Ensitrelvir for mild-to-moderate COVID-19: Phase 3 part of Phase 2/3 study

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COI disclosure of presenter

Takeki Uehara is an employee of Shionogi & Co., Ltd., and the Phase 2/3 study was funded by Shionogi & Co., Ltd.

Clinical Development: Ph3 Part of Ph 2/3 Clinical Trial (SCORPIO-SR[#])

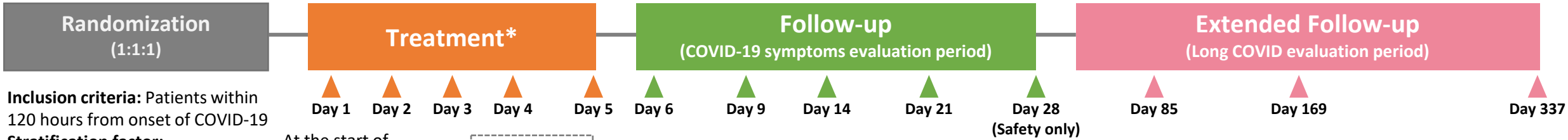
[#]: ClinicalTrials.gov Identifier: NCT05305547

■ Purpose

To evaluate the efficacy and safety of ensitrelvir once-daily, 5 days oral treatment in patients with mild/moderate SARS-CoV-2 infection, aged 12-69 years regardless of SARS-CoV-2 vaccination, and risk factors for severe disease.

■ Study design

Multicenter, randomized, double-blinded, placebo-controlled study conducted in Japan, South Korea and Vietnam from February to July (last patient in) in 2022, Omicron variant dominant period.



Inclusion criteria: Patients within 120 hours from onset of COVID-19

Stratification factor:
- Vaccinated, unvaccinated
- Time from onset to randomization (<72 hours, ≥72 hours)

*Ensitrelvir 125 mg (375 mg on Day 1 only), Ensitrelvir 250 mg (750 mg on Day 1 only), or placebo once daily

No data at Day 337 is available

post-acute sequelae of SARS-CoV-2 (PASC) questionnaire

24 symptoms including 14 COVID-19 symptoms and 4 neurological symptoms

■ End point

- Primary endpoint: Time to resolution of 5 COVID-19 symptoms
- Key secondary endpoint: Change from baseline on Day 4 in the amount of SARS-CoV-2 viral RNA, Time to the first negative SARS-CoV-2 viral titer
- Other secondary endpoint: Safety (by Day 28)
- Exploratory endpoint: Presence of Long COVID symptoms evaluated by PASC questionnaire (by Day 169)

Baseline Characteristics

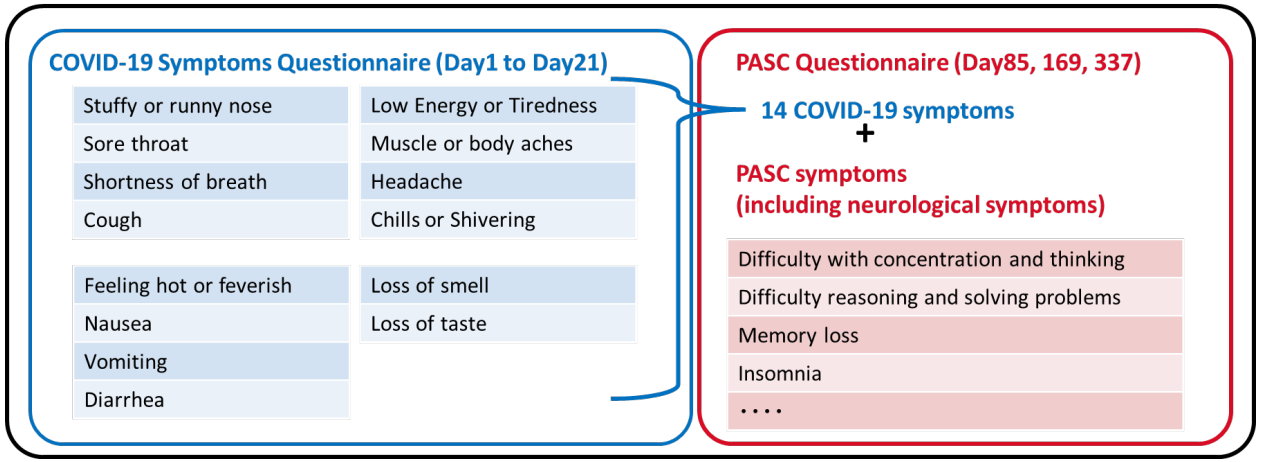
	COVID-19 onset to randomization : **<72 hours**			COVID-19 onset to randomization : **≤120 hours**		
	Ensitrelvir 125 mg (n=347)	**Ensitrelvir 250 mg (n=340)**	**Placebo (n=343)**	**Ensitrelvir 125 mg (n=603)**	**Ensitrelvir 250 mg (n=595)**	**Placebo (n=600)**
Gender, Male (%)	55.6%	54.4%	50.7%	52.7%	54.3%	51.8%
Age (years), mean (SD)	35.7 (12.5)	35.3 (12.2)	34.7 (12.2)	35.9 (12.7)	35.9 (12.7)	35.3 (12.6)
SARS-CoV-2 vaccination history (%)	92.8%	92.1%	91.8%	93.2%	92.6%	92.2%
Viral RNA level (log_{10} copies/mL), mean (SD)	6.976 (1.006)	6.889 (1.014)	6.933 (0.993)	6.825 (1.048)	6.727 (1.079)	6.770 (1.074)
Race, Asian (%)	99.4%	99.4%	99.4%	99.7%	99.7%	99.7%
Confirmed Omicron infection* (%)	89.6%	87.4%	88.0%	89.7%	87.4%	89.0%

