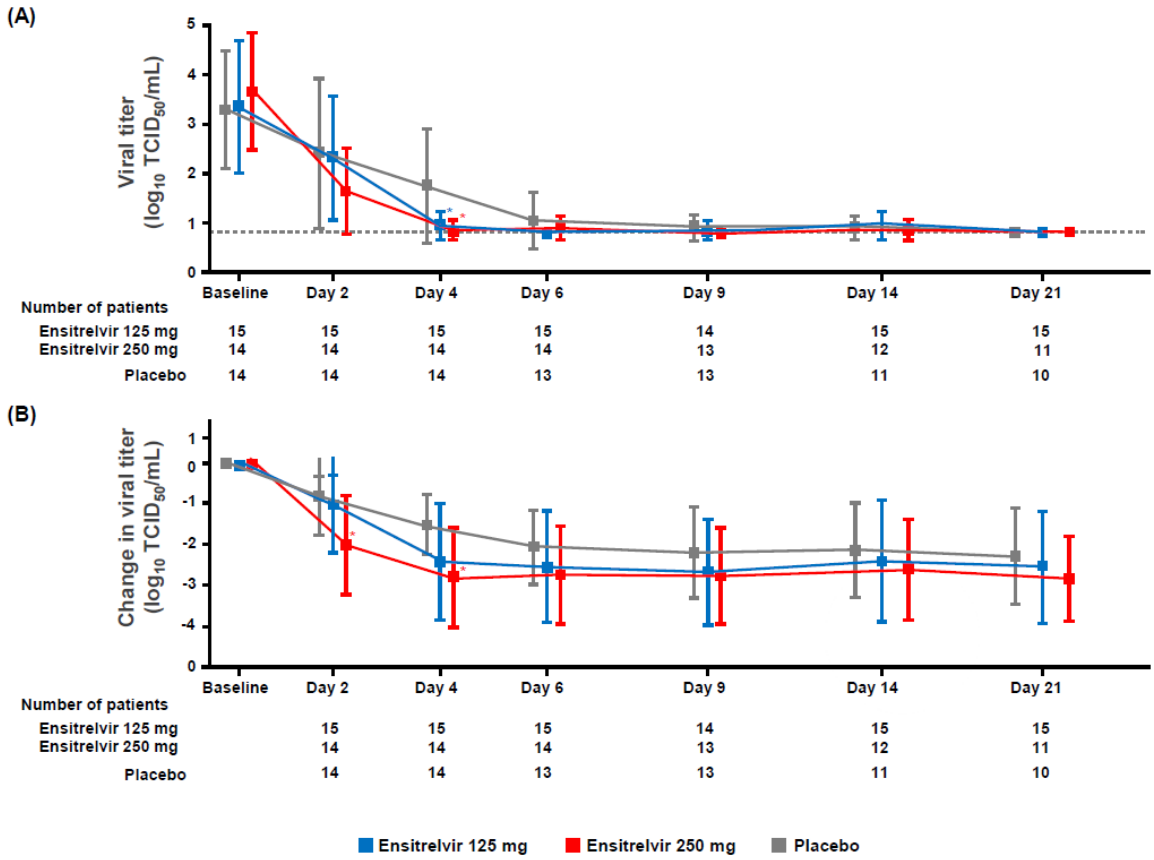
No prespecified statistical hypothesis was set because this ph… conducted in an exploratory manner. Results from these endpoints are observational in nature; as such, they should be interpreted w…
Abbreviations SARS-CoV-2, severe acute respiratory syndrom… SD, standard deviation; $TCID_{50}$, 50% tissue culture infectious dose

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PHASE 2/3 STUDY RESULTS

Figure 2. SARS-CoV-2 Viral Titer as (A) Absolute Values and (B) Change From Baseline (mITT Population)[1]



Abbreviations: mITT, modified intention to treat; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; TCID50, 50% tissue culture infectious dose.
*P < 0.05 vs placebo.
No prespecified statistical hypothesis was set because this phase 2a part was conducted in an exploratory manner. Results for this endpoint are
observational in nature; as such, they should be interpreted with caution.
Data are presented as mean ± SD. The gray, dotted, horizontal lines in panel A indicate the lower limit of detection of viral titer (0.8 log10 TCID50/mL)
Figure adapted from Mukae et al. Antimicrob Agents Chemother. 2022.

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PHASE 2/3 STUDY RESULTS

Table 1. Change in SARS-CoV-2 Viral Titer From Baseline on Day 4[1]

Change in log_{10} 50% tissue culture infectious dose [$TCID_{50}$]/mL	Ensitrelvir 125 mg	Ensitrelvir 250 mg	Placebo
Mean (SD)	−2.42 (1.42)	−2.81 (1.21)	−1.54 (0.74)
Difference from placebo	−0.88	−1.27	–
P value	0.0712	0.0083	–

No prespecified statistical hypothesis was set because this phase 2a part was conducted in an exploratory manner. Results for these endpoints are observational in nature; as such, they should be interpreted with caution.
Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; $TCID_{50}$, 50% tissue culture infectious dose.

level below viral detection (0.8 log_{10} 50% tissue culture infectious dose [$TCID_{50}$]/mL) up to Day 21. Reduction in viral titer from baseline to Day 4 was greater with ensitrelvir vs placebo (Figure 2 and Table 1)[2]

Figure 2. SARS-CoV-2 Viral Titer as (A) Absolute Values and (B) Change From Baseline (mITT Population)[2]

Table 1. Change in SARS-CoV-2 Viral Titer From Baseline on Day 4[2]

Change in Titer	Ensitrelvir 125 mg	Ensitrelvir 250 mg	Placebo
Mean (SD)	−2.42 (1.42)	−2.81 (1.21)	−1.54 (0.74)
Difference from placebo	−0.88	−1.27	–
P value	0.0712	0.0083	–

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PHASE 2/3 STUDY RESULTS

Phase 2a Part (cont'd)

- Secondary Endpoints:
  - A reduction from baseline in viral RNA was seen in ensitrelvir 125 mg and 250 mg groups by Day 4 (difference from placebo, –1.408 and –1.492, respectively; $P<0.05$)[1]
  - The median time to the first negative SARS-CoV-2 viral titer was shorter by 2 days with both doses of ensitrelvir compared with placebo (difference from placebo was −49.8 h [$P=0.0159$] and −48.4 h [$P=0.0205$] in the 125 mg and 250 mg groups, respectively)[1]
  - Evaluation of clinical symptoms showed that compared with placebo, the mean change from baseline in the total score of the 12 COVID-19 symptoms was numerically larger in the ensitrelvir 125 mg and 250 mg groups[1]

No prespecified statistical hypothesis was set because this phase 2a part was conducted in an exploratory manner. Results for these endpoints are observational in nature; as such, they should be interpreted with caution.

