Effect of Ensitrelvir on Long COVID in Patients with Mild-to-Moderate COVID-19: A Post-Hoc Analysis of the Phase 3 SCORPIO-SR Study

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BACKGROUND

- Post-COVID-19 condition (Long COVID) occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis [1]
  - Common symptoms of Long COVID may include, but are not limited to, fatigue, shortness of breath, and cognitive dysfunction [1]
  - It has been reported there might be a correlation between viral persistence and the risk of Long COVID [2]
  - Treatment of COVID-19 with antivirals is expected to clear virus and reduce the risk of Long COVID
- Ensitrelvir is an oral SARS-CoV-2 3CL protease inhibitor approved under the emergency regulatory approval system in Japan for the treatment of mild-to-moderate COVID-19 [3]
  - We previously reported interim analysis data (3- and 6-month follow-up) on the efficacy of ensitrelvir on reducing the risk of Long COVID as a post-hoc analysis of the phase 3 SCORPIO-SR study [4]
- Herein, we report the 1-year follow-up data for Long COVID from the SCORPIO-SR study

METHODS

- SCORPIO-SR is the phase 3 part of a seamless, multicenter, randomized, double-blind, placebo-controlled, phase 2/3 study (Japan Registry of Clinical Trials identifier: jRCT2031210350) [5]
  - The study was conducted in Japan, South Korea, and Vietnam (study period: February 2022–July 2022), during the Omicron variant dominant period
  - Patients (aged 12 to <70 years) with mild-to-moderate COVID-19 within 120 hours of positive SARS-CoV-2 testing were eligible for participation, regardless of SARS-CoV-2 vaccination status and presence of risk factors for severe disease
  - Eligible patients were randomized (1:1:1) to orally receive once-daily ensitrelvir 125 mg (375 mg on Day 1), 250 mg (750 mg on Day 1), or placebo for 5 days
- Long COVID assessments were performed during the exploratory period (Days 85, 169, and 337) using the PASC questionnaire developed by the authors and Shionogi & Co., Ltd.
  - Patients self-assessed their symptoms and recorded the results in a diary
  - The PASC questionnaire was developed to assess the severity of 27 symptoms and their relationship with COVID-19
  - Investigators and patients remained blinded on treatment assignment

RESULTS

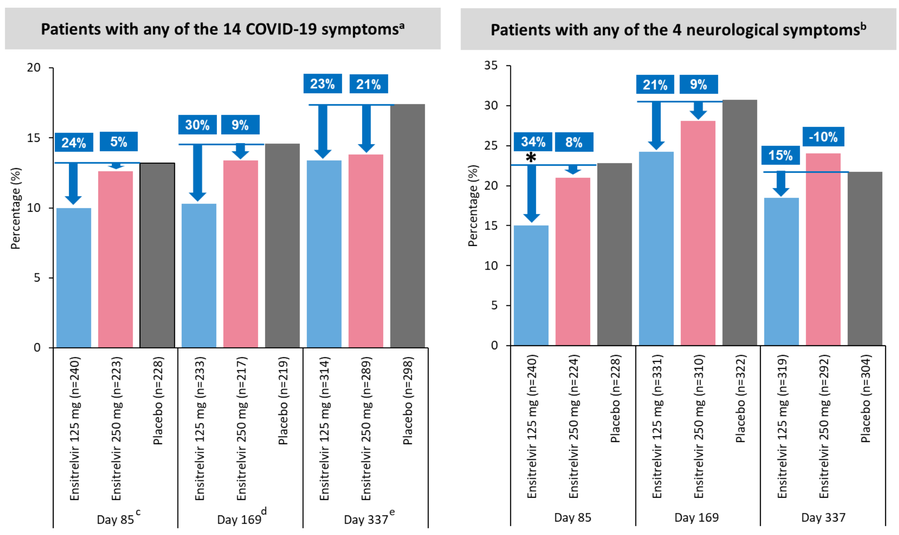
Table 1. Demographics and baseline clinical characteristics