Analysis in the intention-to-treat population (all cases confirmed positive for SARS-CoV-2 viral RNA at baseline), SD = Standard Deviation

* BA.2 major (approx. 70%), others including BA.1, BA.1.1.529, BA.4, BA.5, BA.2.12.1.

Entry Status of PASC Questionnaire for Long COVID Evaluation

Questionnaire at Day 85, 169 (already data available), Day 337 (data not yet available)



	COVID-19 onset to randomization : **≤120 hours**		
	Ensitrelvir 125 mg (n=603)	**Ensitrelvir 250 mg (n=595)**	**Placebo (n=600)**
Day 85	240 (39.8%)	224 (37.6%)	228 (38.0%)
Day 169	330 (54.7%)	310 (52.1%)	321 (53.5%)
Day 85 or Day 169	338 (56.1%)	317 (53.3%)	331 (55.2%)

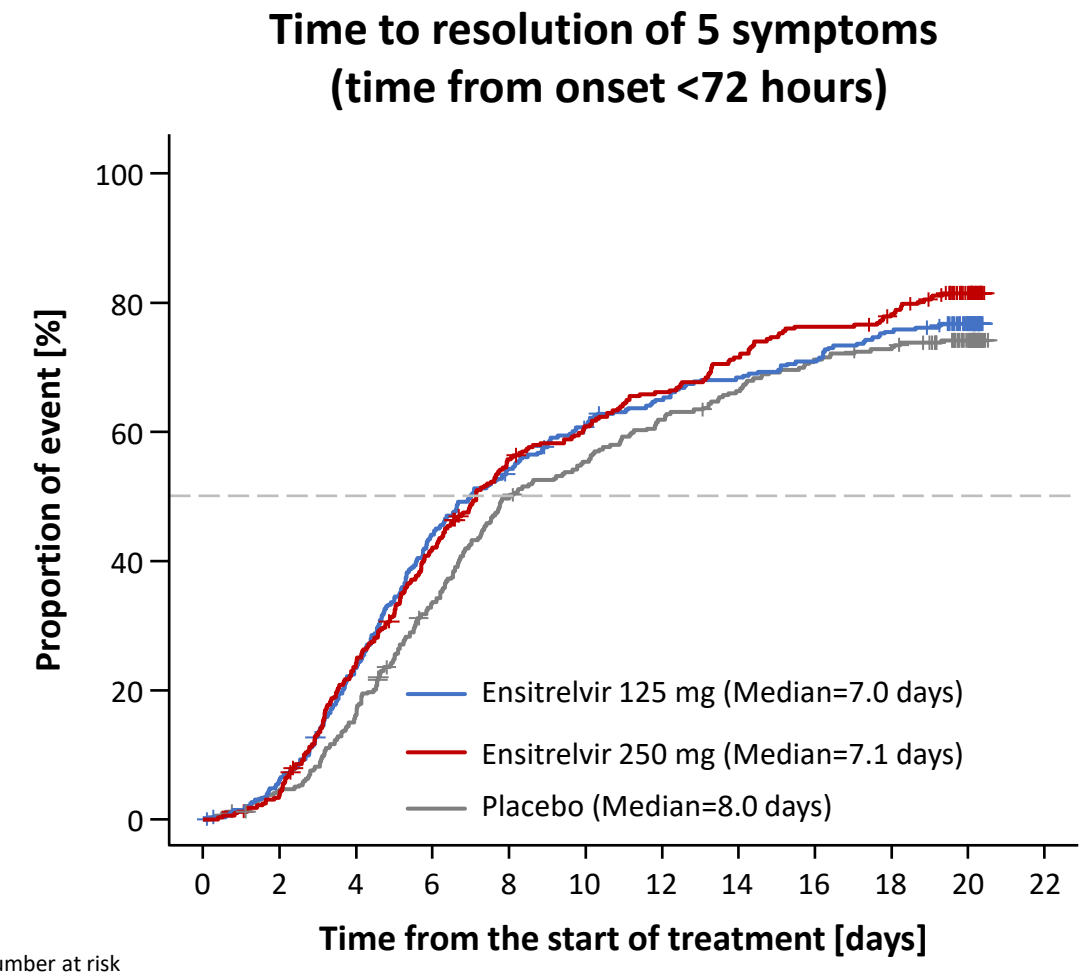
PASC= post-acute sequelae of SARS-CoV-2

Primary Endpoint: Time to Resolution of 5 COVID-19 Symptoms