Safety

- Severity of all treatment-emergent adverse events (TEAEs) was mild to moderate (ensitrelvir 125 mg, 11/21 [52.4%] patients; ensitrelvir 250 mg, 16/23 [69.6%] patients; placebo, 9/24 [37.5%] patients)[1]
  - The TEAE observed most commonly was reduction in high-density lipoprotein (HDL; ensitrelvir 125 mg, 3/21 [14.3%]; ensitrelvir 250 mg, 12/23 [52.2%]; placebo, 2/24 [8.3%])[1]
  - Treatment-related transient decreases in HDL cholesterol and increases in triglycerides (TGs) occurred after treatment initiation and were resolved without additional treatment[1]
  - No deaths or serious TEAEs, and no TEAEs leading to treatment discontinuation were reported[1]
- Treatment-related adverse events were observed in 5/21 (23.8%) and 10/23 (43.5%) patients in the ensitrelvir 125 mg and 250 mg groups, respectively[1]

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PHASE 2/3 STUDY RESULTS

Phase 2b Part

- Of 437 patients screened, 428 were randomized to the ensitrelvir 375/125 mg (n=142), ensitrelvir 750/250 mg (n=143), or placebo (n=143) groups. The efficacy analysis (ITT population) included 114, 116, and 111 patients in the ensitrelvir 125 mg, ensitrelvir 250 mg, and placebo groups, respectively[2]
- This study was conducted after the Omicron variant was identified and the majority (>80%) of patients were vaccinated against SARS-CoV-2 infection[2]

Efficacy

- Primary Endpoints:
  - Ensitrelvir demonstrated significant reduction in the infectious SARS-CoV-2 virus for both doses, irrespective of vaccination status and time from onset (<72 h or ≥72 h)[2]
  - The least squares (LS) mean change from baseline in SARS-CoV-2 viral titer ($log_{10}TCID_{50}$/mL) was significantly larger for both ensitrelvir doses than placebo on Day 4[2]
    - Compared with placebo, the difference in the change in viral titer at Day 4 was statistically significant for both doses (**Figure 3** and **Table 2**)[2]

Figure 3. SARS-CoV-2 Viral Titer as (A) Absolute Values and (B) Change From Baseline[2]

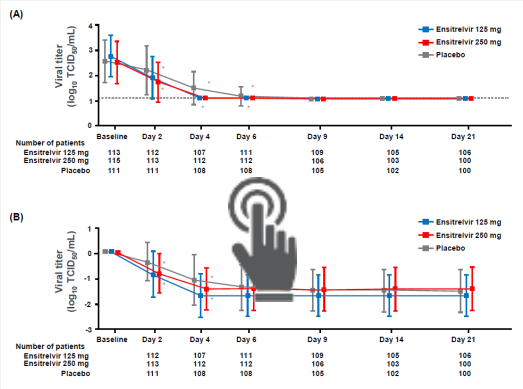


Table 2. Change in SARS-CoV-2 Viral Titer (log_{10} TCID$_{50}$/mL) From Baseline on Day 4[2]

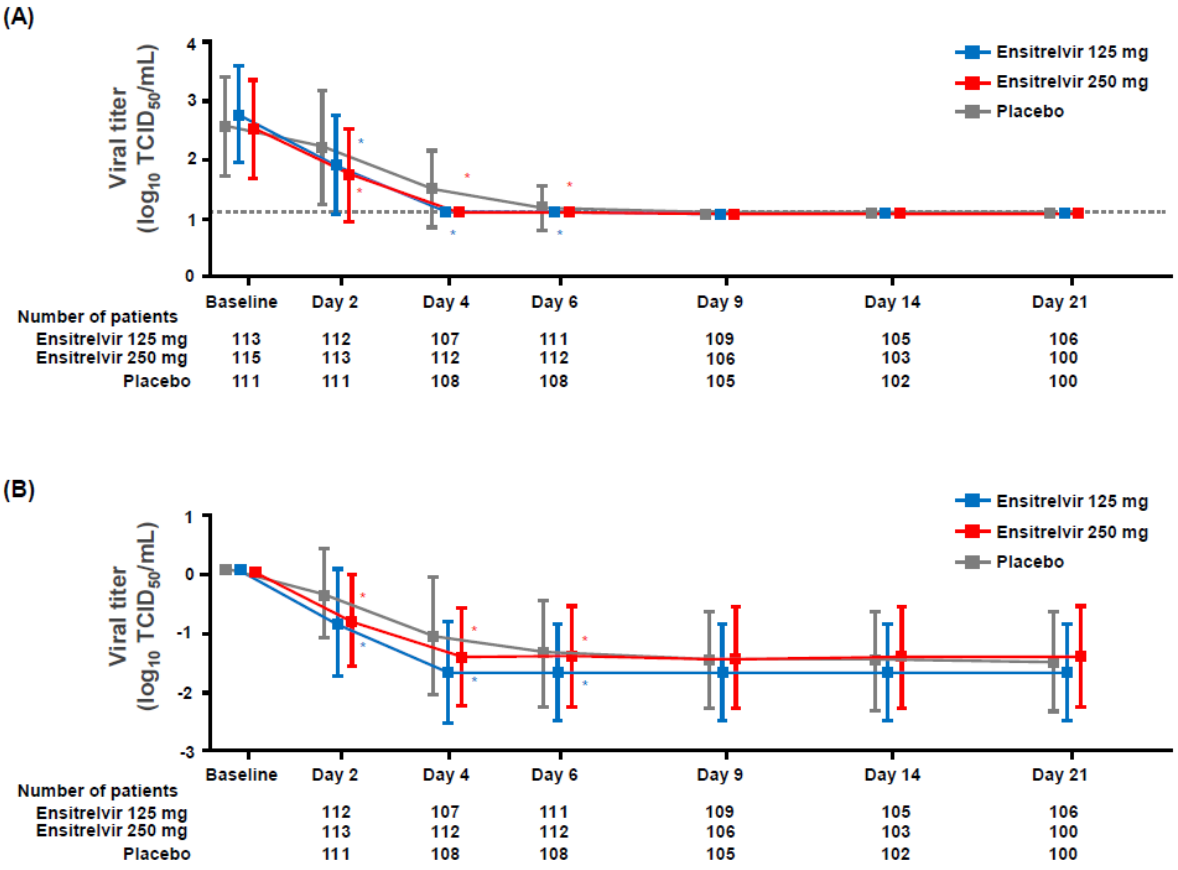
Change in Titer	Ensitrelvir 125 mg	Ensitrelvir 250 mg	Placebo
LS mean (SE)	−1.49 (0.04)	−1.49 (0.04)	−1.08 (0.04)
Difference from placebo (95% CI)	−0.41 (−0.51 to −0.31)	−0.41 (−0.51 to −0.31)	–
P value	<0.0001	<0.0001	–

- The difference in the mean total score of 12 COVID-19 symptoms was not statistically significant between both ensitrelvir doses and placebo (time-weighted average change from baseline up to 120 h)[2]

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Figure 3. SARS-CoV-2 Viral Titer as (A) Absolute Values and (B) Change From Baseline[2]



Abbreviations: SARS CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; TCID50, 50% tissue culture infectious dose.
Note: Data are presented as mean ± SD. Dotted lines indicate the lower limit of detection for SARS-CoV-2 viral titer (1.1 log10 TCID50/mL).
*P < 0.05 vs placebo group.
Figure adapted from Mukae et al. Clin Infect Dis. 2023.

