Exploratory evaluation on the effect of ensitrelvir for Long COVID: a post-hoc analysis of Phase 3 part of Phase 2/3 in patients with mild-to-moderate COVID-19

◎Akimasa Fukushi[1], Hiroshi Yotsuyanagi[2], Norio Ohmagari[3], Yohei Doi[4], Masaya Yamato[5], Takumi Imamura[1], Hiroki Sakaguchi[1], Takuhiro Sonoyama[1], Takao Sanaki[6], Genki Ichihashi[1], Yuko Tsuge[1], Takeki Uehara[1], Hiroshi Mukae[7]

1. Drug Development and Regulatory Science Division, Shionogi & Co., Ltd., Osaka, Japan
2. The Institute of Medical Science, The University of Tokyo, Tokyo, Japan
3. Disease Control and Prevention Center, National Center for Global Health, Tokyo, Japan
4. Departments of Microbiology and Infectious Diseases, Fujita Health University School of Medicine, Toyoake, Japan
5. Department of General Medicine and Infectious Diseases, Rinku General Medical Center, Izumisano, Japan
6. Research Division, Shionogi & Co., Ltd., Osaka, Japan
7. Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

COI disclosure by the presenter

Post-hoc Analysis of Phase 3 Part of Phase 2/3 Clinical Trial (SCORPIO-SR#)
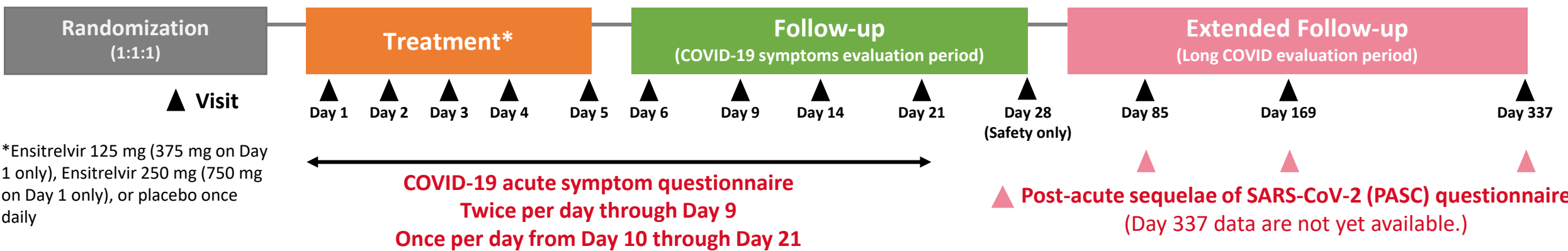
#: ClinicalTrials.gov Identifier: NCT05305547

■ Purpose

To evaluate the effect of ensitrelvir, a 3CL protease inhibitor, on long COVID in patients with mild/moderate COVID-19.

■ Study design

A 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.

Randomization (1:1:1)	Treatment*	Follow-up (COVID-19 symptoms evaluation period)	Extended Follow-up (Long COVID evaluation period)

▲ Visit

Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 9 Day 14 Day 21 Day 28 (Safety only) Day 85 Day 169 Day 337

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

**COVID-19 acute symptom questionnaire
Twice per day through Day 9
Once per day from Day 10 through Day 21**

▲ **Post-acute sequelae of SARS-CoV-2 (PASC) questionnaire**
(Day 337 data are not yet available.)

■ Exploratory evaluation

- Presence of long COVID symptoms evaluated by PASC questionnaire (through Day 169). Investigators and patients were blinded to the information about drug assignment.

Items in PASC* Questionnaire
for Long COVID Evaluation (Day 85, 169, 337**)

Items in PASC questionnaire

Please Indicate the severity of your symptoms **over the past 4 weeks** (absent/mild/moderate/severe, COVID-19 related: Yes/No/Not sure)

COVID-19 acute symptoms
(14 acute symptoms)

Stuffy or runny nose	Low Energy or Tiredness
Sore throat	Muscle or body aches
Shortness of breath	Headache
Cough	Chills or Shivering
Feeling hot or feverish	Loss of smell
Nausea	Loss of taste
Vomiting	Diarrhea

+

Other symptoms
(including neurological symptoms)

Difficulty with concentration and thinking	Palpitations or fast heart beat
Difficulty reasoning and solving problems	Join pain
	Decreased appetite
Memory loss	Dizziness
Insomnia	Chest pain
	Skin rash
Hair loss	Muscle weakness

Entry Status of PASC Questionnaire for Long COVID Evaluation

Approximately 90% of the patients who stayed in the study to the extended follow-up (Long COVID evaluation period) responded to the PASC questionnaire.