Ensitrelvir 125 mg demonstrated the earlier (1 day) resolution of 5 COVID-19 symptoms than placebo.

	COVID-19 onset to randomization : <72 hours (Primary analysis)		
	Ensitrelvir 125 mg (n=347)	Ensitrelvir 250 mg (n=340)	Placebo (n=343)
Kaplan-Meier estimates (hours)			
Median [95% CI]	167.9 [145.0, 197.6]	171.2 [150.8, 190.3]	192.2 [174.5, 238.3]
Difference in median vs. placebo [95% CI]	**-24.3** [-78.7, 11.7]	-21.0 [-73.8, 7.2]	---
Stratified Peto-Prentice's generalized Wilcoxon test [a]			
p-value (two-sided)	**0.0407**	0.0203	---

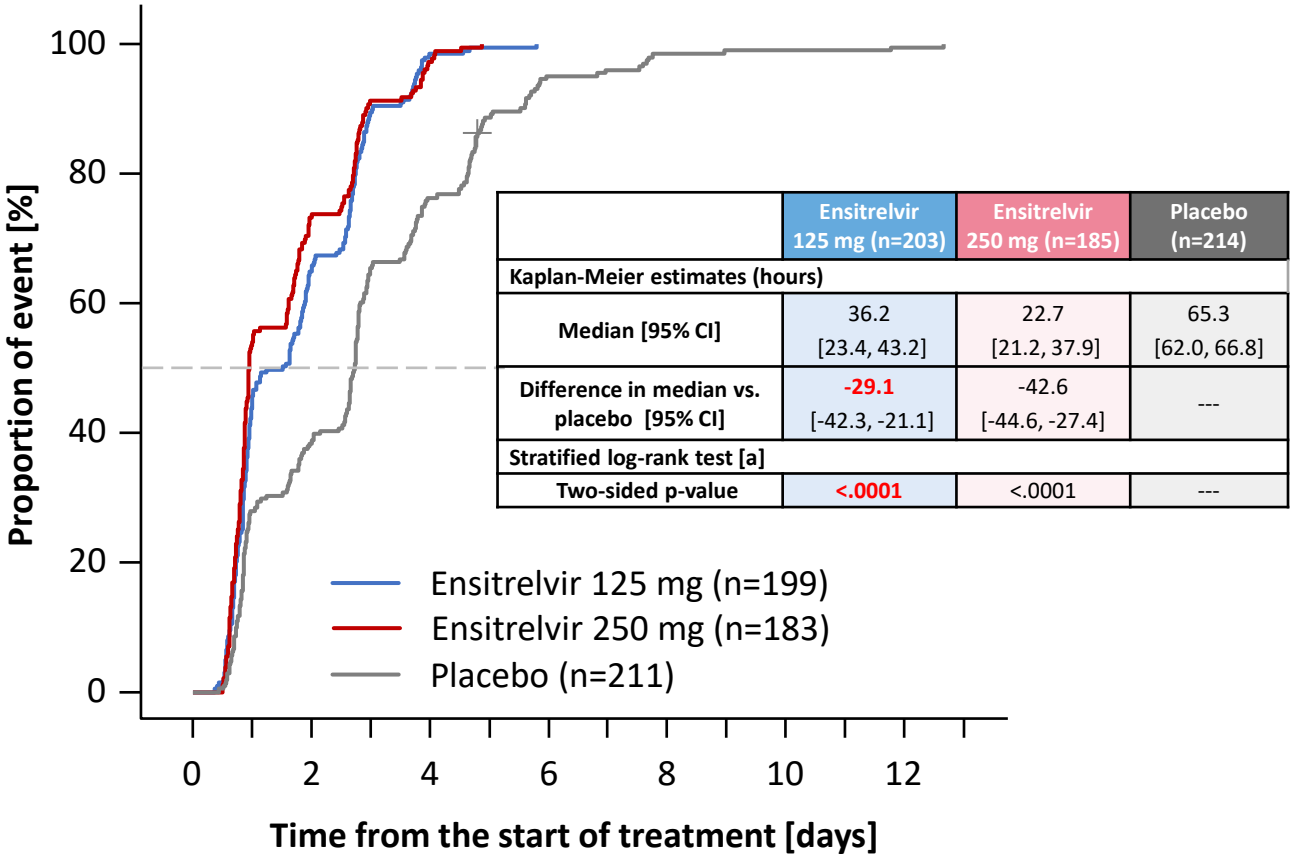
Analysis in the intention-to-treat population (all cases confirmed positive for SARS-CoV-2 viral RNA at baseline) with any of 5 symptoms at baseline
CI = Confidence Interval, 5 Symptoms: stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness
[a] Adjusted for SARS-CoV-2 vaccination history.