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PHASE 2/3 STUDY RESULTS

Table 2. Change in SARS-CoV-2 Viral Titer (log_{10} $TCID_{50}$/mL) From Baseline on Day 4[2]

Change in Titer	Ensitrelvir 125 mg	Ensitrelvir 250 mg	Placebo
LS mean (SE)	−1.49 (0.04)	−1.49 (0.04)	−1.08 (0.04)
Difference from placebo (95% CI)	−0.41 (−0.51 to −0.31)	−0.41 (−0.51 to −0.31)	–
P value	<0.0001	<0.0001	–

Abbreviations: CI, confidence interval; LS, least squares; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, standard error; $TCID_{50}$, 50% tissue culture infectious dose.

– The least squares (LS) mean change from baseline in SARS-CoV-2 viral titer (log_{10} $TCID_{50}$/mL) was significantly larger for both ensitrelvir doses than placebo on Day 4[3]

- Compared with placebo, the difference in the change in viral titer at Day 4 was statistically significant for both doses (Figure 3 and Table 2)[3]

Figure 3. SARS-CoV-2 Viral Titer as (A) Absolute Values and (B) Change From Baseline[3]

Table 2. Change in SARS-CoV-2 Viral Titer (log_{10} $TCID_{50}$/mL) From Baseline on Day 4[3]

Change in Titer	Ensitrelvir 125 mg	Ensitrelvir 250 mg	Placebo
LS mean (SE)	−1.49 (0.04)	−1.49 (0.04)	−1.08 (0.04)
Difference from placebo (95% CI)	−0.41 (−0.51 to −0.31)	−0.41 (−0.51 to −0.31)	–
P value	<0.0001	<0.0001	–

– The difference in the mean total score of 12 COVID-19 symptoms was not statistically significant between both ensitrelvir doses and placebo (time-weighted average change from baseline up to 120 h)[3]

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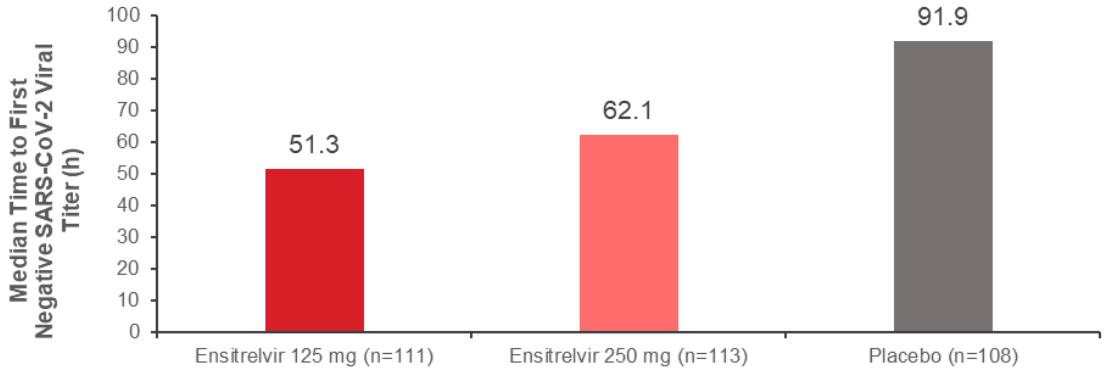
PHASE 2/3 STUDY RESULTS

Phase 2b Part (cont'd)

Efficacy (cont'd)

- Secondary Endpoints:
  - A fixed sequence procedure was applied only to the primary outcomes of the phase 2b part. Results for secondary endpoints are observational in nature; as such, they should be interpreted with caution[2]
  - Ensitrelvir showed a significant reduction in infectious viral RNA from baseline on Days 2, 4, 6, and 9 compared with placebo (difference vs placebo in the LS mean change from baseline in viral RNA, under −1.0 $\log_{10}$ copies/mL on Day 4 at each dose)[2]
  - Infectious viral shedding (time to first negative SARS-CoV-2 viral titer) was shortened by approximately 1 to 2 days with both doses of ensitrelvir compared with placebo. The median time difference between ensitrelvir 125 mg (51.3 h) and ensitrelvir 250 mg (62.1 h) compared with placebo (91.9 h) was −40.6 and −29.8 h, respectively (*P*<0.0001; **Figure 4**)[2]

Figure 4. Time to First Negative SARS-CoV-2 Viral Titer[2]



Abbreviations: h, hours; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

  - After the third dose of ensitrelvir (Day 4), the proportion of patients with positive viral titer decreased by ≈90% for the ensitrelvir 125 and 250 mg groups and was significantly lower compared with the placebo group (P<0.0001 for both doses)[2]
  - Subtotal scores of the 12 COVID-19 symptoms were significantly greater in the ensitrelvir 125 and 250 mg groups vs placebo for respiratory symptoms (*P*=0.0153 and *P*=0.0033, respectively), and in the 250-mg group for acute symptoms and main clinical symptoms (*P*=0.007 and *P*=0.0149, respectively)[2]

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PHASE 2/3 STUDY RESULTS

Phase 2b Part (cont'd)

Safety

- The safety analysis population included 140 patients each in the ensitrelvir 125-mg and 250-mg groups and 141 in the placebo group[2]
- TEAEs were generally mild in the ensitrelvir groups (ensitrelvir 125 mg, n=48 [34.3%]; ensitrelvir 250 mg, n=60 [42.9%]) compared with the placebo group (n=44 [31.2%])[2]
  - The most frequent TEAEs (occurring in >5% of patients) in the ensitrelvir groups were decrease in HDL and increase in blood TGs. No SAEs or deaths were reported in the ensitrelvir groups[2]
- Treatment-related AEs were reported in 19 (13.6%), 31 (22.1%), and 7 (5.0%) patients in the ensitrelvir 125-mg, ensitrelvir 250-mg, and placebo groups, respectively[2]
  - The most frequent treatment-related AE (occurring in ≥5% of patients) was decrease in HDL[2]
- Transient and asymptomatic changes in HDL and TGs were observed on Day 6 in both ensitrelvir groups which resolved without additional treatment[2]

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PHASE 2/3 STUDY RESULTS

Phase 3 (SCORPIO-SR)

Among the 1821 patients who were randomized, the following were randomized to receive ensitrelvir 125 mg (n=607), ensitrelvir 250 mg (n=606), or placebo (n=608). Patient characteristics were similar across both study arms.[3]

Among the 1030 patients in the primary analysis population (ensitrelvir 125 mg, n=347; ensitrelvir 250 mg, n=340; placebo, n=343), 53.6% were men and the mean age was 35.2 years. Majority of patients were Asian (99.4%) and majority of patients had received 2 or more doses of the SARS-CoV-2 vaccine (91%). Most patients were infected with either Omicron BA.1 (16.7%) or BA.2 (69.4%).[3]

Efficacy

- Primary Endpoint:
  - The time to resolution of 5 COVID-19 symptoms (primary endpoint) was significantly reduced with ensitrelvir 125 mg vs placebo in the primary analysis population (*P*=0.04)[3]
  - A difference in median time to symptom resolution with ensitrelvir 125 mg vs placebo in the primary analysis population was –24.3 h as depicted in **Table 3**[3]

Table 3. Primary Endpoint: Time to Resolution of 5 COVID-19 Symptoms[3,a]

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

The efficacy analysis group comprised of the ensitrelvir 125 mg treatment arm and placebo arm.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 19; h, hours; ITT, intention-to-treat; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Five COVID-19 symptoms were runny or stuffy nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness. [b]Analysis in the ITT population (all cases confirmed positive for SARS-CoV-2 viral RNA at baseline) with any of the 5 symptoms at baseline. [c]Adjusted for SARS-CoV-2 vaccination status.