	Ensitrelvir 125 mg (n=379)	Ensitrelvir 250 mg (n=345)	Placebo (n=362)
Day 85	240 (63.3%)	224 (64.9%)	228 (63.0%)
Day 169	330 (87.1%)	310 (89.9%)	321 (88.7%)
Day 85 or Day 169	338 (89.2%)	317 (91.9%)	331 (91.4%)

Characteristics of Patients for Long COVID Evaluation

In each group, the average age of the population evaluated was in the mid-30s, >90% had vaccination history, and the mean baseline total score for the 14 acute phase COVID-19 symptoms was approximately 9, with no imbalance among groups.

		Ensitrelvir 125 mg n = 338	Ensitrelvir 250 mg n = 317	Placebo n = 331
Gender, male (%)		54.7%	53.3%	58.0%
Age (years), mean (SD)		36.3 (12.7)	36.5 (12.6)	35.6 (12.1)
BMI (kg/m^2), mean (SD)		23.28 (4.26)	23.00 (3.93)	22.80 (3.65)
Race, Asian (%)		100.0%	99.7%	100.0%
Time from onset to randomization	Less than 72 hours (%)	56.5%	58.4%	58.9%
	More than 72 hours (%)	43.5%	41.6%	41.1%
SARS-CoV-2 vaccination history (%)		91.4%	92.1%	92.7%
Sympton Score at baseline[a]	Sample size	331	309	324
	Mean (SD)	9.5 (4.3)	9.3 (4.6)	9.2 (4.2)
	<9 (%)	44.7%	50.8%	45.0%
	≥9 (%)	53.3%	46.7%	52.9%

[a]COVID-19 acute phase 14-symptom total score. Patients self-assessed taste disorder and smell disorder using a 3-point scale of 0 to 2, and the other 12 symptoms using a 4-point scale of 0 to 3. Patients who had symptoms/symptom scores at the start of administration were tabulated.

Definition of Long COVID Symptoms in Post-hoc Analysis

If the subject met the following criteria, the subject is considered as having Long COVID.
- Symptoms listed in the 14 COVID-19 symptom questionnaire
  - ✓A mild or severe symptom continuing from the last observation in the follow up (e.g., Day 21) to Day 169 at minimum of 2 consecutive time points.

- 4 neurological symptoms* listed only in PASC questionnaire
  - ✓One mild or more severe symptom at Day 85 OR Day 169

- Relationship of the symptoms with COVID-19
  - ✓ Yes (related) or unknown (exclude No (not related))

*Difficulty with concentration and thinking, Difficulty reasoning and solving problems, Memory loss, Insomnia

