Xocova - Prevention of Long-COVID-19

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1. SUMMARY

- The SCORPIO-PEP Phase 3 clinical trial assessed the use of ensitrelvir for post-exposure prophylaxis of acute COVID-19 and was not designed to evaluate the incidence of Long COVID.[1,2]
- SCORPIO-HR was a global Phase 3, multicenter, randomized, double-blind, parallel-group, 24-week clinical study that assessed the clinical and antiviral effects of ensitrelvir vs placebo in nonhospitalized patients with acute COVID-19 with or without high risk factors for severe COVID-19.[3]
    - Primary endpoint: The time to sustained resolution of 15 common COVID-19 related symptoms (completely absent for at least 2 days) through day 29 demonstrated a numerical reduction in ensitrelvir vs. placebo but was not statistically significant, making data from secondary endpoints descriptive (such results should be interpreted with caution). Most treatment-emergent adverse events (TEAEs) were mild to moderate in severity and no serious adverse events were treatment-related.[3]
    - Secondary endpoints - Persistent and/or late-onset COVID-19 symptoms (mITT):
        - The occurrence of persistent and/or late-onset symptoms through Week 24 was 49.2% (465/945) in the ensitrelvir group and 48% (453/943) in the placebo group (RR: 1.02 [95% CI: 0.934,1.124], *P*=0.6129), with no severe symptoms in ≥1.0% of patients.[4]
        - At Week 24, 30 (5.3%) ensitrelvir treated patients and 33 (5.8%) placebo-treated patients had not returned to their pre-COVID-19 health, and 13 (2.3%) ensitrelvir-treated patients and 9 (1.6%) of the placebo-treated patients required urgent medical care.[4]
        - Fewer than 1% of patients in either group had serious complications.[4]
- The Phase 2/3 study of patients with acute mild-to-moderate or asymptomatic SARS-CoV-2 infection in Asia which include the Phase 2a, Phase 2b, Phase 3, and Phase 2b/3 (exploratory) parts, evaluated patients that were randomized 1:1:1 to receive ensitrelvir 125 mg or 250 mg or placebo.[5-9]
    - **Yotsuyanagi et al. (2024)** – Phase 3 part (SCORPIO-SR):
        - Primary endpoint (ITT): The time to resolution of 5 COVID-19 symptoms was significantly reduced with both doses of ensitrelvir (*P*=0.04 with a Peto-Prentice generalized Wilcoxon test for ensitrelvir 125 mg vs placebo) as well as ensitrelvir 250 mg vs placebo (*P*=0.203).[8] The most common TEAEs in the ensitrelvir 125 mg group were decreased HDL, increased triglycerides, and increased bilirubin.[8]
        - Exploratory Long COVID analysis (ITT): A numerical reduction in risk was observed with both ensitrelvir doses vs placebo for developing any COVID-19 and neurological symptoms at Days 85, 169, and 337 using the PCC questionnaire.[8] Exploratory data should be interpreted with caution. For more information, see **Table 7** and **Table 8**.
    - **Imamura et al. (2024)** reported on the efficacy of ensitrelvir in SARS-CoV-2 infected patients who were either asymptomatic or had mild symptoms from the exploratory Phase 2b/3 part.[10]
        - Main analysis (ITT): The proportion of asymptomatic participants experiencing the development of 14 COVID-19 symptoms or fever by Day 10 was reduced with ensitrelvir 125 mg vs placebo. Most TEAEs were mild to moderate in severity.[10]

        - Long COVID analysis: The proportion of patients that reported that their health status had not returned to usual levels on Day 337 in the ensitrelvir 125 mg, ensitrelvir 250 mg, and placebo groups was 4.3% (5/115), 3.4% (4/117), and 8.8% (11/125), respectively.[10] Exploratory data should be interpreted with caution. For more information, see **Table 10** and **Figure 3**.
- **Hibino et al. (2026)** conducted a large, prospective, nationwide Japanese cohort study (ANCHOR-01 Study) evaluating oral antivirals' effect on the development of post-COVID-19 condition (PCC) in outpatients aged ≥12 years with acute symptomatic COVID-19.[11,12]
    - Unadjusted PCC incidence (primary endpoint) was 24.3% (530 /2181) of the antiviral group vs 26.2% (1443/5518) of the no-antiviral group; when adjusted for baseline characteristics, PCC incidence was 21.5% antiviral vs 25.1% no-antiviral and risk ratio for antivirals was 0.86 (95% CI: 0.78-0.93; *P*<0.001) at both Days 28 and 84.[11,12]
- **Abe et al. (2024)** conducted a retrospective study evaluating 18 outpatients with acute mild-to-moderate SARS-CoV-2 infection and a history of vaccination and who were treated with ensitrelvir for the development of post-acute sequalae of COVID-19[13]
    - None of the 18 patients reported PASC symptoms by Day 60.[13]
    - There were no reports of adverse events.[13]