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PHASE 2/3 STUDY RESULTS

Phase 3 (SCORPIO-SR) (cont'd)

Efficacy (cont'd)

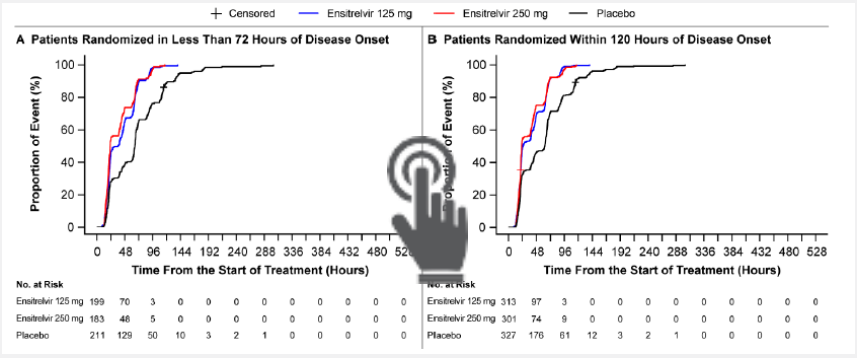
- Key Secondary Endpoints:
  - Compared with placebo, ensitrelvir 125 mg significantly shortened the median time to first confirmed negative SARS-CoV-2 viral titer by 29 h as depicted in **Table 4** and **Figure 5**[3]

Table 4. Key Secondary Endpoint: Time to First Confirmed Negative SARS-CoV-2 Viral Titer[3]

	Ensitrelvir 125 mg (n=199)	Ensitrelvir 250 mg (n=183)	Placebo (n=211)
Kaplan-Meier estimator (h)			
Median (95% CI)	36.2 (23.4, 43.2)	22.7 (21.2, 37.9)	65.3 (62.0, 66.8)
Difference vs. placebo (95% CI)	−29.1 (−42.3, −21.1)	−42.6 (−44.6, −27.4)	–
Stratified log-rank test[a]			
Two-sided *P* value	<0.001	<0.0001	–

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

Figure 5. Key Secondary Endpoint: Time to First Confirmed Negative SARS-CoV-2 Viral Titer[3,a,b]



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PHASE 2/3 STUDY RESULTS

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Difference vs. placebo (95% CI)	−29.1 (−42.3, −21.1)	−42.6 (−44.6, −27.4)	–
Stratified log-rank test[a]			
Two-sided *P* value	<0.001	<0.0001	–

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

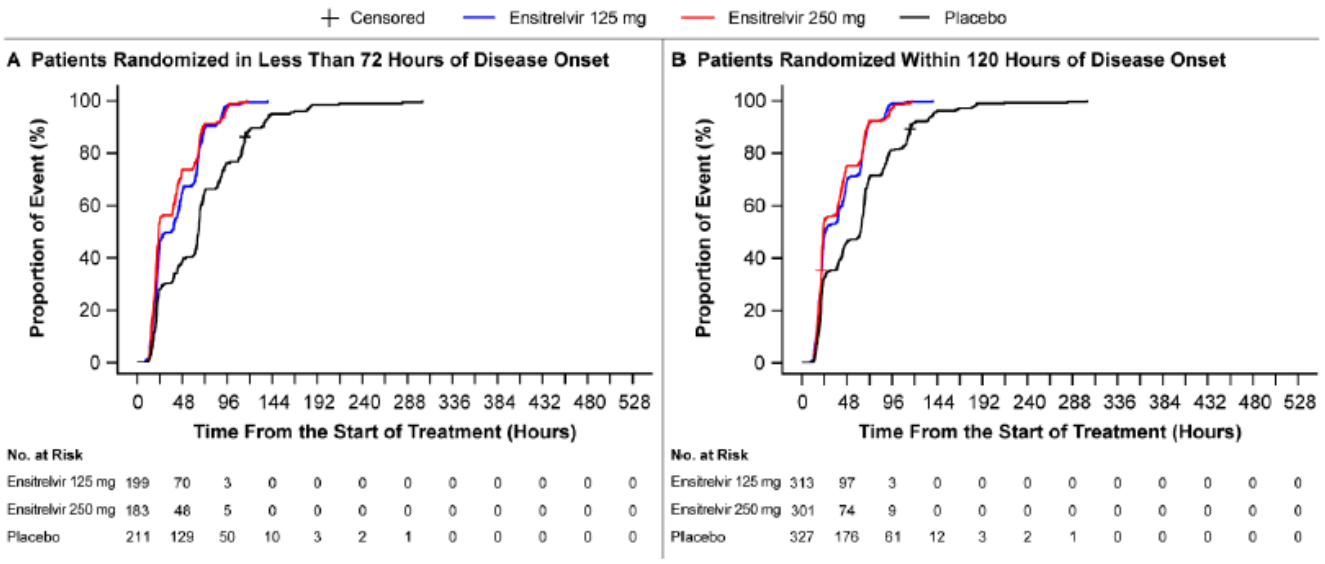
Figure 5. Key Secondary Endpoint: Time to First Confirmed Negative SARS-CoV-2 Viral Titer[3,a,b]

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PHASE 2/3 STUDY RESULTS

Figure 5. Key Secondary Endpoint: Time to First Confirmed Negative SARS-CoV-2 Viral Titer[3,a,b]



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Abbreviations: mITT, modified intention-to-treat; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]mITT population. [b]The analysis was performed for all patients who tested positive for SARS-CoV-2 viral RNA, with a detectable SARS-CoV-2 viral titer at baseline. Patients randomized in less than 72 hours of disease onset in the 125-mg ensitrelvir group were defined as the primary analysis population. A stratified log-rank test was applied to test the statistical significance vs placebo. The test was stratified by SARS-CoV-2 vaccination history (yes or no) for patients randomized in less than 72 hours (panel A) and time from onset to randomization (<72 hours or ≥72 hours) and SARS-CoV-2 vaccination history (yes or no) for patients randomized within 120 hours (panel B).