Proportion of Patients with Long COVID

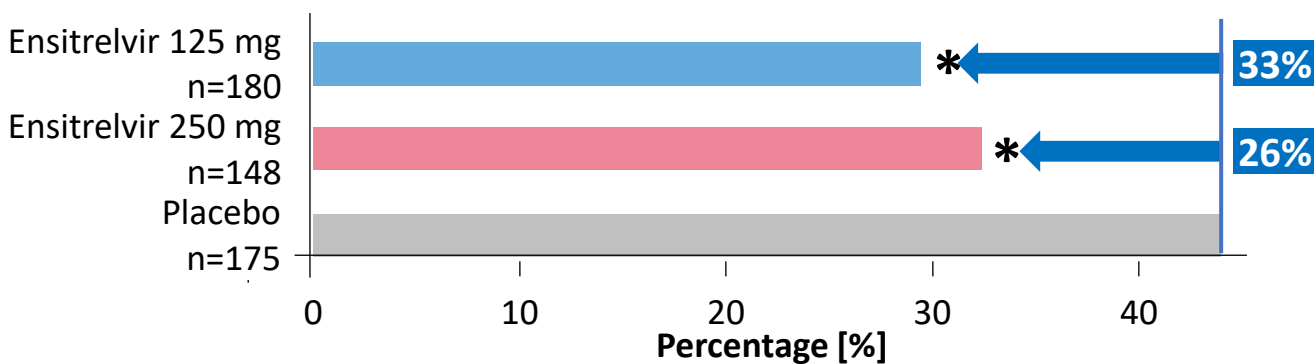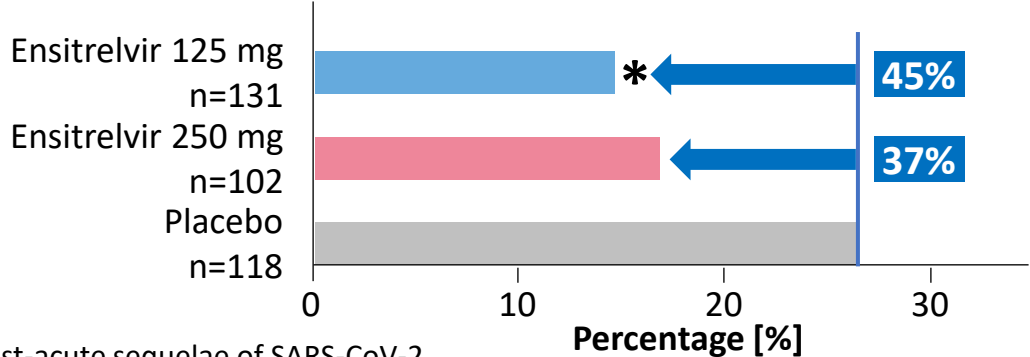Onset of COVID-19 to randomization: ≤120 hours

Proportion of patients with ongoing symptoms (14 COVID-19 symptoms)	Proportion of patients with 4 neurological symptoms in PASC Questionnaire

Overall population (patients with mild/moderate COVID-19)
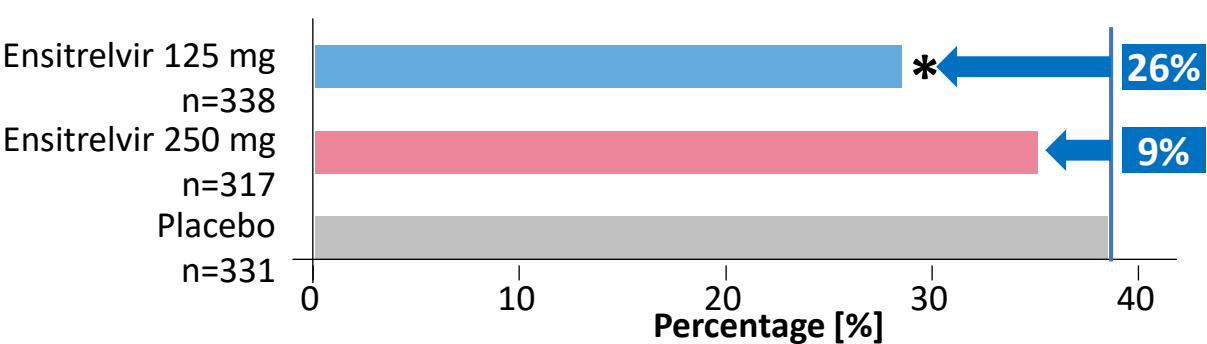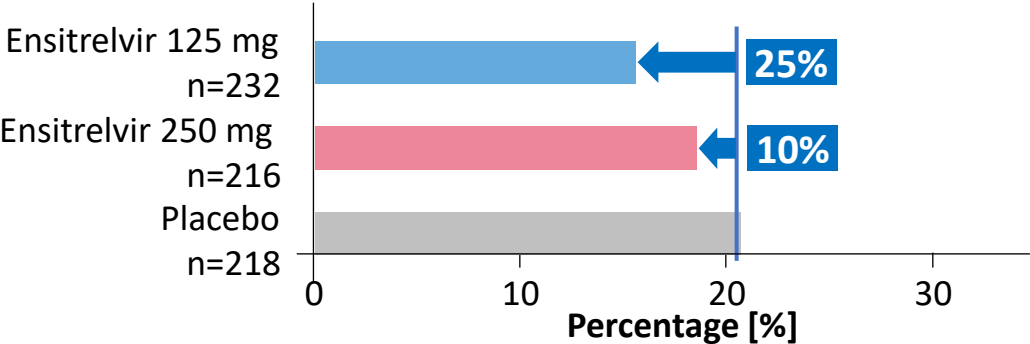
Subpopulation of patients with median or higher symptom score at the start of treatment[a]
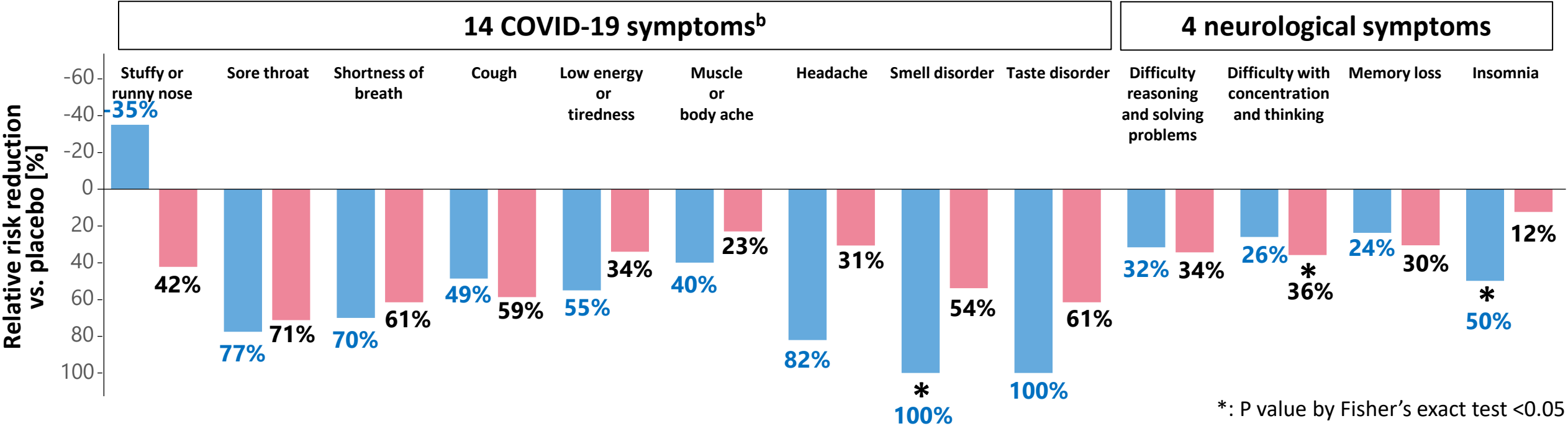