Key Secondary Endpoint: SARS-CoV-2 Viral Titer

Ensitrelvir 125 mg significantly shorten the time to cessation of SARS-CoV-2 viral shedding compared with placebo.
Ensitrelvir 125 mg showed 87% reduction of patient with positive viral titer at Day 4 compared with placebo.

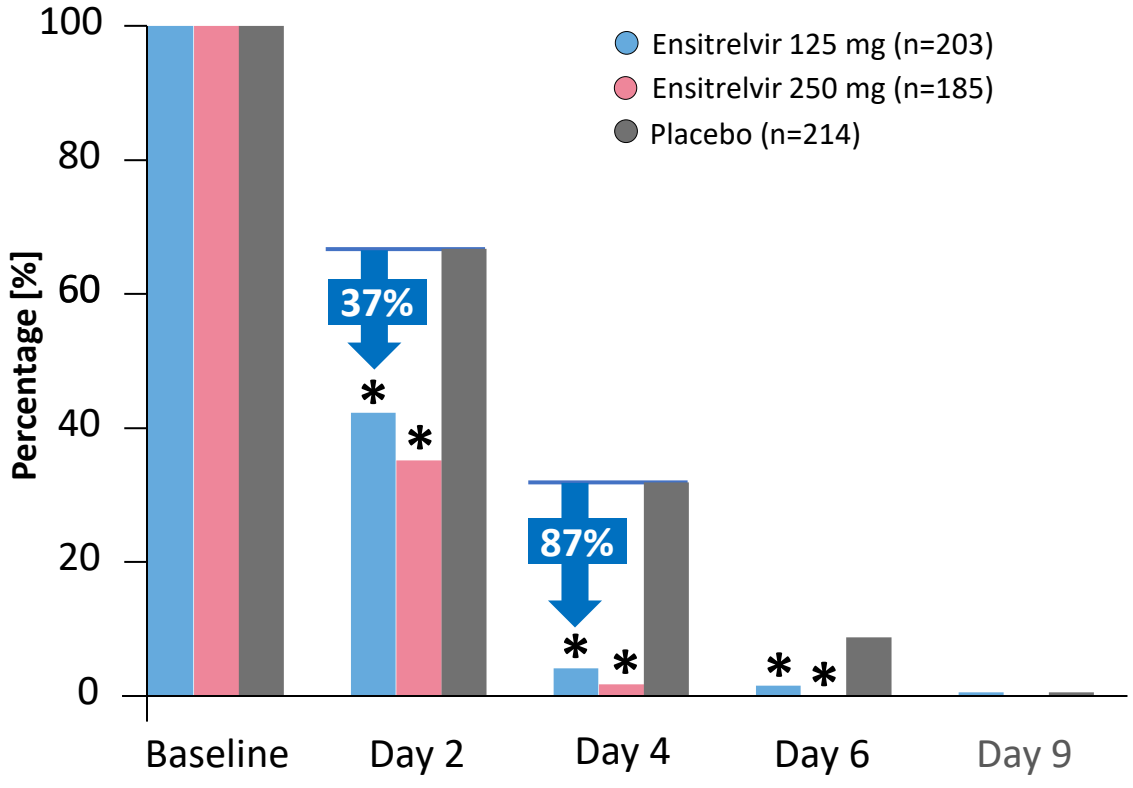
Time to first confirmed negative SARS-CoV-2 viral titer