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PHASE 2/3 STUDY RESULTS

Phase 3 (SCORPIO-SR) (cont'd)

Efficacy (cont'd)

- Key Secondary Endpoints (cont'd):
  - Ensitrelvir 125 mg reduced viral RNA by 2.48 $\log_{10}$ copies/mL on Day 4, a difference from placebo of −1.47 $\log_{10}$ copies/mL (*P*<0.001 [CI −1.63 to −1.31]).[3] Please see **Table 5** for additional efficacy data

Table 5. Change From Baseline to Day 4 in SARS-CoV-2 RNA Levels (Key Secondary Endpoint), Time to Resolution of 12 COVID-19 Symptoms (Secondary Endpoint), and Time to Resolution of 14 COVID-19 Symptoms (Secondary Endpoint)[3,a]

	Ensitrelvir 125 mg (n=347)[b]	Ensitrelvir 250 mg (n=340)	Placebo (n=343)
Change from baseline to Day 4 in SARS-CoV-2 RNA level			
Patients, number	340	333	337
LS mean (SE), $\log_{10}$ copies/mL[c]	−2.48 (0.08)	−2.49 (0.08)	–1.01 (0.08)
Difference from placebo, LS mean (SE) [95% CI], $\log_{10}$ copies/mL[c]	−1.47 (0.08) [−1.63 to −1.31]	−1.48 (0.08) [−1.64 to −1.32]	NA
P value[c]	<0.001	<0.001	NA
Time to resolution of 12 COVID-19 symptoms[d]			
Patients, number	336	330	321
Median (95% CI), h	179.2 (152.1 to 212.1)	184.9 (168.9 to 226.2)	213.2 (185.8 to 253.8)
Difference from placebo, median (95% CI), h	−34.0 (−5.9 to 8.3)	−28.3 (−72.8 to 14.7)	NA
P value	0.07	0.08	
Time to resolution of 14 COVID-19 symptoms[f]			
Patients, number	336	330	321
Median (95% CI), h	187.8 (156.4 to 217.0)	190.3 (171.4 to 244.0)	231.8 (192.1 to 265.8)
Difference from placebo, median (95% CI), h	−44.1 (−95.3 to 4.5)	−41.5 (−81.2 to 27.3)	NA
P value[e]	0.03	0.05	NA

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Abbreviations: CI, confidence interval; h, hours; ITT, intention-to-treat; LS, least-squares; NA, not applicable, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Results are for the ITT population of patients randomized in <72 hours of disease onset. [b]Primary analysis population. [c]Analysis of covariance using baseline SARS-CoV-2 RNA and SARS-CoV-2 vaccination history (yes or no) as covariates. [d]Low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath (difficulty breathing), nausea, vomiting, and diarrhea. [e]Based on a Peto-Prentice generalized Wilcoxon test stratified by SARS-CoV-2 vaccination history (yes or no).
There was no statistically significant difference between the treatment arms in terms of the time to resolution of 12 COVID-19 symptoms.

- A fixed-sequence hierarchical testing procedure was applied to control type 1 errors for the primary endpoint and 2 key secondary endpoints.[3] Results for all other secondary endpoints in the phase 3 study are observational in nature; as such, they should be interpreted with caution

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PHASE 2/3 STUDY RESULTS

Phase 3 (SCORPIO-SR) (cont'd)

Safety

- Ensitrelvir therapy was well tolerated. The most common TEAEs in the ensitrelvir 125-mg group were decreased HDL (31.1%), increased triglycerides (8.1%), and increased bilirubin (6%)[3]
- There was 1 report of a serious TEAE in the ensitrelvir 125-mg group (heavy menstrual bleeding), and 1 serious TEAE in the placebo group (acute cholecystitis)—neither was deemed treatment related, and there were no deaths in either group. The safety profile is summarized in **Table 6**[3]

Table 6. Safety Profile in the Safety Analysis Population[3,a]

Adverse Event – n (%)	Ensitrelvir 125 mg (n=604)	Ensitrelvir 250 mg (n=599)	Placebo (n=605)
TEAEs	267 (44.2)	321 (53.6)	150 (24.8)
Treatment-related AEs	148 (24.5)	217 (36.2)	60 (9.9)
TEAEs leading to discontinuation[b]	4 (0.7)	6 (1.0)	2 (0.3)
Serious TEAEs other than death[c]	1 (0.2)	0	1 (0.2)
Death	0	0	0
TEAEs occurring in ≥2% of patients in either group			
High-density lipoprotein decreased	188 (31.1)	231 (38.6)	23 (3.8)
Blood triglycerides increased	49 (8.1)	74 (12.4)	32 (5.3)
Blood bilirubin increased	36 (6.0)	56 (9.3)	6 (1.0)
Blood cholesterol decreased	20 (3.3)	28 (4.7)	3 (0.5)
Bilirubin conjugated increased	15 (2.5)	20 (3.3)	3 (0.5)
Blood creatinine phosphokinase increased	14 (2.3)	8 (1.3)	11 (1.8)
Headache	13 (2.2)	20 (3.3)	14 (2.3)
Blood lactate dehydrogenase increased	6 (1.0)	15 (2.5)	6 (1.0)
Diarrhea	6 (1.0)	9 (1.5)	12 (2.0)
Aspartate aminotransferase level increased	4 (0.7)	9 (1.5)	12 (2.0)
Treatment-related AEs in ≥2% of patients in either group			
High-density lipoprotein decreased	111 (18.4)	157 (26.2)	9 (1.5)
Blood bilirubin increased	17 (2.8)	35 (5.8)	3 (0.5)
Blood triglycerides increased	16 (2.6)	37 (6.2)	17 (2.8)
Blood cholesterol decreased	8 (1.3)	12 (2.0)	1 (0.2)
Headache	4 (0.7)	13 (2.2)	2 (0.3)

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

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EXPLORATORY/POST-HOC ANALYSES

Phase 2b/3 Part

The phase 2b/3 trial included individuals with asymptomatic SARS-CoV-2 infection and patients with mild COVID 19 symptoms and was conducted at 57 medical institutions in Japan, South Korea, and Vietnam (study period: January 6–August 14, 2022). Eligible patients aged 12 to 69 years old who tested positive for SARS-CoV-2 within 5 days prior to randomization were randomized (1:1:1) to the ensitrelvir 125 mg group, ensitrelvir 250 mg group, or placebo group, received the allocated intervention orally, and were followed up until Day 28.[4]

The proportion of participants that developed (asymptomatic individuals) or experienced worsening of (patients with mild COVID-19 symptoms) fever or one of the 14 COVID-19 symptoms in the first 10 days of treatment was used to assess the clinical efficacy of ensitrelvir. Participants self-rated the severity of each symptom and measured their body temperature using a thermometer. Virologic efficacy data was collected using nasopharyngeal swabs.[4]

Results

The ITT population included 572 patients randomized into the ensitrelvir 125 mg (n=194), ensitrelvir 250 mg (n=189), and placebo (n=189) groups. The population was divided into 12.2% who were asymptomatic (n=70) and 87.8% who had mild symptoms (n=502). A history of COVID-19 vaccination was reported in 525 patients (91.8%).[4]

Efficacy

- The proportion of asymptomatic participants experiencing the development of 14 COVID-19 symptoms or fever or of patients with mild symptoms experiencing a worsening of the 14 COVID-19 symptoms or fever can be viewed in **Table 7**
- Ensitrelvir 125 mg (n=191) and 250 mg (n=185) groups showed a greater reduction from baseline in viral RNA on Day 4 compared to placebo (n=185)[4]
- On Days 2 and 4, the proportion of those with a positive viral titer was lower for both ensitrelvir groups when compared to the placebo group as shown in **Figure 6**[4]
- The time to first negative SARS-CoV-2 culture was shorter with ensitrelvir 125 mg (n=89) and 250 mg (n=104) compared to placebo (n=75), with a median time of 38.3 hours and 38.9 hours, versus 66.7 hours, respectively[4,12]
- Results for exploratory analyses are observational in nature; as such, they should be interpreted with caution

Table 7. Proportion of Participants Experiencing the Development or Worsening of 14 COVID-19 Symptoms or Fever by Day 10 (ITT population)[4]