PASC= post-acute sequelae of SARS-CoV-2
*: P value by Fisher's exact test <0.05
[a]The total score of 14 symptoms at baseline being ≥ 9. The median total score for the 14 symptoms at baseline in the analysis population was 9 in the ensitrelvir 125 mg and 250 mg group, the placebo group.

Summary of Long COVID Symptoms for Patients with Median or Higher Symptom Score at the Start of Treatment[a]

[a]The total score of 14 symptoms at baseline being ≥ 9
[b]Symptoms presented in 3 or more patients in the placebo arm were shown

14 COVID-19 symptoms[b] | 4 neurological symptoms

Relative risk reduction vs. placebo [%]

Stuffy or runny nose: -35%, 42%
Sore throat: 77%, 71%
Shortness of breath: 70%, 61%
Cough: 49%, 59%
Low energy or tiredness: 55%, 34%
Muscle or body ache: 40%, 23%
Headache: 82%, 31%
Smell disorder: 100% *, 54%
Taste disorder: 100%, 61%
Difficulty reasoning and solving problems: 32%, 34%
Difficulty with concentration and thinking: 26%, 36% *
Memory loss: 24%, 30%
Insomnia: 50% *, 12%

*: 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

The analysis population for the 14 COVID-19 symptoms and PASC questionnaires consists of those with observations in the last time of avilable diary from Day1 to Day 21, Day 85 and Day 169 in the ITT population and those with observations at either Day 85 or Day 169 in the ITT population, respectively.

Summary

- Based on this exploratory evaluation up to Day 169 in SCORPIO-SR,

  ✓ Proportion of patients who experienced long COVID in overall population was lower in the ensitrelvir 125 mg and 250 mg groups than that in the placebo group.

  ✓ In subpopulation with a high symptom score at baseline, a statistically significant 26 - 45% reduction in some long COVID endpoints was observed.