2. CLINICAL TRIALS

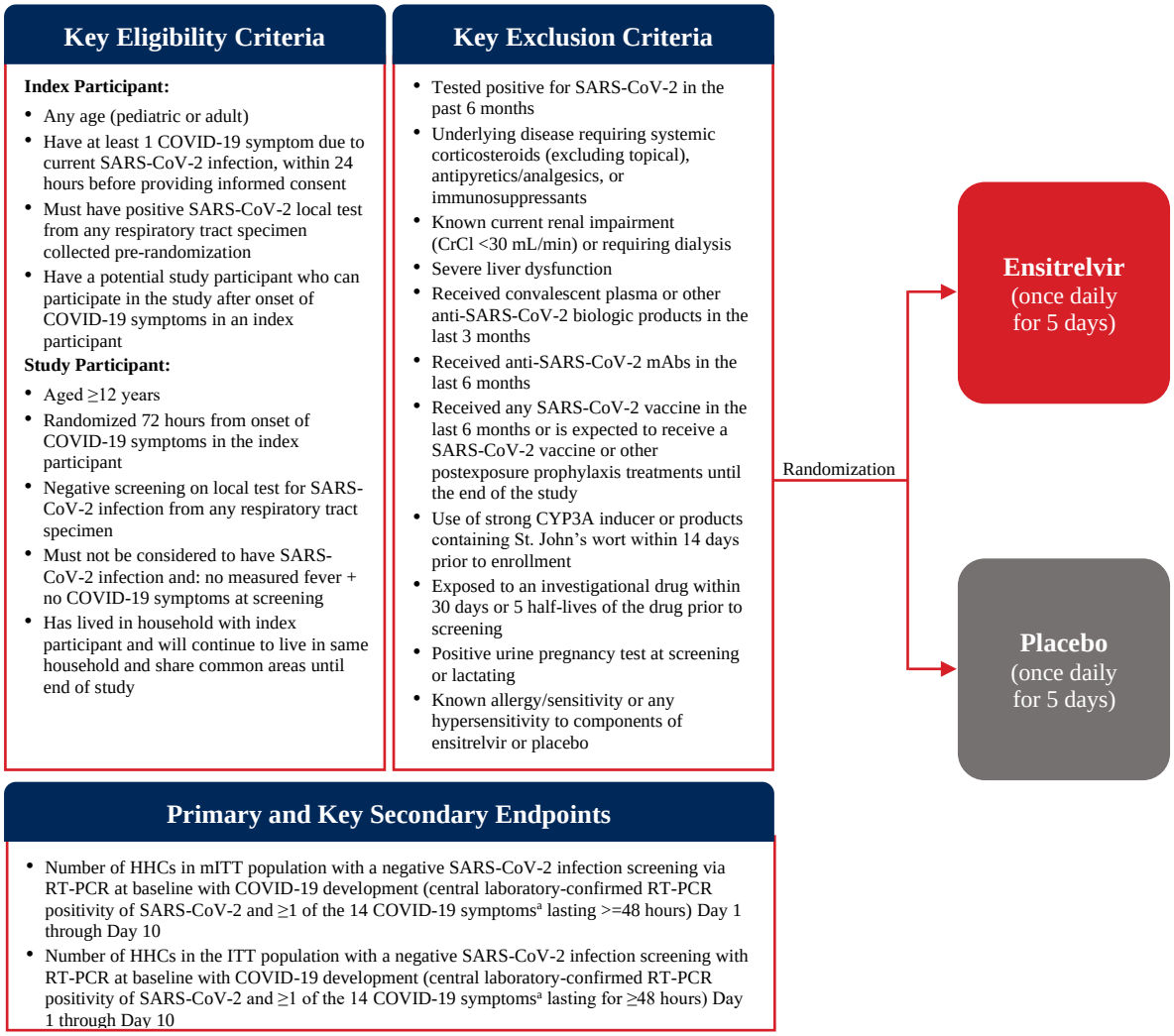
SCORPIO-PEP (Phase 3)

Study Design

SCORPIO-PEP (**NCT05897541**) is a Phase 3 randomized, double-blind, placebo-controlled, 28-day trial evaluating the efficacy and safety of ensitrelvir as post-exposure prophylaxis for preventing symptomatic SARS-CoV-2 infection in household contacts aged ≥12 and older of individuals with symptomatic COVID-19 that tested positive for COVID-19 (**Figure 1**).[1,14]

Household contacts that were exposed to COVID-19 received either ensitrelvir (375 mg on Day 1 and 125 mg on Days 2-5) or placebo for 5 days in a 1:1 ratio within 72 hours after symptom onset in the index patient.[1]

Figure 1. SCORPIO-PEP Study Design[1,14]



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

- **Primary Endpoint**: proportion of HHCs with symptomatic COVID-19 development through Day 10 in the mITT population[1]
  - The mITT population was defined as participants who were negative on both a local test antigen or Reverse Transcription Polymerase Chain Reaction (RT-PCR) and on a central RT-PCR test at baseline[1]
  - Symptomatic COVID-19 was defined as having a central laboratory-confirmed RT-PCR positivity of SARS-CoV-2 and ≥1 of the 14 COVID-19 symptoms lasting ≥48 hours[1]
  - The 14 COVID-19 symptoms studied were: fever, shortness of breath or difficulty breathing, cough, sore throat, nasal congestion or runny nose, chills, fatigue, body or muscle pain or aches, headache, nausea, vomiting, diarrhea, change in the sense of taste, and change in the sense of smell[15]

- **Key Secondary Endpoint**: proportion of HHCs with symptomatic COVID-19 development through Day 10 in the ITT population[1]
    - The ITT population was defined all randomized patients with a negative local test at baseline, regardless of whether they had a negative or positive central RT-PCR test at baseline[1]
- The study continued to assess household contacts through Day 28 as part of the secondary endpoints, which included other COVID-19-symptom-related endpoints as well as virology (viral RNA) endpoints. None of the study endpoints evaluated the incidence of Long COVID in patients who developed acute COVID-19 during the trial.[2,15]

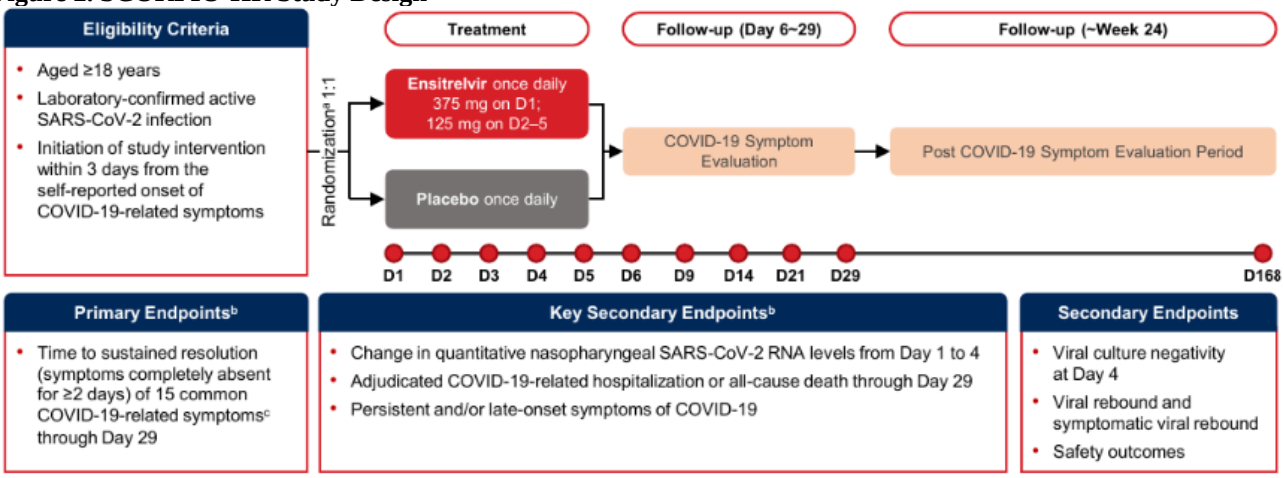
SCORPIO-HR (NCT05305547) is a global Phase 3, multicenter, randomized, double-blind, parallel-group, 24-week clinical study that assessed the clinical and antiviral effects of ensitrelvir (oral once daily for five days) vs placebo in nonhospitalized patients with acute COVID-19 with or without high risk factors for severe COVID-19 (**Figure 2**).[3]

- 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). [3]
- This study was conducted when Omicron variant infection was predominant and among a mostly vaccinated population.[3,16,17]
- The primary endpoint for SCORPIO-HR was time to sustained resolution (completely absent for at least 2 days) of 15 common COVID-19 related symptoms through day 29.[3]

Methods

The study design and follow-up timeline for the SCORPIO-HR study is seen below **(Figure 2)**.