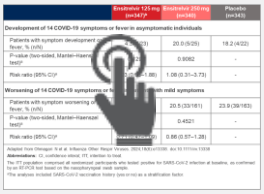
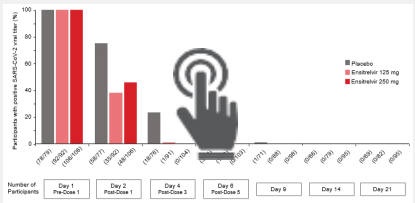


Figure 6. Proportion of Participants with a Positive SARS-CoV-2 Viral Titer (mITT population)[4]



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EXPLORATORY/POST-HOC ANALYSES

Table 7. Proportion of Participants Experiencing the Development or Worsening of 14 COVID-19 Symptoms or Fever by Day 10 (ITT population)[4]

	Ensitrelvir 125 mg (n=347)[b]	Ensitrelvir 250 mg (n=340)	Placebo (n=343)
Development of 14 COVID-19 symptoms or fever in asymptomatic individuals			
Patients with symptom development or fever, % (n/N)	4.3 (1/23)	20.0 (5/25)	18.2 (4/22)
P-value (two-sided, Mantel–Haenszel test)[a]	0.1293	0.9082	-
Risk ratio (95% CI)[a]	0.23 (0.03–1.88)	1.08 (0.31–3.73)	-
Worsening of 14 COVID-19 symptoms or fever in patients with mild symptoms			
Patients with symptom worsening or fever, % (n/N)	17.4 (29/167)	20.5 (33/161)	23.9 (39/163)
P-value (two-sided, Mantel–Haenszel test)[a]	0.1210	0.4521	-
Risk ratio (95% CI)[a]	0.71 (0.47–1.09)	0.86 (0.57–1.28)	-

Adapted from Ohmagari N et al. Influenza Other Respir Viruses. 2024;18(6):e13338. doi:10.1111/irv.13338

Abbreviations: CI, confidence interal; ITT, intention to treat.

The ITT population comprised all randomized participants who tested positive for SARS-CoV-2 infection at baseline, as confirmed by an RT-PCR test based on the nasopharyngeal swab sample.

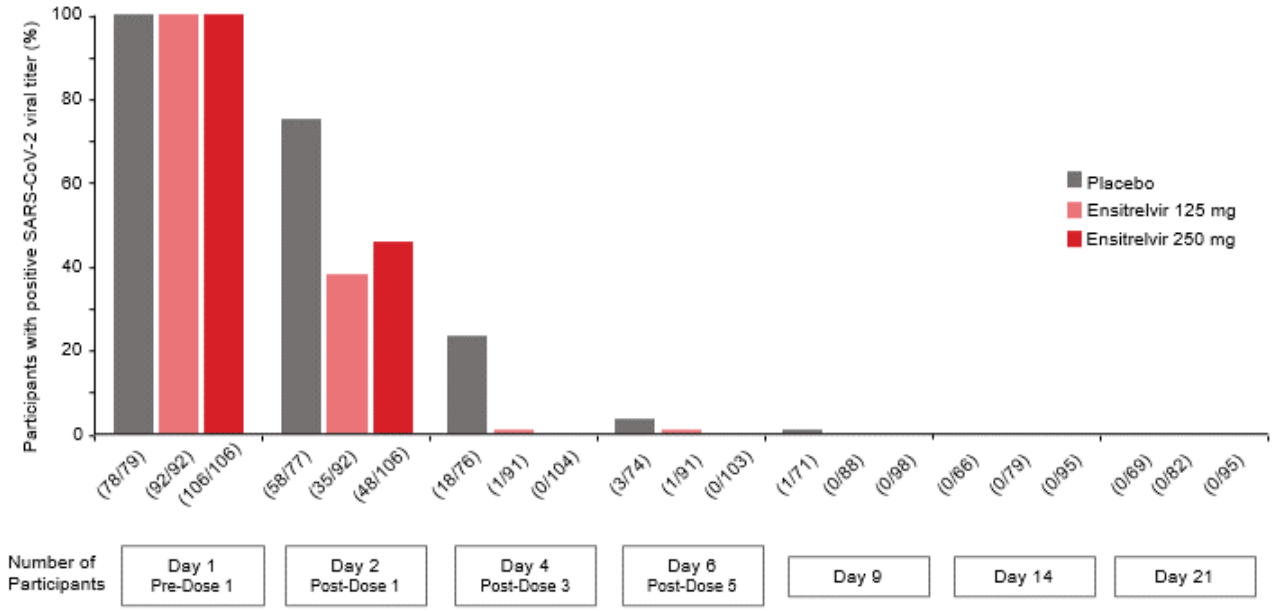
[a]The analyses included SARS-CoV-2 vaccination history (yes or no) as a stratification factor.

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EXPLORATORY/POST-HOC ANALYSES

Figure 6. Proportion of Participants with a Positive SARS-CoV-2 Viral Titer (mITT population)[4]



Adapted from Ohmagari et al. 2024.
Abbreviations: mITT, modified intention to treat; $TCID_{50}$, 50% tissue culture infectious dose.
The mITT population comprised all randomized participants who tested positive for SARS-CoV-2 infection and had detectable SARS-CoV-2 viral titers at baseline. A positive SARS-CoV-2 viral titer was defined as ≥0.75 log_{10} $TCID_{50}$/mL.

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EXPLORATORY/POST-HOC ANALYSES

Phase 2b/3 Part (cont'd)

Safety

Of the 604 patients included in the safety analysis population, TEAEs were reported in 43.8% (n=88), 56.9% (n=115), and 21.4% (n=43) in the ensitrelvir 125 mg, 250 mg, and placebo groups respectively. The most common TEAEs, occurring in ≥2% of patients in either group, were:[4]

- HDL decreased (30.3% [n=61] in the ensitrelvir 125 mg, 45.0% [n=91] in the ensitrelvir 250 mg, and 2.0% [n=4] in the placebo groups)
- Blood TG increased (7.0% [n=14] in the ensitrelvir 125 mg, 10.9% [n=22] in the ensitrelvir 250 mg, and 4.5% [n=9] in the placebo groups)
- Blood bilirubin increased (3.5% [n=7] in the ensitrelvir 125 mg, 7.4% [n=15] in the ensitrelvir 250 mg, and 0% in the placebo groups)

The most common treatment-related AEs, occurring in ≥2% of patients in either group, were:[10]

- HDL decreased (17.4% [n=35] in the ensitrelvir 125 mg, 32.7% [n=66] in the ensitrelvir 250 mg, and 1.0% [n=2] in the placebo groups)
- Blood bilirubin increased (1.0% [n=2] in the ensitrelvir 125 mg, 2.5% [n=5] in the ensitrelvir 250 mg, and 0% in the placebo groups)
- Blood TG increased (0% in the ensitrelvir 125 mg, 2.5% [n=5] in the ensitrelvir 250 mg, and 0.5% [n=1] in the placebo groups)

Most TEAEs were mild to moderate in severity. Two serious TEAEs were reported in the ensitrelvir 250 mg group (diverticulitis and nausea); neither event was considered treatment-related. No deaths were reported in either arm.[4] Three patients in the ensitrelvir arm discontinued treatment due to TEAEs (one patient in the 125 mg and two patients in the 250 mg group).[13]