	Ensitrelvir 125 mg (n=203)	Ensitrelvir 250 mg (n=185)	Placebo (n=214)
Kaplan-Meier estimates (hours)			
Median [95% CI]	36.2 [23.4, 43.2]	22.7 [21.2, 37.9]	65.3 [62.0, 66.8]
Difference in median 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	**<.0001**	<.0001	---

Analysis in the modified intention-to-treat population (all pretreatment RT-PCR-positive patients with detectable SARS-CoV-2 viral titers at baseline) with any observations after the start of treatment, CI = Confidence Interval
[a] Adjusted for SARS-CoV-2 vaccination history

Patients with positive viral titer



vs Placebo *< 0.05
Mantel-Haenszel test stratified by SARS-CoV-2 vaccination history

Viral titer negative (<0.75 $\log_{10}$ ($TCID_{50}$/mL))
Viral titer positive (≥0.75 $\log_{10}$ ($TCID_{50}$/mL))

Safety: COVID-19 Onset to Randomization, ≤120 hours

No new safety concerns were identified and ensitrelvir was well tolerated.

Safety population	Ensitrelvir 125 mg n=604 (%)	Ensitrelvir 250 mg n=599 (%)	Placebo n=605 (%)
Treatment-emergent adverse events (TEAE)	**267 (44.2%)**	**321 (53.6%)**	**150 (24.8%)**
Death	**0**	**0**	**0**
Serious TEAEs other than death	**1 (0.2%)**	**0**	**1 (0.2%)**
TEAEs leading to discontinuation	**4 (0.7%)**	**6 (1.0%)**	**2 (0.3%)**
TEAE occurring in ≥2% of patients in either group			
Headache	13 (2.2%)	20 (3.3%)	14 (2.3%)
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 creatine phosphokinase increased	14 (2.3%)	8 (1.3%)	11 (1.8%)
Blood lactate dehydrogenase increased	6 (1.0%)	15 (2.5%)	6 (1.0%)
Treatment-related adverse event (AE)	**148 (24.5%)**	**217 (36.2%)**	**60 (9.9%)**
Treatment-related AEs in ≥2% of patients in either group			
Headache	4 (0.7%)	13 (2.2%)	2 (0.3%)
High density lipoprotein decreased	111 (18.4%)	157 (26.2%)	9 (1.5%)
Blood triglycerides increased	16 (2.6%)	37 (6.2%)	17 (2.8%)
Blood bilirubin increased	17 (2.8%)	35 (5.8%)	3 (0.5%)
Blood cholesterol decreased	8 (1.3%)	12 (2.0%)	1 (0.2%)

Long COVID Symptoms, ≤120 hours

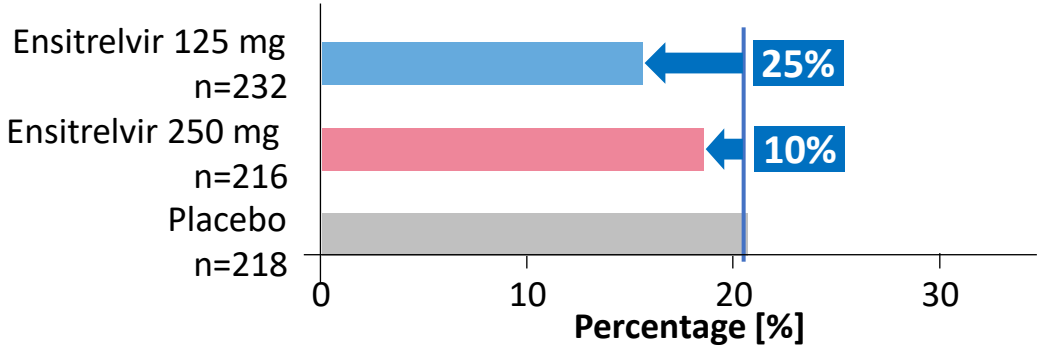
Definition for presence of Long COVID symptoms in post-hoc analysis