Figure 2. SCORPIO-HR Study Design[3]



Abbreviations: COVID-19, coronavirus disease 19; 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.

Secondary Objectives – Post-COVID-19 Condition

Secondary objects related to the development of persistent, or late-onset symptoms include:

- The prevalence, severity, and types of persistent and/or late-onset symptoms through the end-of-study follow-up (Week 24) in adult outpatients who started treatment for mild and moderate COVID-19 within 3 days of symptom onset.[4]
- To explore measures of functional health, health-related QOL, and psychological health through end-of-study follow-up (Week 24) in adult outpatients with mild and moderate COVID-19 starting intervention within 3 days of symptom onset.[4]

A post-acute COVID-19 questionnaire was completed by patients at Weeks 12, 24 and if premature study discontinuation occurred. This included questions related to general health, medical care, COVID-19 symptom severity, and the return to pre-COVID-19 health.[4]

Results

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).[3]

Safety

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

Post-COVID-19 Condition Results

Primary and key secondary endpoints were tested using a fixed-sequence hierarchical approach at two-sided significance level of 0.05. For SCORPIO-HR, the primary efficacy endpoint was not statistically significant, therefore secondary endpoint results are descriptive in nature; as such, secondary endpoints should be interpreted in an exploratory manner.[3]

Occurrence of Persistent and/or Late-Onset Symptoms (mITT):[2]

Week 12: Ensitrelvir: 227/945 (24%) **vs.** Placebo: 221/943 (23.4%) (Risk Ratio: 1.02 [95% CI: 0.872, 1.205], *P*= 0.7869)

Week 24: Ensitrelvir: 465/945 (49.2%) **vs.** Placebo: 453/943 (48.0%) (Risk Ratio: 1.02 [95% CI: 0.934, 1.124], *P*= 0.6129)

Most Common Persistent Symptoms at Week 12 and 24:[2]

At Weeks 12 and 24, for both the ensitrelvir and placebo groups, no significant differences in symptom prevalence were seen and most were considered mild or moderate. In both treatment groups, there were no individual symptoms considered severe in ≥1.0% of patients.

The most commonly reported persistent symptoms for both groups as Weeks 12 and 24 are provided in **Table 1** and **Table 2**.[4]

Table 1. Week 12 Persistent Symptoms with Overall Prevalence of >5% in Either Group (mITT)[4]

Symptom	Ensitrelvir (n=945) n/N (%)	Placebo (n=943) n/N (%)	Risk Difference (%% CI)	*P*-value[a]
Body pain/muscle pain/aches	106/850 (12.5)	89/855 (10.4)	1.2 (0.9, 1.6)	0.1812
Cough	79/850 (9.3)	71/855 (8.3)	1.1 (0.8, 1.5)	0.4705
Decreased appetite	41/850 (4.8)	44/855 (5.1)	0.9 (0.6, 1.4)	0.7595
Difficulty concentrating/thinking	86/850 (10)	83/855 (9.7)	1 (0.8, 1.4)	0.8395
Difficulty reasoning/ problem solving	48/850 (5.6)	57/855 (6.7)	0.8 (0.6, 1.2)	0.3812
Dizziness/balance issues	67/850 (7.9)	50/855 (5.8)	1.3 (0.9, 1.9)	0.0966
Fatigue/decrease energy	120/850 (14.1)	124/855 (14.5)	1.0 (0.8, 1.2)	0.8203
Hair loss	101/850 (11.9)	96/855 (11.2)	1.1 (0.8, 1.4)	0.6726
Headache	115/850 (13.5)	105/855 (12.3)	1.1 (0.9, 1.4)	0.4419
Insomnia	103/850 (12.1)	101/855 (11.8)	1.0 (0.8, 1.3)	0.8463
Joint pain	99/850 (11.6)	86/855 (10.1)	1.2 (0.9, 1.5)	0.2916
Memory loss (short or long-term)	71/850 (8.4)	74/855 (8.7)	1 (0.7, 1.3)	0.8231
Muscle weakness	68/850 (8)	56/855 (6.5)	1.2 (0.9, 1.7)	0.2489
Nasal discharge	83/850 (9.8)	72/855 (8.4)	1.2 (0.9, 1.6)	0.3346
Nasal obstruction or congestion	93/850 (10.9)	77/855 (9)	1.2 (0.9, 1.6)	0.1823
Palpitations or fast heart beat	55/850 (6.5)	54/855 (6.3)	1 (0.7, 1.5)	0.8961
Shortness of breath or difficulty breathing	56/850 (6.6)	49/855 (5.7)	1.1 (0.8, 1.7)	0.4616
Sore throat	57/850 (6.7)	39/855 (4.6)	1.5 (1.0, 2.2)	0.0548
Skin rash	44/850 (5.2)	39/855 (4.6)	1.1 (0.7, 1.7)	0.5551

Abbreviations: CI, confidence interval, N, number of patients in analysis set; n, number of patients
[a]*P*-values have not been adjusted for multiplicity and should be considered to be nominal.
Persistent symptoms at Week 12 were defined as any of the targeted symptoms remaining (not absent) at Week 12 follow-up.
The risk ratio estimate, associated 95% CI, and *P*-value are from the comparison of study intervention vs placebo.

Table 2. Week 24 Persistent Symptoms with Overall Prevalence of >5% in Either Group (mITT)[4]