Conclusion

- Ensitrelvir potentially reduces the risk of long COVID in mild/moderate COVID-19 patients.

Thank you for your attention

Ensitrelvir inhibits SARS-CoV-2 3CL protease and prevents viral replication by blocking polyprotein cleavage
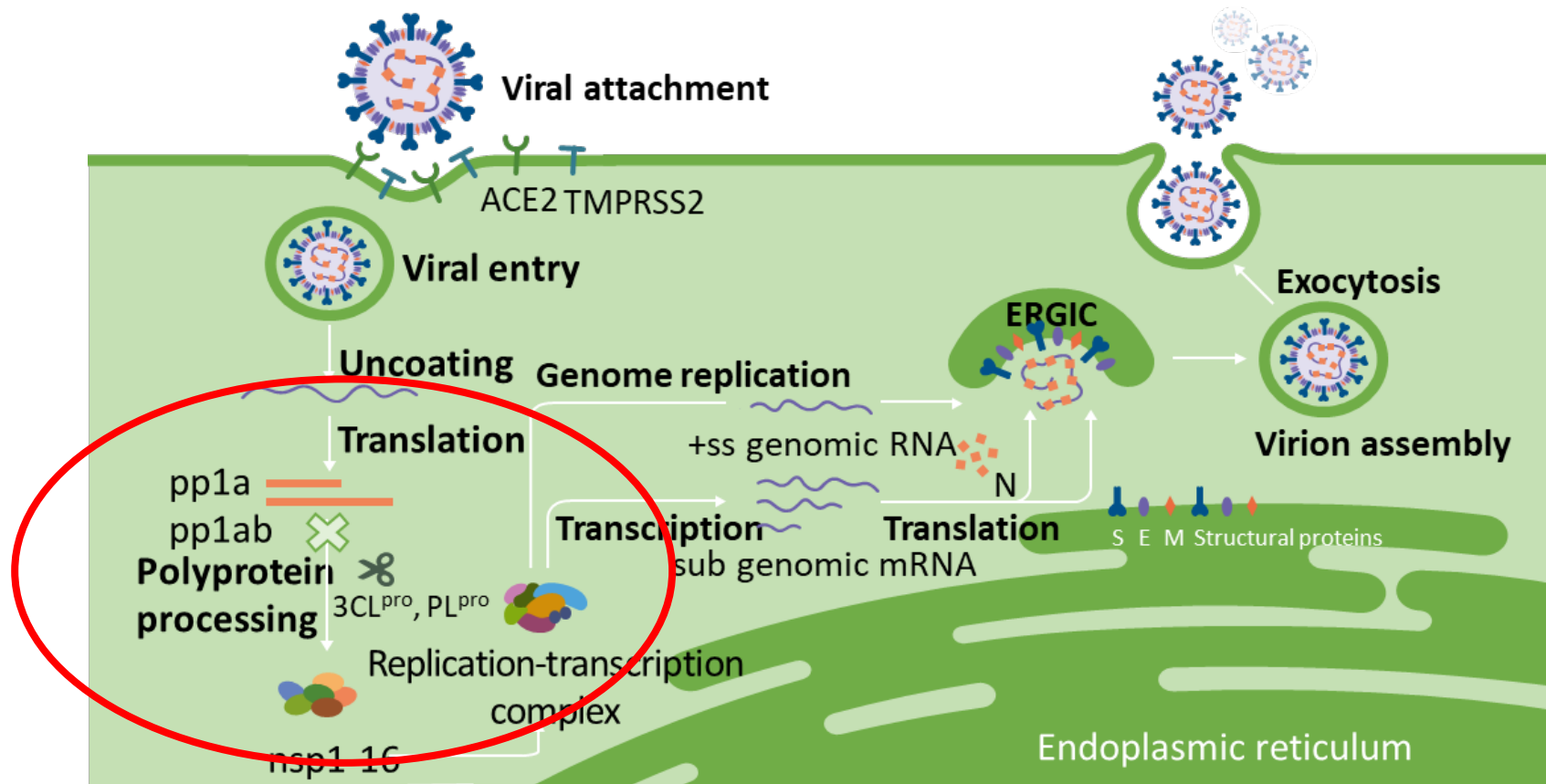
Unoh, Y et al. J. Med. Chem. 2022

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.