- Patient characteristics were generally balanced across treatment groups
- The median total score of the 14 COVID-19 symptoms at baseline was 8.0 to 9.0

	Ensitrelvir 125 mg N = 341	Ensitrelvir 250 mg N = 317	Placebo N = 333
Male sex, n (%)	187 (54.8)	169 (53.3)	194 (58.3)
Age (years), mean±SD	36.4±12.7	36.5±12.6	35.6±12.1
BMI (kg/m^2), mean±SD	23.3±4.3	23.0±3.9	22.8±3.6
SARS-CoV-2 vaccination received, n (%)	312 (91.5)	292 (92.1)	309 (92.8)
Total score of 14 symptoms[a] at baseline			
N	334	309	326
Median (range)	9.0 (1–30)	8.0 (0–30)	9.0 (2–28)

Data are summarized for patients who completed the PASC questionnaire for at least one timepoint in the Intention-To-Treat (ITT) population.
[a] 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, and loss of taste. Each symptom was self-assessed using a 4-point scale of 0 to 3 (3-point scale of 0 to 2 for loss of smell and loss of taste).
BMI, body mass index; SD, standard deviation; range, minimum-maximum

Figure 1. Proportion of patients with Long COVID and risk reduction versus placebo [presence of at least one symptom, with a self-judgment of its relationship to COVID-19]



Data are summarized for patients who completed the PASC questionnaire for at least one timepoint in the ITT population.
[a] 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.
[b] Difficulty with concentration and thinking, difficulty reasoning and solving problems, memory loss, or insomnia.
[c] Patients who perceived any of the symptoms at both last observation in the follow-up period (e.g., Day 21) and Day 85.
[d] Patients who perceived any of the symptoms at both Day 85 and Day 169.
[e] Patients who perceived any of the symptoms at both Day 169 and Day 337.
*P value of <0.05 using Fisher's exact test.

- The proportion of patients with Long COVID symptoms in the ensitrelvir 125-mg (approved dose in Japan) was lower than that in the placebo group at all the timepoints.
- The proportion of patients with Long COVID symptoms (any of the 14 COVID-19 symptoms) generally increased toward Day 337, which is not consistent with the natural course of Long COVID [6]
- As patients may not be able to accurately assess the relationship to COVID-19, especially at later time points, this definition may not be suitable for assessing Long COVID at Day 337.

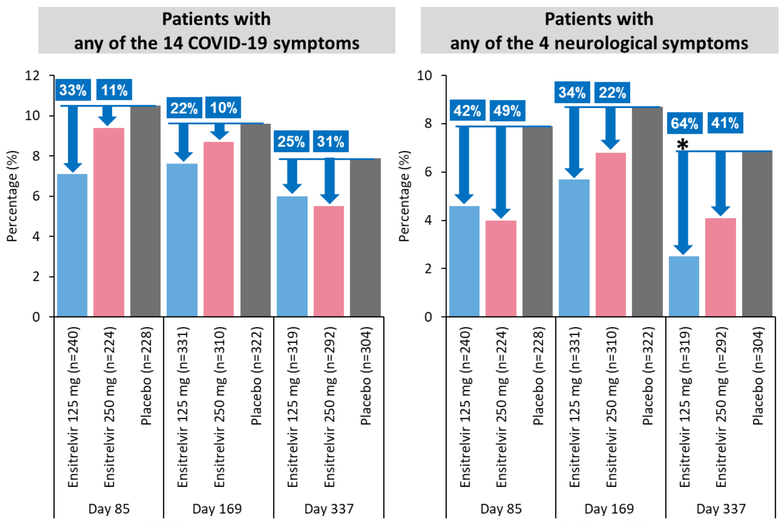
Table 2. Proportion of patients who did not return to usual (pre-COVID) health

- The proportion of patients not having returned to usual health in the ensitrelvir treatment group was lower than that in placebo group at all the timepoints.