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EXPLORATORY/POST-HOC ANALYSES

Long COVID-19 Symptoms

- The presence of long COVID-19 symptoms was assessed in patients (intention-to-treat population) who continued into the exploratory period of the phase 3 part of the phase 2/3 study at Days 85, 169, and 337 using post COVID-19 condition (PCC) questionnaires of 14 symptoms, 4 neurological symptoms, and 27 symptoms[5]
  - Self-assessment of COVID-19 symptoms and their severity were recorded by patients that responded “not having returned to pre-COVID health” in a double-blind exploratory analysis[5]

Responses to the Comprehensive Questions in the PCC Questionnaire

- In the ensitrelvir 125 mg and ensitrelvir 250 mg groups, the proportion of patients who experienced mild, moderate, or severe symptoms of COVID-19 in the 4 weeks prior to Day 85 was lower (6.3% and 7.6%, respectively) than in the placebo group (9.6%). At Day 169 and Day 337, these rates were similar between all groups (**Table 8**)[5]
- Results for exploratory analysis are observational in nature; as such, they should be interpreted with caution

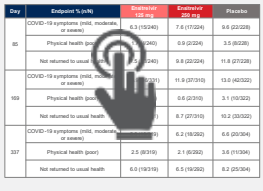
Proportion of Patients with ≥1 of 14 COVID-19 Symptoms or ≥1 of 4 Neurological Symptoms as PCC (Definition 1: presence of at least one mild, moderate, or severe symptom regarded as COVID-19–related)

- As seen in **Table 9**, which utilized Definition 1, ensitrelvir treatment showed a tendency for risk reduction in any of the 14 COVID-19 symptoms. The same trend is seen for risk reduction in any of the 4 neurological symptoms, except at Day 337 in the ensitrelvir 250 mg group.[5]
- Results for exploratory analysis are observational in nature; as such, they should be interpreted with caution

Proportion of Patients with ≥1 of 14 COVID-19 Symptoms or ≥1 of 4 Neurological Symptoms as PCC (Definition 2: presence of at least one mild, moderate, or severe symptom and general health not returning to the usual level)

- **Table 10**, which utilized Definition 2, shows the relative risk reduction of reporting at least one of 14 COVID-19 symptoms or 4 neurological symptoms at Days 85, 169, or 337 in both ensitrelvir 125 mg and 250 mg groups vs placebo.[5]
- Results for exploratory analysis are observational in nature; as such, they should be interpreted with caution

Table 8. Responses to the Comprehensive Questions in the PCC Questionnaire[5]



Day	Endpoint % (n/N)	Ensitrelvir 125 mg	Ensitrelvir 250 mg	Placebo
85	COVID-19 symptoms (mild, moderate, or severe)	6.3 (15/240)	7.6 (17/224)	9.6 (22/228)
	Physical health (poor)	2.5 (6/240)	0.9 (2/224)	3.5 (8/228)
	Not returned to usual health	9.2 (22/240)	9.8 (22/224)	11.8 (27/228)
169	COVID-19 symptoms (mild, moderate, or severe)	11.9 (37/310)	13.0 (42/322)	
	Physical health (poor)	0.6 (2/310)	3.1 (10/322)	
	Not returned to usual health	8.7 (27/310)	10.2 (33/322)	
337	COVID-19 symptoms (mild, moderate, or severe)	6.2 (18/292)	6.6 (20/304)	
	Physical health (poor)	2.5 (8/319)	2.1 (6/292)	3.6 (11/304)
	Not returned to usual health	6.0 (19/319)	6.5 (19/292)	8.2 (25/304)

Table 9. Proportion of Patients with any of 14 COVID-19 Symptoms[b] or 4 Neurological Symptoms[c] as PCC, Definition 1[5,a]

Day	Ensitrelvir 125 mg (% risk reduction vs placebo)		Ensitrelvir 250 mg (% risk reduction vs placebo)	
	14 COVID-19 Symptoms[b]	4 Neurological Symptoms[c]	14 COVID-19 Symptoms[b]	4 Neurological Symptoms[c]
85[d]	24%	34%	5%	8%
169[e]	30%	21%	9%	9%
337[f]	23%	15%	21%	-10%

Table 10. Proportion of Patients with any of 14 COVID-19 Symptoms[b] or 4 Neurological Symptoms[c] as PCC, Definition 2[5,a]

Day	Ensitrelvir 125 mg (% risk reduction vs placebo)		Ensitrelvir 250 mg (% risk reduction vs placebo)	
	14 COVID-19 Symptoms[b]	4 Neurological Symptoms[c]	14 COVID-19 Symptoms[b]	4 Neurological Symptoms[c]
85[d]	33%	40%	11%	49%
169[e]	22%	34%	10%	22%
337[f]	25%	64%	31%	41%

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Table 8. Responses to the Comprehensive Questions in the PCC Questionnaire[5]

Day	Endpoint % (n/N)	Ensitrelvir 125 mg	Ensitrelvir 250 mg	Placebo
85	COVID-19 symptoms (mild, moderate, or severe)	6.3 (15/240)	7.6 (17/224)	9.6 (22/228)
	Physical health (poor)	1.7 (4/240)	0.9 (2/224)	3.5 (8/228)
	Not returned to usual health	7.5 (18/240)	9.8 (22/224)	11.8 (27/228)
169	COVID-19 symptoms (mild, moderate, or severe)	13.9 (46/331)	11.9 (37/310)	13.0 (42/322)
	Physical health (poor)	2.7 (9/331)	0.6 (2/310)	3.1 (10/322)
	Not returned to usual health	7.6 (25/331)	8.7 (27/310)	10.2 (33/322)
337	COVID-19 symptoms (mild, moderate, or severe)	6.0 (19/319)	6.2 (18/292)	6.6 (20/304)
	Physical health (poor)	2.5 (8/319)	2.1 (6/292)	3.6 (11/304)
	Not returned to usual health	6.0 (19/319)	6.5 (19/292)	8.2 (25/304)

Adapted from Yotsuyanagi H, et al. Antiviral Res. 2024;229:105958. doi:10.1016/j.antiviral.2024.105958.
Abbreviations: PCC, post COVID-19 condition.
Data were summarized for patients who completed the PCC questionnaire on each assessment day (days 85, 169, and 337) in the intention to treat population.

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Table 9. Proportion of Patients with any of 14 COVID-19 Symptoms[b] or 4 Neurological Symptoms[c] as PCC, Definition 1[5,a]

Day	Ensitrelvir 125 mg (% risk reduction vs placebo)		Ensitrelvir 250 mg (% risk reduction vs placebo)	
	14 COVID-19 Symptoms[b]	4 Neurological Symptoms[c]	14 COVID-19 Symptoms[b]	4 Neurological Symptoms[c]
85[d]	24%	34%	5%	8%
169[e]	30%	21%	9%	9%
337[f]	23%	15%	21%	-10%

Abbreviation: COVID-19, coronavirus disease 19; PCC, post COVID-19 condition.
Data were summarized for patients who completed the PCC questionnaire on each assessment day (days 85, 169, and 337) in the intention to treat population.
Symptoms marked as "Yes" or "Not sure" to the question "Symptom: COVID-19 Related?" in the PCC questionnaire were regarded as COVID 19–related.
[a]Definition 1: presence of at least one mild, moderate, or severe symptom regarded as COVID-19–related.
[b]Stuffy or runny nose, sore throat, shortness of breath, cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea, vomiting, diarrhea, loss of smell, or loss of taste.
[c]Difficulty with concentration and thinking, difficulty in reasoning and solving problems, memory loss, or insomnia.
[d]Patients who perceived any of the symptoms at the last observation in the follow-up period (e.g., day 21) and on day 85.
[e]Patients who perceived any of the symptoms on both days 85 and 169.
[f]Patients who perceived any of the symptoms on both days 169 and 337.