Symptom	Ensitrelvir (n=945) n/N (%)	Placebo (n=943) n/N (%)	Risk Difference ((%% CI)	*P*-value[a]
Body pain/muscle pain/aches	61/568 (10.7)	63/569 (11.1)	1 (0.7, 1.4)	0.8572
Cough	35/568 (6.2)	39/569 (6.9)	0.9 (0.6, 1.4)	0.6362
Decreased appetite	25/568 (4.4)	18/569 (3.2)	1.4 (0.8, 2.5)	0.2739
Difficulty concentrating/thinking	57/568 (10)	40/569 (7)	1.4 (1, 2.1)	0.0697
Difficulty reasoning/ problem solving	44/568 (7.7)	29/569 (4.6)	1.7 (1.1, 2.7)	0.0258
Dizziness/balance issues	34/568 (6)	22/569 (3.9)	1.5 (0.9, 2.6)	0.0987
Fatigue/decrease energy	72/568 (12.7)	75/569 (13.2)	1 (0.7, 1.3)	0.7997
Hair loss	50/568 (8.8)	39/569 (6.9)	1.3 (0.9, 1.9)	0.2213
Headache	55/568 (8.8)	55/569 (9.7)	1 (0.7, 1.4)	0.9923
Insomnia	62/568 (10.9)	44/569 (7.7)	1.4 (1, 2)	0.0650
Joint pain	60/568 (10.6)	44/569 (7.7)	1.4 (0.9, 2)	0.0978
Memory loss (short or long-term)	44/568 (7.7)	50/569 (8.8)	0.9 (0.6, 1.3)	0.5240
Muscle weakness	39/568 (6.9)	34/569 (6)	1.1 (0.7, 1.8)	0.5401
Nasal discharge	38/568 (6.7)	45/569 (7.9)	0.8 (0.6, 1.3)	0.4297
Nasal obstruction or congestion	39/568 (6.9)	53/569 (9.3)	0.7 (0.5, 1,1)	0.1301
Palpitations or fast heartbeat	31/568 (5.5)	31/569 (5.4)	1 (0.6, 1.6)	0.9943
Shortness of breath or difficulty breathing	27/568 (4.8)	27/569 (4.7)	1 (0.6, 1.7)	0.9947
Sore throat	25/568 (4.4)	22/569 (3.9)	1.1 (0.6, 2)	0.6505
Skin rash	17/568 (3)	12/569 (2.1)	1.4 (0.7, 2.9)	0.3445

Abbreviations: CI, confidence interval, N, number of patients in analysis set; n, number of patients
[a]*P*-values have not been adjusted for multiplicity and should be considered to be nominal.
Persistent symptoms at Week 24 were defined as any of the targeted symptoms remaining (not absent) at Week 24 follow-up.
The risk ratio estimate, associated 95% CI, and *P*-value are from the comparison of study intervention vs placebo.

Return to Usual Health

At Week 12, 57 (6.7%) ensitrelvir treated patients and 71 (8.3%) placebo treated patients had not returned to their pre-COVID-19 health and at Week 24, 30 (5.3%) ensitrelvir treated patients and 33 (5.8%) placebo treated patients had not returned to their pre-COVID-19 health.[2]

The number of patients in the mITT population that had not returned to usual health and had ≥1 of the primary 27 symptoms at Week 12 and Week 24 is provided in **Table 3**.[2]

Table 3. Patients with the long COVID question for "Not Returning to Usual Health" and "Having ≥1 Symptom of all 27 Symptoms[a]" at Week 12 and Week 24 (mITT)[4]

Not returned to pre-COVID-19 health and ≥1 symptom	Ensitrelvir (N=945) n (%)	Placebo (N=943) n (%)	Estimated risk ratio (95% CI)	*P* -value
Week 12				
Yes	142 (15)	138 (14.6)	1.03 (0.827, 1,275)	0.8460
No	803 (85)	805 (85.4)		
Week 24				
Yes	396 (41.9)	394 (41.8)	1 (0.902, 1.115)	0.9628
No	549 (58.1)	549 (58.2)		

Abbreviations: CI, confidence interval; N, number of participants in analysis set; n, number of participants.
[a]27 target symptoms included Cough; Shortness of breath or difficulty breathing; Feeling feverish; Chills; Fatigue (low energy); Body pain or muscle pain or aches; Diarrhea; Nausea; Vomiting; Headache; Sore throat; Nasal obstruction or congestion; Nasal discharge; Muscle weakness; Insomnia; Hair loss; Smell disorder; Palpitations or fast heart beat; Joint pain; Decreased appetite; Taste Disorder; Dizziness/balance issues; Chest pain; Skin rash; Difficulty with concentration and thinking; Difficulty reasoning and solving problems; Memory loss (short or long term)
Participants in whom this endpoint was not able to be evaluated due to missing data in the Post-acute COVID-19 Questionnaire will be treated as those who had at least one symptom and whose general health had not returned at Week 12 and at Week 24.
The risk ratio estimate, associated 95% CI, and *P* -value are from the comparison of study intervention vs placebo.

Urgent Medical Care

Week 12: 33 (3.9%) patients treated with ensitrelvir and 15 (1.8%) that were given placebo required urgent medical care at a clinic or emergency room.[2]

Week 24: 13 (2.3%) ensitrelvir-treated patients and 9 (1.6%) of the placebo-treated patients required urgent medical care.[2]

Serious complications: For both time periods, fewer than 1% of patients in either group were diagnosed with cerebrovascular accident, deep vein thrombosis, myocardial infarction, or pulmonary embolism, or were prescribed corticosteroids or anticoagulants.[2]

PHASE 2/3 STUDY

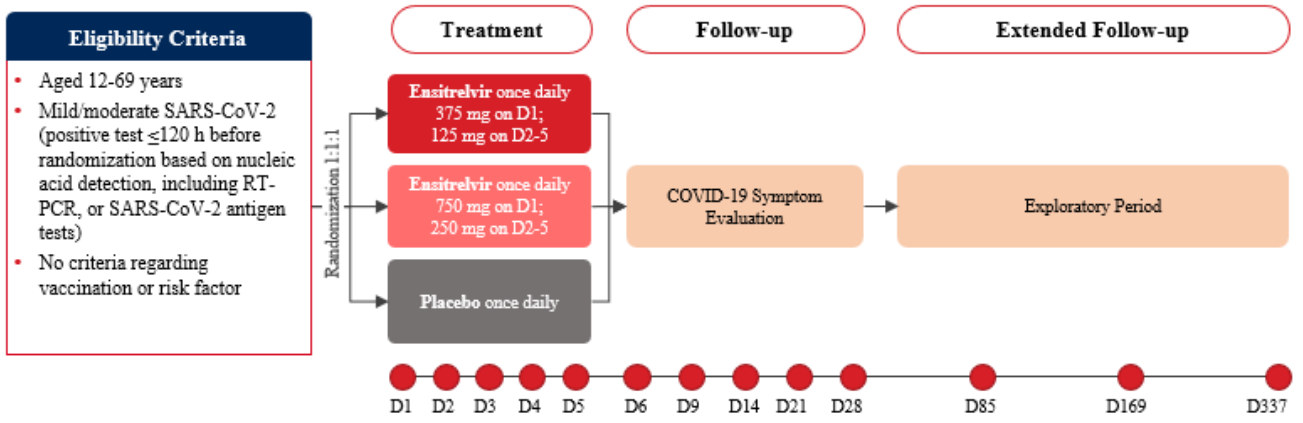
Phase 3 (SCORPIO-SR)

The SCORPIO-SR (Phase 3 part) trial is part of the phase 2/3, multicenter, randomized, double-blind, placebo-controlled clinical study and evaluated the efficacy (clinical symptom improvement and antiviral effect) and safety of ensitrelvir administered orally, once daily for five days in patients with acute SARS-CoV-2 infection**.** SCORPIO-SR was conducted in Japan, South Korea, and Vietnam.[5]

Methods

The study design and follow-up timeline for the SCORPIO-SR study is seen below **(Figure 3**).