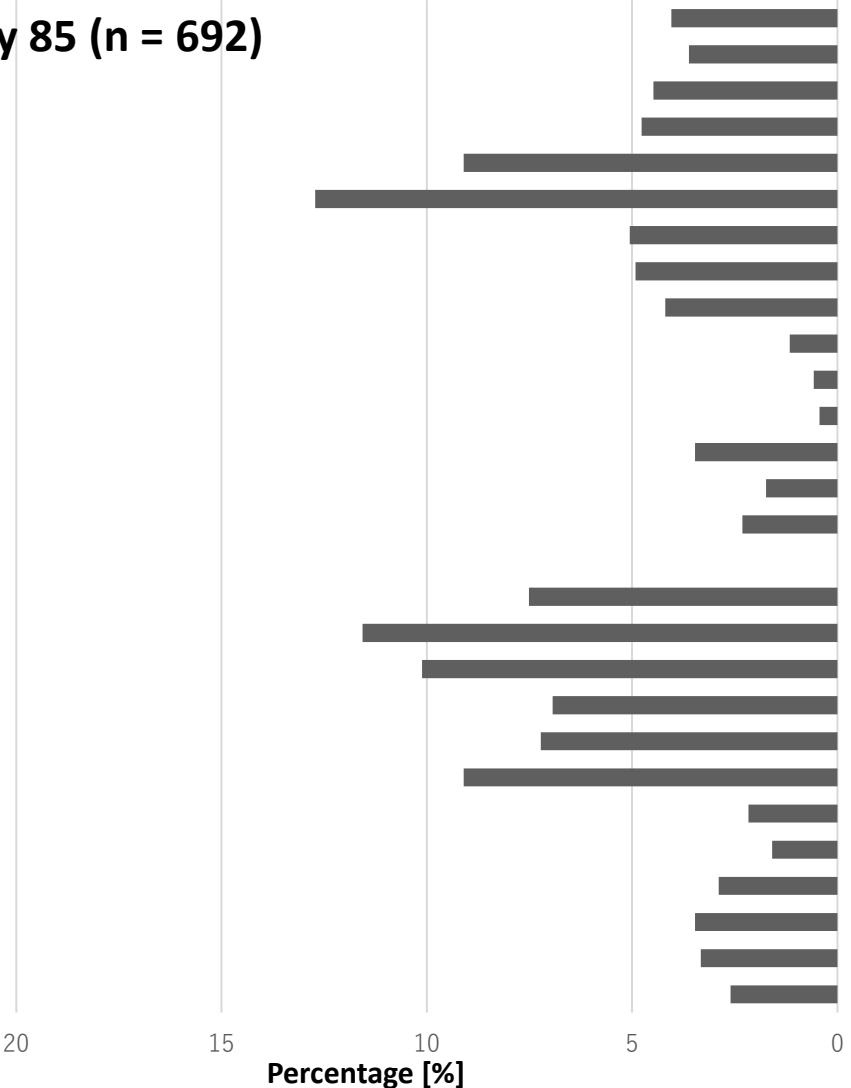# Responses to the Comprehensive Questions in PASC Questionnaire

	Ensitrelvir 125 mg n=338	Ensitrelvir 250 mg n=317	Placebo n=331
On Day85 or Day169, population of 14 COVID-19 symptoms in the past 4 weeks	56 (16.6%)	48 (15.1%)	55 (16.6%)
On Day 85 or Day 169, population of patients who have not fully recovered their physical condition compared to before being infected with COVID-19	37 (10.9%)	41 (12.9%)	50 (15.1%)
On Day85 or Day169, population of patients who are not in good physical health over the past 4 weeks	13 (3.8%)	3 (0.9%)	15 (4.5%)