Timepoint	Endpoint	Ensitrelvir 125 mg N=379	Ensitrelvir 250 mg N=345	Placebo N=362
Day 85	Not returned to usual health[a]	7.5% (18/240)	9.8% (22/224)	11.8% (27/228)
Day 169	Not returned to usual health[a]	7.6% (25/331)	8.7% (27/310)	10.2% (33/322)
Day 337	Not returned to usual health[a]	6.0% (19/319)	6.5% (19/292)	8.2% (25/304)

Data are summarized for patients who accepted to participate in the exploratory period in the ITT population and are presented as percentage (proportion).
[a] Patients who answered “No” to the question “Have you returned to your usual (pre-COVID) health?”.

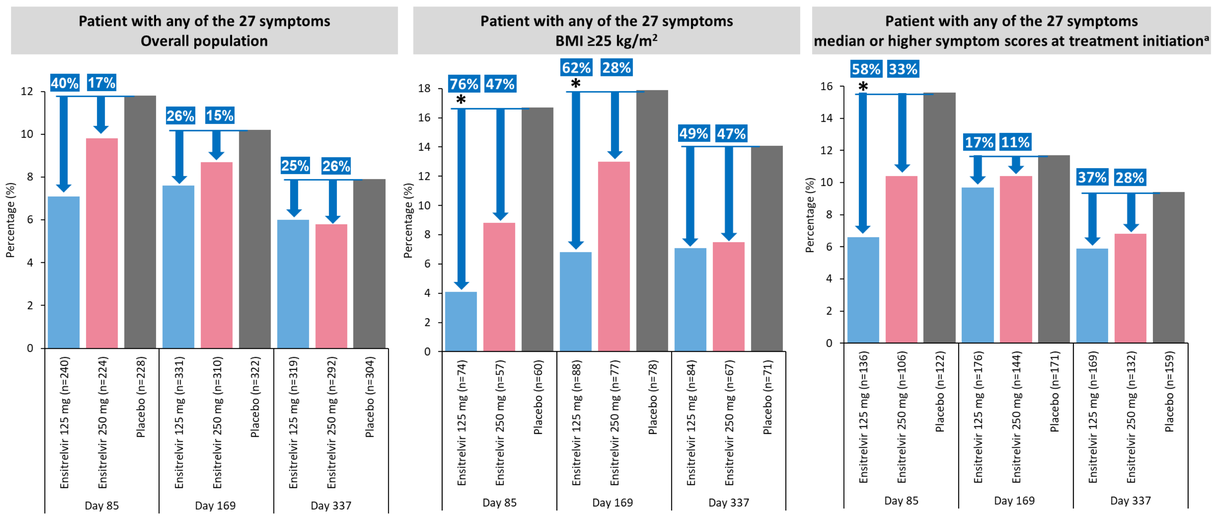
Figure 2. Proportion of patients with Long COVID and risk reduction versus placebo [presence of at least one symptom, not having returned to usual health]



Data are summarized for patients who completed the PASC questionnaire for at least one timepoint in the Intention-To-Treat (ITT) population.
*P value of <0.05 using Fisher's exact test.

- Long COVID was newly defined as having at least one mild or more severe symptom in patients who answered “not returned to pre-COVID health” on Day 85, Day 169, or Day 337.
- Using the new definition, the proportion of patients with Long COVID symptoms (any of the 14 COVID-19 symptoms and any of the 4 neurological symptoms) was lower in the ensitrelvir treatment groups than in the placebo group.