Figure 3. SCORPIO-SR Study Design[7]



Phase 3 Endpoints	Post-hoc Endpoint
Population: Mild/moderate Primary: • Time to resolution of five COVID-19 symptoms Secondary outcomes included: • Change from baseline in SARS-CoV-2 viral RNA on D4, time to first negative SARS-CoV-2 viral titer (key endpoints), and safety by D28	Post-hoc (phase 3 part): Presence of long COVID-19 symptoms through year 1 via COVID-19 symptoms & PCC questionnaires

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

Post-Hoc Post-COVID-19 Condition Analysis

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 PCC questionnaires of 14 symptoms, 4 neurological symptoms, and 27 symptoms. 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.[8]

- Using an electronic patient diary, patients self-evaluated using the PCC questionnaire, which consisted of the following:[8]
  - Questions on the severity of COVID-19 symptoms over the last 4 weeks (27 symptoms including 14 acute-phase symptoms assessed at baseline and 4 neurological symptoms)
  - General physical health over the past 4 weeks
  - Question asking "Have you returned to your usual (pre-COVID) health?"
- The 27 symptoms that were part of the PCC questionnaire can be seen in **Table 4**.[8]

Table 4. List of 27 Symptoms Included in the Post-COVID-19 Condition Questionnaire[18]

Symptoms		
Cough[a]	Shortness of breath or difficulty breathing [a]	Feeling feverish[a]
Chills[a]	Fatigue[a]	Body pain/muscle pain/aches [a]
Diarrhea[a]	Nausea[a]	Vomiting[a]
Headache[a]	Sore throat [a]	Nasal obstruction or congestion[a]
Nasal discharge	Muscle weakness	Insomnia[b]
Hair loss	Smell disorder[a]	Fast heartbeat
Joint pain	Decreased appetite	Taste disorder[a]
Dizziness/balance issues	Chest pain	Skin rash
Difficulty with concentration and thinking[b]	Difficulty in reasoning and solving problems[b]	Memory loss (short or long term)[b]

Abbreviations: COVID-19, coronavirus disease 2019.
[a]Symptoms included in the 14 acute-phase symptoms.
[b]Symptoms included in the 4 neurological symptoms.
Table adapted from Yotsuyanagi et al. *Antiviral Research*. 2024.

- This analysis defined PCC using the following two definitions:[8]
  - Definition 1: Patients were regarded as having PCC when they had at least one mild, moderate, or severe symptom regarded as COVID-19–related.
  - Definition 2: Patients were regarded as having PCC when they had at least one mild, moderate, or severe symptom and their general health had not returned to the pre-COVID health level.

Results

Primary Endpoint

Primary endpoint: The time to resolution of five COVID-19 symptoms (primary endpoint) was significantly reduced with ensitrelvir 125 mg vs placebo in the primary analysis population (P = 0.04 with a Peto-Prentice generalized Wilcoxon test) (See **Table 5**).[7]

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

	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	-

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 19; h, hours; ITT, intention-to-treat; RNA, ribonucleic acid;SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Five COVID-19 symptoms were runny or stuffy nose, sore throat, cough, feeling hot or feverish, and malaise (fatigue).
[b]Analysis in the ITT population (all cases confirmed positive for SARS-CoV-2 viral RNA at baseline) with any of the 5 symptoms at baseline.
[c]Adjusted for SARS-CoV-2 vaccination status.
The efficacy analysis group comprised of the ensitrelvir 125 mg treatment arm and placebo arm.
Table adapted from Yotsuyanagi et al. *JAMA*. 2024.

Safety

Most treatment-related adverse events (TRAEs) were mild in severity, and a decrease in high-density lipoprotein (HDL) was the most commonly reported TRAE. There were two serious adverse events (AEs) reported in the study (one in the ensitrelvir 125 mg arm and one in the placebo arm), both of which were judged as not treatment related.[7]

Post-COVID-19 Condition Results

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

- In the ensitrelvir 125 mg, 250 mg, and placebo groups, 379, 345, and 362 patients participated in the extended follow-up period, respectively and >80% of participants from each group had complete PCC questionnaires at day 337.[8]

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 (See **Table 6**).[8]

Table 6. SCORPIO-SR Responses to the Comprehensive Questions in the PCC Questionnaire[8]

Day	Question n/N (%)	Ensitrelvir 125 mg n/N (%)	Ensitrelvir 250 mg n/N (%)	Placebo n/N (%)
Day 85	COVID-19 symptoms[a]	15/240 (6.3%)	17/224 (7.6%)	22/228 (9.6%)
	Poor physical health	4/240 (1.7%)	2/224 (0.9%)	8/228 (3.5%)
	Did not return to usual health	18/240 (7.5%)	22/224 (9.8%)	27/228 (11.8%)
Day 169	COVID-19 symptoms[a]	46/331 (13.9%)	37/310 (11.9%)	42/322 (13.0%)
	Poor physical health	9/331 (2.7%)	2/310 (0.6%)	10/322 (3.1%)
	Did not return to usual health	25/331 (7.6%)	27/310 (8.7%)	33/322 (10.2%)
Day 337	COVID-19 symptoms[a]	19/319 (6.0%)	18/292 (6.2%)	20/304 (6.6%)
	Poor physical health	8/319 (2.5%)	6/292 (2.1%)	11/304 (3.6%)
	Did not return to usual health	19/319 (6.0%)	19/292 (6.5%)	25/304 (8.2%)

Abbreviations: COVID-19, coronavirus disease 2019; ITT, intention to treat; PCC, post COVID-19 condition.
[a]Mild, moderate, or severe COVID-19 symptoms.Data were summarized for patients who completed the PCC questionnaire on each assessment day (days 85, 169, and 337) in the ITT population.
Table adapted from Yotsuyanagi et al. *Antiviral Research*. 2024.

Results Based on Definition 1:

- Risk reductions were observed to be numerically lower with ensitrelvir 125 mg and 250mg vs placebo for developing any of the 14 acute-phase symptoms at Days 85, 169, and 337 (**Table 7**)[8]
- 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]

Table 7. Risk Reduction vs Placebo: Patients with any of 14 COVID-19 Symptoms and any of the 4 Neurological Symptoms as PCC, Definition 1[a,8]

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%

Abbreviations: COVID-19, coronavirus disease 19; PCC, post COVID-19 condition.
[a]Definition 1: presence of at least one mild, moderate, or severe symptom regarded as COVID-19–relate
[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.
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.
Table adapted from Yotsuyanagi et al. *Antiviral Research*. 2024.