The analysis population is the patients who responded to the PASC questionnaire among the patients who were subject to efficacy evaluation in the treatment and follow-up phases and who proceeded to the investigation in the exploratory period.
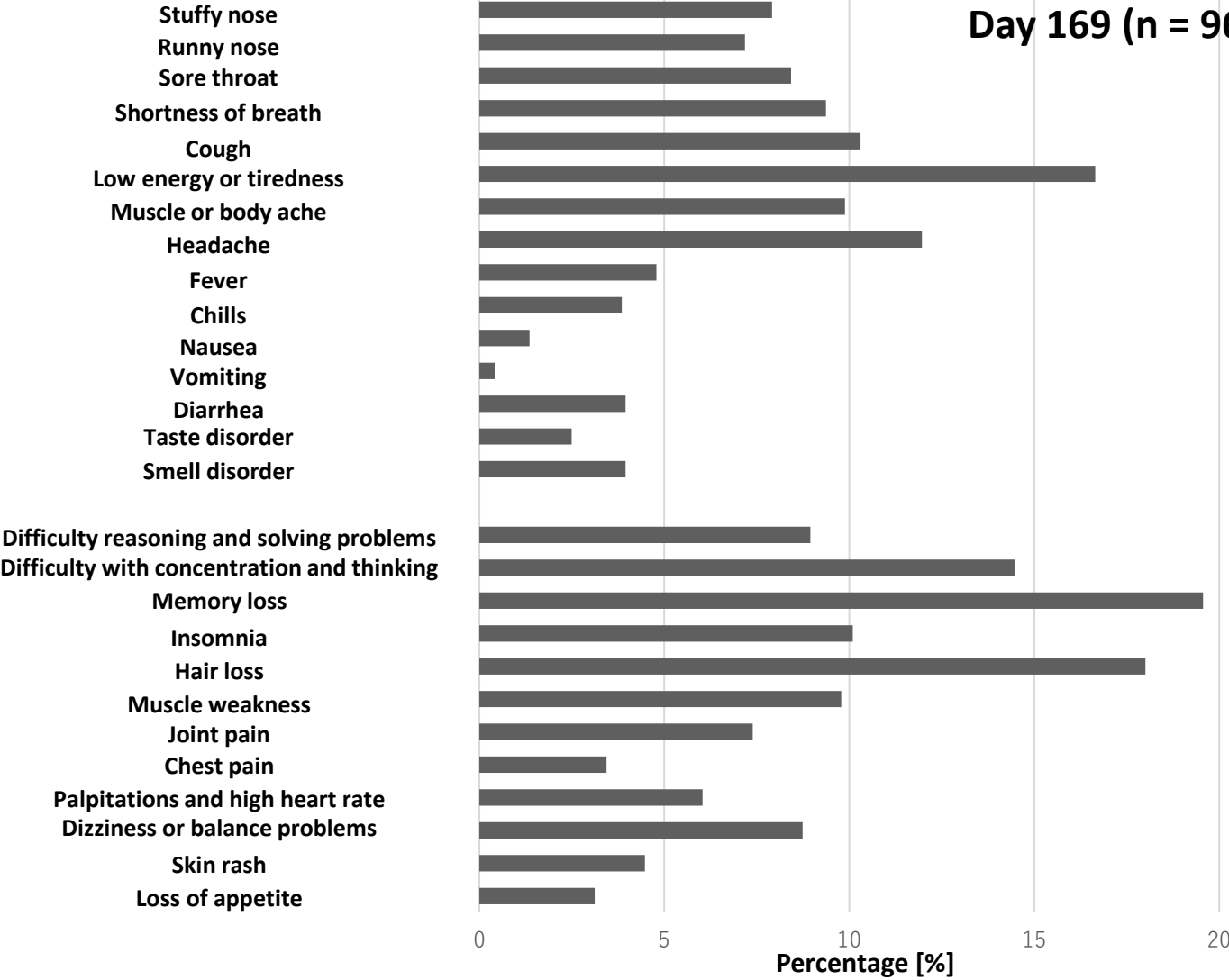
Percentage of Patients Who Have Mild or More Severe Symptom in Each Symptom

Low energy or tiredness, neurological symptoms such as difficulty reasoning and solving problems, difficulty with concentration and thinking, memory loss and insomnia were observed.

Day 85 (n = 692)

Day 169 (n = 961)

Stuffy nose
Runny nose
Sore throat
Shortness of breath
Cough
Low energy or tiredness
Muscle or body ache
Headache
Fever
Chills
Nausea
Vomiting
Diarrhea
Taste disorder
Smell disorder

Difficulty reasoning and solving problems
Difficulty with concentration and thinking
Memory loss
Insomnia
Hair loss
Muscle weakness
Joint pain
Chest pain
Palpitations and high heart rate
Dizziness or balance problems
Skin rash
Loss of appetite

Percentage [%]

Percentage [%]

If the symptom is judged as not related to COVID-19, the symptom is not counted.