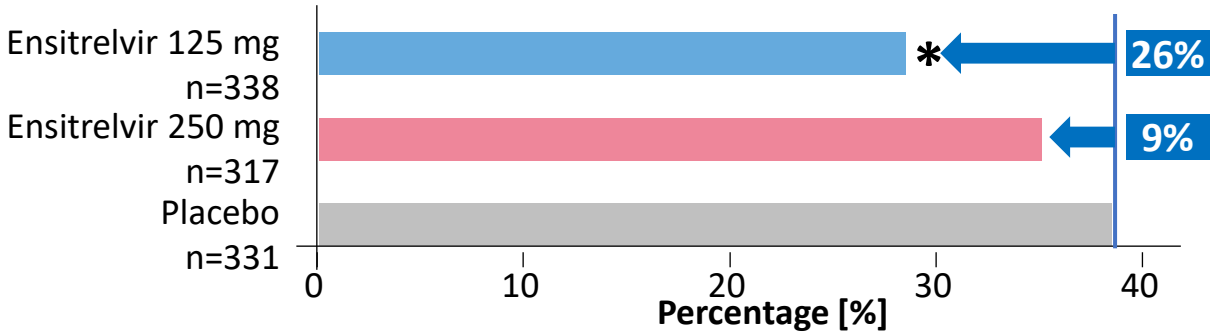
- Symptoms listed in 14 COVID-19 symptom questionnaire
  - ✓At least 2 consecutive time points with a mild or more severe symptom continuing from the last observation in the follow up (e.g., Day 21) to Day 169
- Symptoms listed only in PASC questionnaire
  - ✓One mild or more severe symptom at Day 85 OR Day 169
- Relationship with COVID-19: Yes (related) or unknown symptoms (exclude No (not related))

Proportion with ongoing symptoms (14 COVID-19 symptoms)

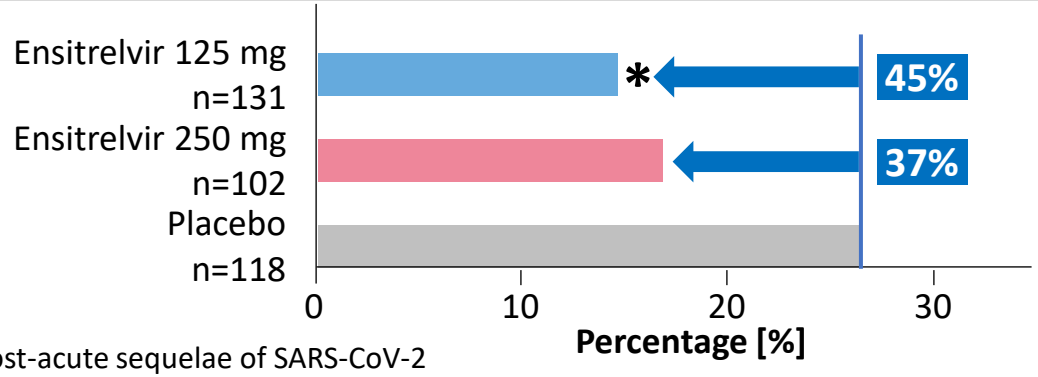
Proportion of 4 neurological symptoms in PASC Questionnaire

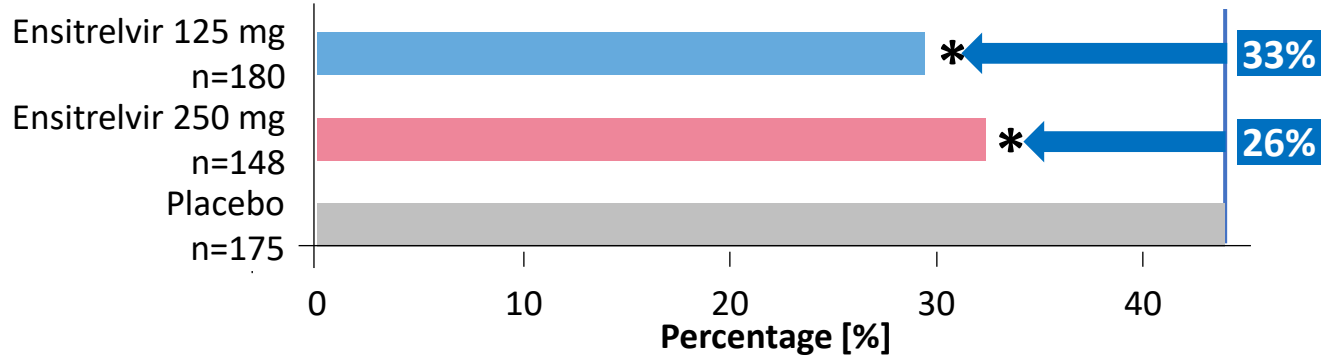
Overall population





Subpopulation of patients who have high symptom score for 14 symptoms at baseline[a]