Proportion of Patients with PCC (Definition 1: presence of at least one mild, moderate, or severe symptom regarded as COVID-19–related)

- As seen in **Table 10**, which utilized Definition 1, ensitrelvir treatment showed a tendency for risk reduction in any of the 14 COVID-19 symptoms. The same trend is seen for risk reduction in any of the 4 neurological symptoms, except at Day 337 in the ensitrelvir 250 mg group.[8]
- Results for exploratory analysis are observational in nature; as such, they should be interpreted with caution

Table 8. Responses to the Comprehensive Questions in the PCC Questionnaire[8]

Table 9. Relative Risk Reduction of Reporting ≥1 of 14 COVID-19 Symptoms or 4 Neurological Symptoms, Definition 2[8,a]

Table 10. Proportion of patients with any of 14 COVID-19 symptoms or 4 neurological symptoms, Definition 1[8,a]

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Table 10. Proportion of Patients with any of 14 COVID-19 Symptoms[b] or 4 Neurological Symptoms[c] as PCC, Definition 2[5,a]

Day	Ensitrelvir 125 mg (% risk reduction vs placebo)		Ensitrelvir 250 mg (% risk reduction vs placebo)	
	14 COVID-19 Symptoms[b]	4 Neurological Symptoms[c]	14 COVID-19 Symptoms[b]	4 Neurological Symptoms[c]
85[d]	33%	42%	11%	49%
169[e]	22%	34%	10%	22%
337[f]	25%	64%	31%	41%

Abbreviation: COVID-19, coronavirus disease 19; PCC, post COVID-19 condition.
Data were summarized for patients who completed the PCC questionnaire on each assessment day (days 85, 169, and 337) in the intention to treat population.
Symptoms marked as "Yes" or "Not sure" to the question "Symptom: COVID-19 Related?" in the PCC questionnaire were regarded as COVID 19–related.
[a]Definition 2: presence of at least one mild, moderate, or severe symptom and general health not returning to the usual level.
[b]Stuffy or runny nose, sore throat, shortness of breath, cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea, vomiting, diarrhea, loss of smell, or loss of taste.
[c]Difficulty with concentration and thinking, difficulty in reasoning and solving problems, memory loss, or insomnia.
[d]Patients who perceived any of the symptoms at the last observation in the follow-up period (e.g., day 21) and on day 85.
[e]Patients who perceived any of the symptoms on both days 85 and 169.
[f]Patients who perceived any of the symptoms on both days 169 and 337.

Proportion of Patients with PCC (Definition 1: presence of at least one mild, moderate, or severe symptom regarded as COVID-19–related)

- As seen in **Table 10**, which utilized Definition 1, ensitrelvir treatment showed a tendency for risk reduction in any of the 14 COVID-19 symptoms. The same trend is seen for risk reduction in any of the 4 neurological symptoms, except at Day 337 in the ensitrelvir 250 mg group.[8]
- Results for exploratory analysis are observational in nature; as such, they should be interpreted with caution

Table 8. Responses to the Comprehensive Questions in the PCC Questionnaire[8]

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EXPLORATORY/POST-HOC ANALYSES

Long COVID-19 Symptoms (cont'd)

Risk Reduction vs Placebo: Patients With ≥1 of 27 COVID-19 Symptoms, Not Having Returned to Usual Health

- The relative risk reduction of reporting at least one of 27 COVID-19 symptoms in patients who reported "Not having returned to usual health" is displayed in **Table 11**, including an analysis in patients with BMI ≥25 kg/m^2.[5]
- Results for exploratory analysis are observational in nature; as such, they should be interpreted with caution.

Table 11. Relative Risk Reduction of Reporting at Least 1 of 27 COVID-19 Symptoms in Patients Who Reported "Not Having Returned to Usual Health"[5,a]

Day	Ensitrelvir 125 mg (% risk reduction vs placebo)			Ensitrelvir 250 mg (% risk reduction vs placebo)		
	27 COVID-19 Symptoms	BMI ≥25 kg/m^2	Median or Higher Symptom Score at Baseline	27 COVID-19 Symptoms	BMI ≥25 kg/m^2	Median or Higher Symptom Score at Baseline
85	40	76	58	17	47	33
169	26	62	17	15	28	11
337	25	49	37	26	47	28

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 19.
[a]The total score of 14 symptoms at baseline of ≥ 9.

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EXPLORATORY/POST-HOC ANALYSES

Post-hoc Analysis Results (Viral Rebound and Symptom Recurrence)

A post-hoc analysis of the phase 3 part of the phase 2/3 study assessed viral rebound and symptom recurrence up to Day 21. Viral RNA rebound by PCR testing was observed in 7.8% in the ensitrelvir 125 mg group (46/590), 6.7% in the ensitrelvir 250 mg group (38/570), and 4.7% in the placebo group (27/574). Of the patients with viral RNA rebound, 0%, 3.6% (1/28), and 0% of patients had symptom recurrence (based on 5 COVID-19 symptoms) in the 125 mg group, 250 mg group, and the placebo group, respectively. Symptom recurrence was not associated with viral RNA rebound. There was one (1/310) low-level viral titer positive observed in the follow-up period (in the ensitrelvir 125 mg group), and no positive viral titers in the other treatment groups.[6]

Results for these endpoints are observational in nature; as such, they should be interpreted with caution.

Xocova - Phase 2 and 3 (SCORPIO-SR) Studies

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RELEVANT PRESCRIBING INFORMATION

INDICATIONS AND USAGE

XOCOVA® is indicated for post-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19.[14]

CONTRAINDICATIONS

XOCOVA® is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[14]

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.[14]

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.

Xocova - Phase 2 and 3 (SCORPIO-SR) Studies

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LITERATURE SEARCH

As of February 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) failed to identify any additional relevant references regarding information on ensitrelvir and its phase 2/3 study.

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

ABBREVIATIONS

3CL	3-chymotrypsin-like
AE	adverse event
BMI	body mass index
CI	confidence interval
COVID-19	Coronavirus disease 19
D	day
h, hr	hours
HDL	high-density lipoprotein
ITT	intention-to-treat
MHLW	Ministry of Health, Labour, and Welfare
mITT	modified intention-to-treat
NA	not available
PCC	post COVID-19 condition
PK	pharmacokinetic
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCORPIO-SR	Stopping COVID-19 pRogression with early Protease InhibitOr-Standard Risk
SD	standard deviation
SE	standard error
$TCID_{50}$	50% tissue culture infectious dose
TEAE	treatment-emergent adverse event
TG	triglyceride

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ENCLOSURE

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