CROI 2023 Follow Up Meeting

February 22, 2023
Shionogi & Co., Ltd.

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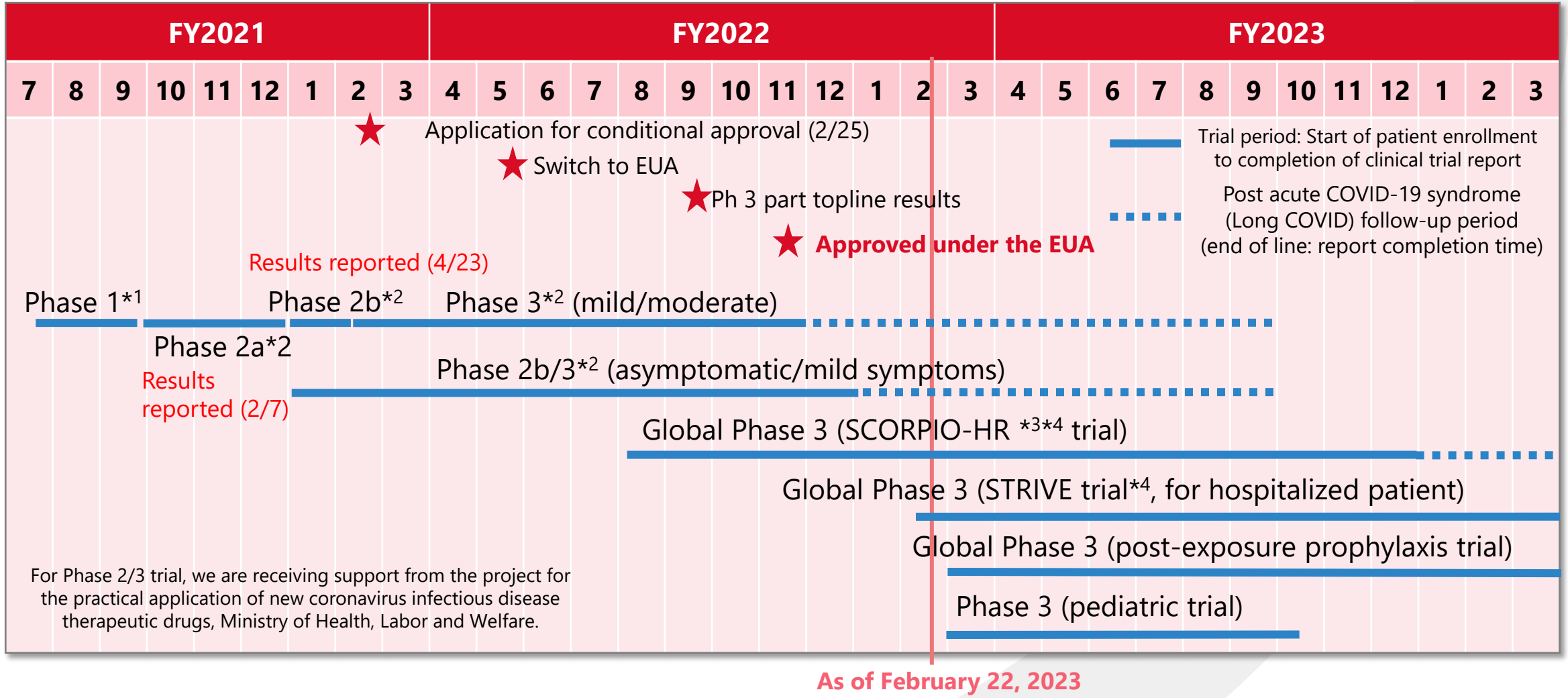
Agenda

- **Progress update and future evidence generation plans for Xocova® (ensitrelvir)**
- **Results from Phase 3 part of Phase 2/3 trial**
  - ✓ Trial outline
  - ✓ Patient background
  - ✓ Primary endpoint (improvement of clinical symptoms)
  - ✓ Key secondary endpoint (antiviral effect)
  - ✓ Exploratory evaluation (effect on Long COVID symptoms)
  - ✓ Summary of trial results

Xocova®: Progress Summary



*1 jRCT2031210202、*2 jRCT2031210350、*3 NCT05305547、*4 NCT05605093

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Latest Update

- **JP: From May 8, 2023, the position of COVID-19 under the Infectious Diseases Act will be changed to Category 5 infectious disease**
- **US: Proclamation on Declaring a National Emergency Concerning COVID-19 Outbreak will be lifted on May 11, 2023**
  - Emergency use authorizations (EUA) for all antibody drugs against COVID-19 have been revoked due to their reduced efficacy against Omicron strains
- **Xocova®: Started global Phase 3 study STRIVE (announced on February 15, 2023)**
  - STRIVE is a new international clinical research program derived from ACTIV, a public-private partnership program led by the National Institute of Allergy and Infectious Diseases (NIAID), a constituent organization of the National Institutes of Health (NIH). The program is funded by NIAID
  - 1,500 inpatients to be enrolled globally, expected to be completed in early 2024

Xocova®: Antiviral Effect Against Mutant Strains*

From the 3rd Quarter of Fiscal 2022 Financial Results (Partially revised)

In vitro antiviral evaluation using VeroE6T cells*

virus strain	Ancestor	alpha strain	beta strain	gamma strain	delta strain	omicron strain								
						BA.1	BA.1.1	BA.2	BA.2.75	BA.4	BA.5	BQ.1.1	XBB.1	XE
EC_{50} (μM)	0.37	0.46	0.40	0.50	0.41	0.29	0.36	0.52	0.30	0.22	0.40	0.48	0.33	0.44