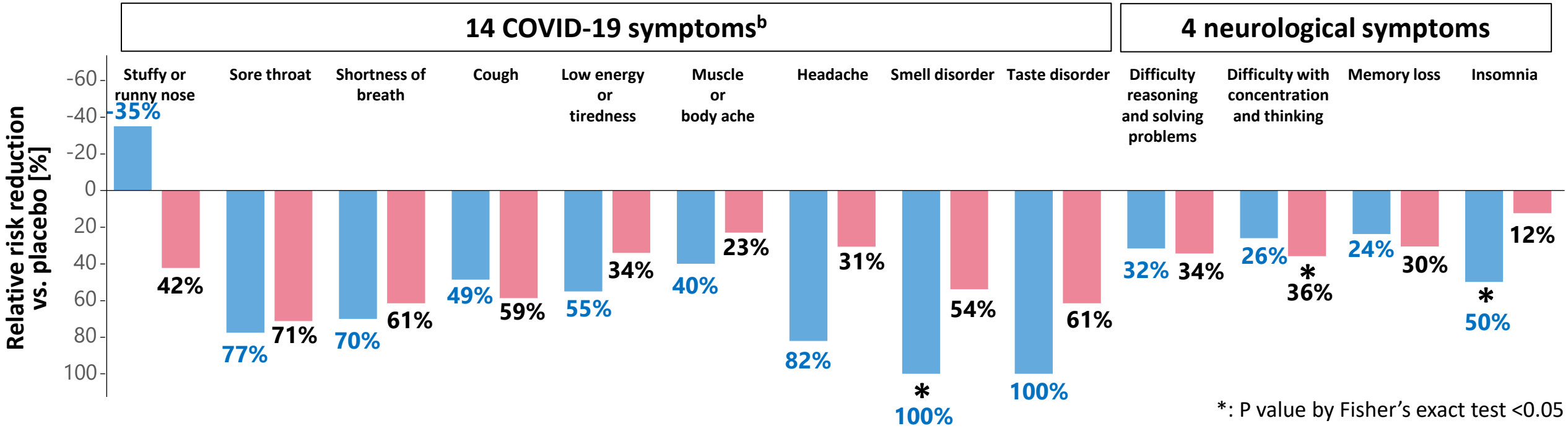


PASC= post-acute sequelae of SARS-CoV-2

*: P value by Fisher's exact test <0.05 [a]high symptom score is defined as the total score of 14 symptoms at baseline ≥ 9

Summary of Long COVID Symptoms for Participants with High Symptom Score for 14 Symptoms at Baseline[a], ≤120 hours

[a]high symptom score is defined as the total score of 14 symptoms at baseline ≥ 9
[b]symptoms presented in 3 or more cases in placebo were shown



*: P value by Fisher's exact test <0.05

	Stuffy or runny nose	Sore throat	Shortness of breath	Cough	Low energy or tiredness	Muscle or body aches	Headache	Smell disorder	Taste disorder	Difficulty reasoning and solving problems	Difficulty with concentration and thinking	Memory loss	Insomnia
Ensitrelvir 125 mg	6/131	1/131	1/131	8/131	7/131	2/131	1/131	0/131	0/131	19/180	35/180	40/180	16/180
Ensitrelvir 250 mg	2/102	1/102	1/102	5/102	8/102	2/102	3/102	2/102	1/102	15/148	25/148	30/148	23/148
Placebo	4/118	4/118	3/118	14/118	14/118	3/118	5/118	5/118	3/118	27/175	46/175	51/175	31/175