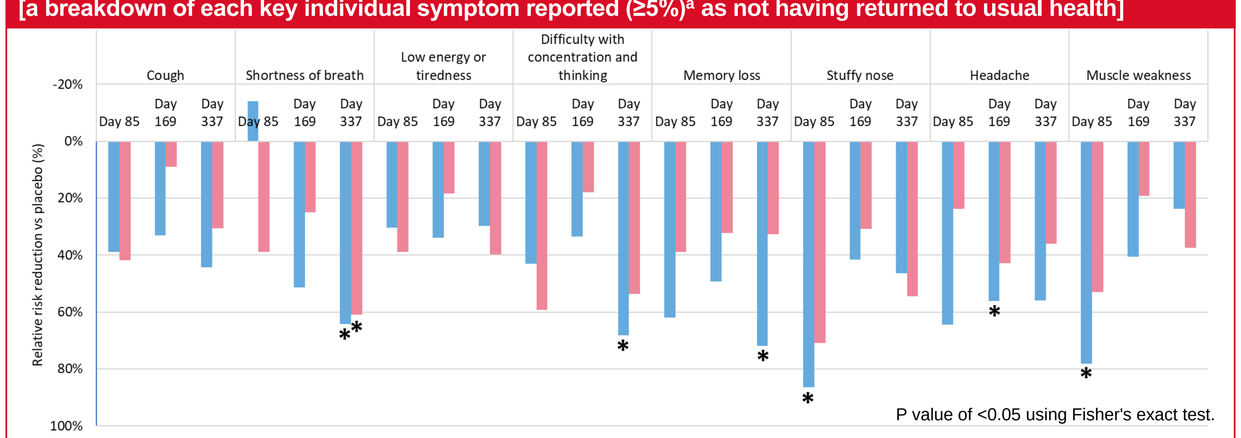
Figure 3. Proportion of patients with Long COVID and risk reduction versus placebo [presence of at least one symptom (among all 27 symptoms), not having returned to usual health]



Data are summarized for patients who completed the PASC questionnaire for at least one timepoint in the Intention-To-Treat (ITT) population.
P value of <0.05 using Fisher's exact test. [a]The total score of 14 symptoms at baseline of ≥ 9. BMI, body mass index

- In patients with body mass index (BMI) ≥25 kg/m^2 and patients with median or higher (≥9) symptom scores at treatment initiation, the proportion of patients with Long COVID in placebo group was higher than that in overall population, which was similar to the previous report [7,8]
- The greater risk reduction was observed in patients who with BMI ≥25 kg/m^2 and patients with median or higher symptom score at the start of treatment

Figure 4. Relative risk reduction of individual Long COVID symptoms in the overall population [a breakdown of each key individual symptom reported (≥5%)[a] as not having returned to usual health]



	Cough			Shortness of breath			Low energy or tiredness			Difficulty with concentration and thinking			Memory loss			Stuffy nose			Headache			Muscle weakness		
	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337	Day 85	Day 169	Day 337
Ensitrelvir 125mg	9/240	11/331	7/319	6/240	9/331	6/319	11/240	19/331	14/319	9/240	13/331	6/319	4/240	12/331	5/319	1/240	9/331	9/319	3/240	9/331	6/319	3/240	11/331	8/319
Ensitrelvir 250mg	8/224	14/310	8/292	3/224	13/310	6/292	9/224	22/310	11/292	6/224	15/310	8/292	6/224	15/310	11/292	2/224	10/310	7/292	6/224	11/310	8/292	6/224	14/310	6/292
Placebo	14/228	16/322	12/304	5/228	18/322	16/304	15/228	28/322	19/304	15/228	19/322	18/304	10/228	23/322	17/304	7/228	15/322	16/304	8/228	20/322	13/304	13/228	18/322	10/304

Data are summarized for patients who completed the PASC questionnaire for at least one timepoint in the Intention-To-Treat (ITT) population.
[a]Long COVID symptoms seen in at least one time point with an incidence of ≥ 5% in placebo group were shown.

- A statistically significant reduction in the risk of developing shortness of breath and cognitive symptoms (difficulty with concentration and thinking; memory loss) with ensitrelvir 125-mg treatment was observed at some time points

CONCLUSIONS

- The results of this exploratory analysis in a patient population included in a randomized controlled study of ensitrelvir indicate that early treatment of COVID-19 with ensitrelvir may reduce the risk of a number of persistent and new late onset symptoms associated with Long COVID.
- Further research is needed

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CONFLICTS OF INTEREST

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