Results Based on Definition 2:

- The relative risk reduction at Days 85, 169, or 337 was numerically lower in both ensitrelvir 125 mg and 250 mg vs. placebo (**Table 8**) for reporting:[8]
  - at least one of 14 COVID-19 symptoms
  - four neurological symptoms
  - at least one of 27 COVID-19 symptoms

Table 8. Risk Reduction vs Placebo: Patients with any of 14 COVID-19 Symptoms[b], 4 Neurological Symptoms[c], or any of the 27 COVID-19 symptoms[d] as PCC, Definition 2[a,8]

Day	Ensitrelvir 125 mg (% risk reduction vs placebo)			Ensitrelvir 250 mg (% risk reduction vs placebo)		
	14 COVID-19 Symptoms[b]	4 Neurological Symptoms[c]	27 COVID-19 Symptoms[d]	14 COVID-19 Symptoms[b]	4 Neurological Symptoms[c]	27 COVID-19 Symptoms[d]
85[e]	33%	42%	40%	11%	49%	17%
169[f]	22%	34%	26%	10%	22%	15%
337[g]	25%	64%	25%	31%	41%	26%

Abbreviation: COVID-19, coronavirus disease 19, PCC, post COVID-19 condition.
[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]The 14 acute-phase symptoms + 4 neurological symptoms + typical PCC symptoms additionally selected (hair loss, palpitations or fast heartbeat, joint pain, decreased appetite, dizziness, chest pain, skin rash, and muscle weakness)
[e]Patients who perceived any of the symptoms at the last observation in the follow-up period (e.g., day 21) and on day 85.
[f]Patients who perceived any of the symptoms on both days 85 and 169.
[g]Patients who perceived any of the symptoms on both days 169 and 337.
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.
Table adapted from Yotsuyanagi et al. *Antiviral Research*. 2024.

Subgroup Analysis:

- A subgroup analysis in patients with BMI ≥25 kg/m^2 reporting at least one of 27 COVID-19 symptoms showed a risk reduction with ensitrelvir 125 mg at days 85 and 169 vs. placebo (see **Table 9**).[8]
- Results from an additional analysis that looked at patients who reported median or higher symptom scores at baseline show that the relative risk reduction of reporting at least one of 27 COVID-19 symptoms was lower with ensitrelvir 125 mg at Day 85 (57.5%) vs. placebo (see **Table 9**).[8]

Table 9. Relative Risk Reduction of Reporting At Least One of 27 COVID-19 Symptoms in Patients Who Reported "Not Having Returned to Usual Health"[8]

Day	Ensitrelvir 125 mg (% risk reduction vs placebo)				Ensitrelvir 250 mg (% risk reduction vs placebo)			
	n	BMI ≥25 kg/m^2	n	Median or Higher Symptom Score at Baseline	n	BMI ≥25 kg/m^2	n	Median or Higher Symptom Score at Baseline
85	74	76%	136	58%	57	47%	106	33%
169	88	62%	176	17%	77	28%	144	11%
337	84	49%	169	37%	67	47%	132	28%

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; PCC, post COVID-19 condition.
Patients were defined as having PCC based on "Definition 2".
At Days 85, 169, and 337 the number of participants in the placebo arm were 60, 78, and 71, respectively for the high BMI experiment.
At Days 85, 169, and 337 the number of participants in the placebo arm were 122,171, and 159, respectively for the median or higher symptom score experiment.
Table adapted from Yotsuyanagi et al. *Antiviral Research*. 2024

Phase 2b/3

Imamura et al (2024) assessed the efficacy of ensitrelvir in preventing PCC in patients with asymptomatic SARS-CoV-2 infection or mild COVID-19 symptoms from the Phase 2b/3 study. PCC was defined based on the self-assessed general health level and severity of a prespecified set of symptoms at Day 337.[8]

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.[7]

Responses to the Comprehensive Questions in the PCC Questionnaire

Patient characteristics were generally balanced across treatment groups. Approximately 90% of the patients had SARS-CoV-2 vaccination history.[8]

The proportion of patients that reported that their health status had not returned to usual levels on Day 337 in the ensitrelvir 125 mg, ensitrelvir 250 mg, and placebo groups was 4.3% (5/115), 3.4% (4/117), and 8.8% (11/125), respectively (**Table 10**).[10]

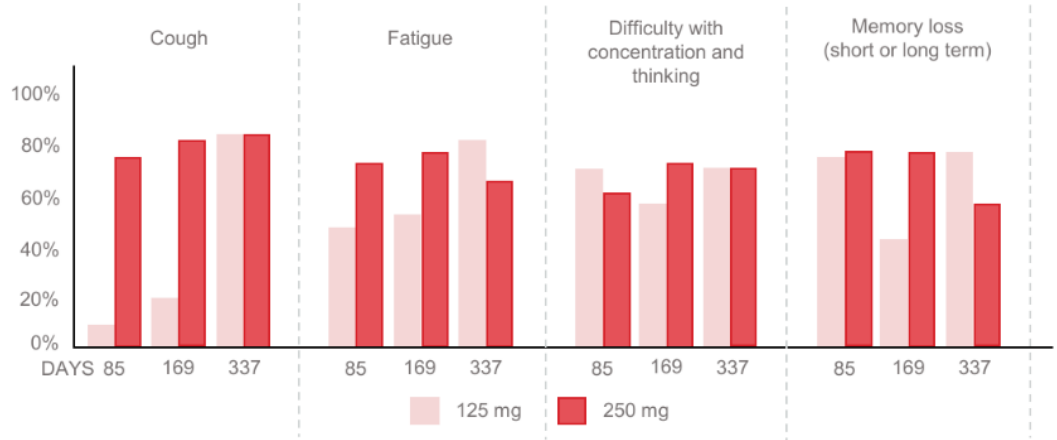
Table 10. Phase 2b/3: Responses to the Comprehensive Questions in the PCC Questionnaire[10]

Day	Question n/N (%)	Ensitrelvir 125mg N=124	Ensitrelvir 250mg N=129	Placebo N=131
Day 85	COVID-19 symptoms[a]	6/114 (5.3%)	2/120 (1.7%)	12/122 (9.8%)
	Poor physical health	2/114 (1.8%)	1/120 (0.8%)	4/122 (3.3%)
	Did not return to usual health	8/114 (7.0%)	4/120 (3.3%)	16/122 (13.1%)
Day 169	COVID-19 symptoms[a]	5/117 (4.3%)	6/125 (4.8%)	8/129 (6.2%)
	Poor physical health	1/117 (0.9%)	2/125 (1.6%)	4/129 (3.1%)
	Did not return to usual health	6/117 (5.1%)	3/125 (2.4%)	10/129 (7.8%)
Day 337	COVID-19 symptoms[a]	1/115 (0.9%)	3/117 (2.6%)	4/125 (3.2%)
	Poor physical health	2/115 (1.7%)	3/117 (2.6%)	6/125 (4.8%)
	Did not return to usual health	5/115 (4.3%)	4/117 (3.4%)	11/125 (8.8%)

Abbreviations: COVID-19, coronavirus disease 2019; ITT, intention to treat; PCC, post COVID-19 condition.
[a]Mild, moderate, or severe COVID-19 symptoms.
Patients in the ITT population who responded to the PCC questionnaire at any of the three time points (Day 85, 169, or 337) are included.
Table adapted from Imamura et al. 2024. Poster presented at IDWeek. 2024.