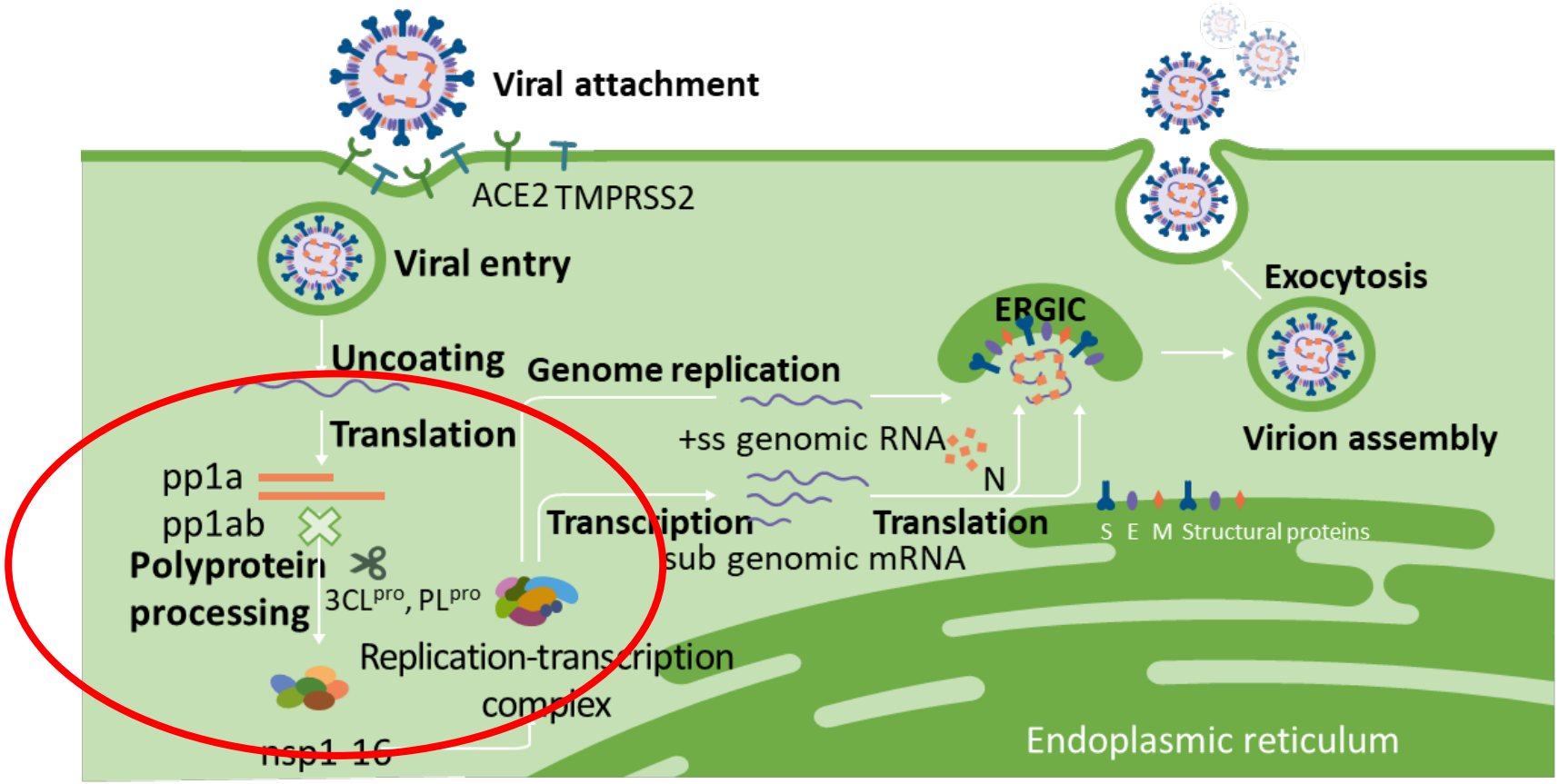
Analysis population for the 14 COVID-19 symptoms and PASC questionnaire is participants with observations at last time of available patient diary (e.g., Day 21), Day 85 and Day 169 in ITT population and participants with observations at either Day 85 or Day 169 in ITT population, respectively.

Conclusion

- SCORPIO-SR enrolled mild/moderate COVID-19 patients
  - ✓Approximately 90% were SARS-CoV-2 vaccinated, Omicron infected
  - ✓With and without risk factors for severe disease
- Ensitrelvir demonstrated earlier COVID-19 symptoms resolution
- Ensitrelvir demonstrated potent antiviral activity
  - ✓Significantly shortened the cessation of infectious virus shedding compared with placebo
  - ✓87% reduction of infectious virus at Day 4 compared with placebo
- Ensitrelvir was well tolerated and no new safety concerns were identified
- Ensitrelvir Ph3 data suggested a reduced risk of Long COVID
  - ✓Reduction observed in overall population
  - ✓In subpopulation with high symptom score at baseline, statistically significant 26 - 45% reduction in some Long COVID endpoints

Thank you for your attention

Ensitrelvir inhibits SARS-CoV-2 3CL protease and prevents viral replication by blocking polyprotein cleavage



Unoh, Y et al. J. Med. Chem. 2022

After entering cells, SARS-CoV-2 viral RNA is translated to viral polyproteins.
Polyproteins exhibit their respective functions after being cleaved, and 3C-like protease (3CL protease) is involved in the cleavage of this polyprotein and is an essential enzyme for replication.