- Of the 33 patients that were asymptomatic (ensitrelvir 125 mg, n=9; ensitrelvir 250 mg, n=12; placebo, n=12):[10]
    - One patient experienced PCC on Day 169 and 337 in the ensitrelvir 125 mg group (any of the 27 symptoms)
    - One patient experienced PCC on Day 85 and Day 169 in the placebo group (any of the 27 symptoms)
- The relative risk reduction of reporting at least one of 27 COVID-19 symptoms at Days 85, 169, or 337 was numerically lower in both ensitrelvir 125 mg and 250 mg vs placebo with a 61% reduction at Day 337 for both doses[10]
- Numerical reductions in reports of four neurological symptoms at 85, 169, and 337 days were seen with ensitrelvir 125 and 250 mg, with a 73% and 60% relative risk reduction in the 125 mg and 250 mg ensitrelvir treatment groups, respectively, at day 337[8]
- A trend towards risk reduction for the most common individual symptoms of PCC was observed in the ensitrelvir 125 mg and 250 mg groups (**Figure 4**)[10]

Figure 4. Relative Risk Reduction vs Placebo for the Most Common Individual Symptoms of PCC[10]



DAY	85	169	337	85	169	337	85	169	337	85	169	337
Placebo	7/122	4/129	5/125	10/122	7/129	9/125	10/122	6/129	8/125	8/122	4/129	5/125
Ensitrelvir 125 mg	6/114	3/117	1/115	5/114	3/117	2/115	2/114	2/117	2/115	2/114	2/117	1/115
Ensitrelvir 250 mg	2/120	1/125	1/117	3/120	2/125	3/117	3/120	1/125	2/117	2/120	1/125	2/117

Abbreviations: PCC, post COVID-19 condition.
Data are summarized for patients who completed the PCC questionnaire for at least one timepoint in the ITT population.
PCC symptoms reported in at least one time point with an incidence ≥5% in the placebo group are presented.
Figure adopted from Imamura et al. 2024. Poster presented at IDWeek. 2024.

3. REAL-WORLD EVIDENCE

The ANCHOR-01 study was a prospective, multi-institutional, nationwide registry-based cohort study conducted in Japan to evaluate the impact of oral antivirals on development of PCC in outpatients, conducted by **Hibino et al (2026)**.[11,12]

Methods

Outpatients aged 12 years and older with confirmed, acute symptomatic SARS-CoV-2 infection were enrolled between February and October 2024 and followed until February 2025. Patients were divided into two groups: those who received oral antivirals (ensitrelvir, nirmatrelvir/ritonavir, or molnupiravir) and those who did not receive oral antivirals, with treatment decisions aligned to national COVID-19 guidelines. Patient-reported outcomes related to PCC were collected via electronic questionnaires on Days 28 and 84.[11,12]

The primary endpoint was the incidence of PCC, defined as the persistence of any of five symptoms (fatigue, cough, dyspnea or respiratory distress, smell disorder, taste disorder) on both Days 28 and 84, excluding symptoms not attributed to COVID-19. Statistical analyses included risk ratios (RRs) and risk differences (estimated using modified Poisson and least squares regression models), adjusted for baseline characteristics.[12]

Results

Generally, baseline characteristics were balanced between groups, but the study population group receiving antivirals had more underlying comorbidities and had a higher median age (58.0 years vs 45.0 years) compared to the no-antiviral group.[12]

Efficacy

- In the unadjusted analysis, 1443/5518 patients (26.2%) in the no-antiviral group developed PCC, compared with 530/2181 patients (24.3%) in the antiviral group (**Table 11**).[11,12]
- After adjusting for covariates, PCC risk was found to be significantly lower among those who received antivirals (21.5% with antivirals vs. 25.1% with no-antivirals), with a risk ratio of 0.86 (95% CI: 0.78 to 0.93; *P* <0.001) and an adjusted risk difference of -4.14 percentage points (95% CI: -6.34 to -1.94; *P* <0.001) (**Table 11**).[11,12]
- When analyzed by specific antiviral and adjusting for covariates, ensitrelvir (21.7%; RR 0.86; 95% CI 0.79–0.95) and molnupiravir (20.4%: RR 0.81; 95% CI 0.67-0.98) notably reduced the incidence of PCC compared to the no-antiviral group (25.1%) (**Table 11**).[11,12]
- The prevalence of individual symptoms showed that the risks of smell and taste disorders were significantly reduced in the antiviral group (**Table 12**), while cough and fatigue exhibited a trend toward reduction.[11,12]
- Risk reduction of PCC seen in subgroups across all ages, regardless of risk factors for severe disease. No adjustment for multiplicity was performed, therefore the 95% Cls are descriptive only and should be interpreted with caution. (**Figure 5**).[11,12]

Table 11. Unadjusted and Adjusted Incidence of PCC According to Antiviral Treatments[11]

Treatment Group	PCC Incidence			Adjusted RR (95% CI)
	Adjusted n/N	Unadjusted (%)	Adjusted (%)	
No-antiviral	**1443/5518**	**26.2**	**25.1**	**Reference**
Antiviral overall	**530/2181**	**24.3**	**21.5**	**0.86 (0.78–0.93)***
Ensitrelvir	**412/1698**	**24.3**	**21.7**	**0.86 (0.79–0.95)***
Nirmatrelvir	**25/98**	**25.5**	**22.2**	**0.88 (0.63–1.24)**
Molnupiravir	**93/385**	**24.2**	**20.4**	**0.81 (0.67–0.98)***

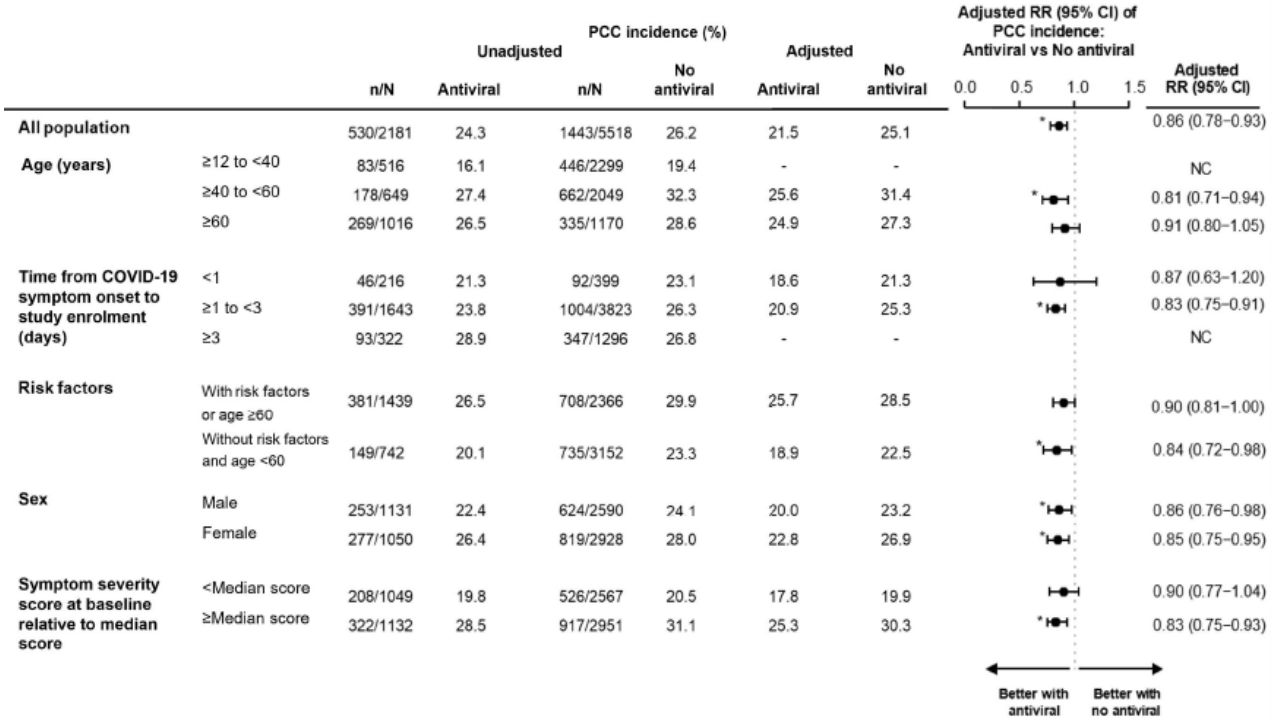
Abbreviations: PCC, post-COVID-19 condition; RR, risk ratio; CI, confidence interval.
*P<0.05.
Table adapted from Hibino et al. 2025. Poster presented at AVG and IMRP. 2025.

Table 12. Incidence of Five Prespecified PCC Symptoms Persisting from Day 28 to 84 in Patients without Antivirals, and their RR in the Antiviral versus No-Antiviral Groups[11]

Symptom	Frequency of PCC Unadjusted %(n/N)	Adjusted RR (95% CI)
Cough	**15.3 (843/5518)**	**0.89 (0.78-1.00)**
Dyspnea	**3.7 (206/5518)**	**0.99 (0.77-1.28)**
Fatigue	**13.0 (715/5518)**	**0.92 (0.80 – 1.05)**
Smell Disorder	**5.3 (292/5518)**	**0.43 (0.32-0.58)***
Taste Disorder	**4.6 (251/5518)**	**0.59 (0.45-0.78)***

Abbreviations: PCC, post-COVID-19 condition; RR, risk ratio; CI, confidence interval.
*P<0.05.
Table adapted from Hibino et al. 2025. Poster presented at AVG and IMRP. 2025.

Figure 5. Incidence of PCC According to Prespecified Subgroups[11]



No adjustment for multiplicity was performed; hence, the 95% Cls are descriptive only and should be interpreted with caution.
Abbreviations: PCC, post-COVID-19 condition; RR, risk ratio; CI, confidence interval.
*P<0.05.
Figure adopted from Hibino et al. Poster presented at AVG and IMRP. 2025.

Abe et al (2024) conducted a retrospective study that evaluated 18 outpatients with acute mild-to-moderate SARS-CoV-2 infection and a history of vaccination and who were treated with a 5-day regimen of oral ensitrelvir for the development of post-acute sequalae of COVID-19. Viral load was assessed on Days 0, 3, 6, and 9, and patients were followed through Day 60 for symptoms of post-acute sequelae of COVID-19 (PASC).[13]

- The maximum duration of symptoms until disappearance was 6 days for any patient. [13]
- SARS-CoV-2 RNA was undetectable in most patients by day 9 (12/18). [13]
- During the 60-day follow-up period, none of the 18 patients exhibited symptoms associated with PASC. [13]
- There were no reports of symptom recurrence or reports of adverse events. [13]

4. RELEVANT PRESCRIBING INFORMATION

Indications and Usage

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

Contraindications

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[19]

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.[19]

Please read the attached XOCOVA **Full Prescribing Information**. The use of XOCOVA in any manner other than as described in the Full Prescribing Information approved by the U.S. Food and Drug Administration (FDA) is not recommended.

5. LITERATURE SEARCH

As of May 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has identified additional relevant references regarding ensitrelvir use in the prevention of long COVID-19. For your review, these references are listed in the bibliography that follows:

Konishi K, Yamamoto S, Sada RM, et al. Research to evaluate safety and impact of long COVID intervention with Ensitrelvir for National Cohort (RESILIENCE Study): A protocol for a randomized, double-blind, placebo-controlled trial. *PLoS One*. 2025;20(11):e0335609. Published 2025 Nov 3.

Namie H, Takazono T, Kawasaki R, et al. Analysis of risk factors for long COVID after mild COVID-19 during the Omicron wave in Japan. *Respir Investig*. 2025;63(3):303-310.

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

ABBREVIATIONS

3CL, 3-chymotrypsin-like
ACTG, AIDS Clinical Trials Group
ACTIV-2, Accelerating COVID-19 Therapeutic Interventions and Vaccines-2
AE, Adverse Event
BMI, body mass index
CI, confidence interval
COVID-19, Coronavirus disease 19
D, Day
hr, hours
HDL, high-density lipoprotein
ITT, intention-to-treat
MHLW, Ministry of Health, Labour, and Welfare
mITT, modified intention-to-treat
mITT1, modified intention-to-treat 1
N, number of patients in analysis set
n, number of patients
NIH, National Institutes of Health
PASC, post-acute sequelae of COVID-19
PCC, post COVID-19 condition
PK, pharmacokinetic
QOL, quality of life
RNA, ribonucleic acid

RT-PCR, reverse transcription polymerase chain reaction
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
TRAE, treatment-related adverse event
US, United States
WHO, World Health Organization

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ENCLOSURE

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