- **Xocova® shows antiviral efficacy against a wide range of strains, including past prevalent strains and recent Omicron mutant strains (BQ.1.1, XBB.1).**
- **Xocova® has also been reported to exhibit in vitro activity against the Omicron mutant XBB.1.5****
- **Xocova® shows antiviral efficacy against viruses resistant to other drugs (no cross-resistance)**

* Nakashima et al OPTIONS-XI P-205 Sep 2022, Sho Kawashima et al Biochemical and Biophysical Research Communications 645 (2023) P.132-136

** Antiviral and bivalent vaccine efficacy against an omicron XBB.1.5 isolate - The Lancet Infectious Diseases

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Xocova®: Overall Picture of the Current Situation and Future Plans

From the 3rd Quarter of Fiscal 2022 Financial Results (Partially revised)

With the emergence of new mutant strains, the need for antiviral drugs remains Accumulating further evidence for the role of Xocova® in "with COVID" phase

Japan
Approved

Asia
Korea：Submitted
China：Preparing to apply

Global

Development

- **Phase 2/3 trial（Japan･Asia）**
  - ✓ Antiviral effect
  - ✓ Symptom improvement effect
  - → Continue follow up
    - ✓ Assess the post-acute symptoms

Additional data from Phase 3 part presented at CROI 2023

Global expansion
Global Phase 3 trial
- **SCORPIO-HR trial** — In Progress
  Patients: Non-hospitalized
  （Patients with and without vaccination and risk factors)
- **STRIVE trial** — In Progress
  Patients: SARS-CoV-2 infected patients that are hospitalized

Prevention
Global Phase 3 trial — In Preparation
- **SCORPIO-PEP* trial**

Pediatric indication — In Preparation
- **Phase 3 Pediatric trial (Japan)**
  - ✓ 6-12 year old
- **Global Phase 3 trial (Global including Japan)** — Planned
  - ✓ 0-12 year old

Long COVID
- **Data analysis of Phase 2/3 trial**
- **Physician-initiated trial** — Planned
  Investigation of efficacy for patients with long COVID-19

Supply

Japan
- 10 million people annually
  (For 3.5 million people in FY2022)

China
- 20 million people annually

US
- Production system under construction

LMICs
- License agreement with Medicines Patent Pool

* Post Exposure Prophylaxis Study

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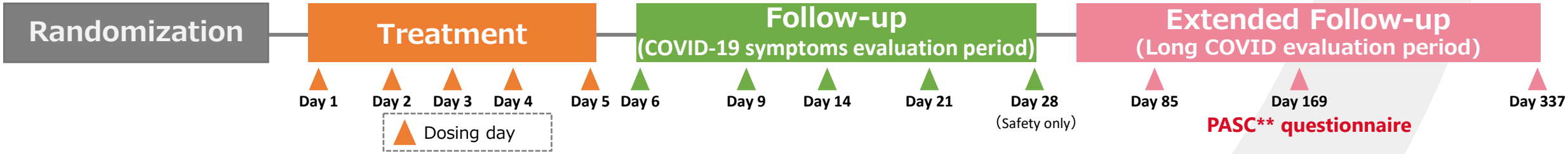
Phase 3 part of Phase 2/3 trial Outline

- **Trial 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
- **Trial design**
  - ➢ Multicenter, randomized, double-blinded, placebo-controlled study conducted in Japan, South Korea and Vietnam from February to November in 2022, Omicron variant dominant period



- **Main evaluation items**
  - ➢ Primary endpoint：Time to resolution* of five key Covid-19 symptoms
  - ➢ Key secondary endpoint：antiviral effect（viral RNA amount、virus titer）
    - ✓ Viral titer: Amount of infectious virus (living virus) contained in the sample
    - ✓ Viral RNA: Amount of viral RNA (including fragments of the dead virus genome) contained in the sample
  - ➢ Safety（Until the Day 28）
  - ➢ Exploratory endpoint: Presence of Long COVID symptoms evaluated by PASC questionnaire (by Day 169)

* Time to return to pre symptomatic state, defined as time to “recovery” in the trial protocol ** post-acute sequelae of SARS-CoV-2

Summary Patient Background

※The trial results only include the domestically approved dose of 125 mg of ensitrelvir. (See Appendix for results at 250 mg)

Background information on the ITT* population

	Time from onset to randomization : <72 hours		Time from onset to randomization : <120 hours	
	125 mg N = 347	**Placebo** N = 343	**125 mg** N = 603	**Placebo** N = 600
Sex, Male （%）	55.6%	50.7%	52.7%	51.8%
Mean age (years)	35.7	34.7	35.9	35.3
Vaccination for SARS-Cov-2	92.8%	91.8%	93.2%	92.2%
Viral RNA amount (log_{10} copies/mL)	6.976	6.933	6.825	6.770
Race: Asian (%)	99.4%	99.4%	99.7%	99.7%
Omicron strain infection rate (%)	89.6%	88.0%	89.7%	89.0%

* Intention-to-treat (ITT)：All subjects who were randomly assigned to the trial intervention and had a SARS-Cov-2 infection based on RT-PCR. 1,798 subjects excluding 23 subjects that were PCR negative at baseline (from 1,821 subjects)

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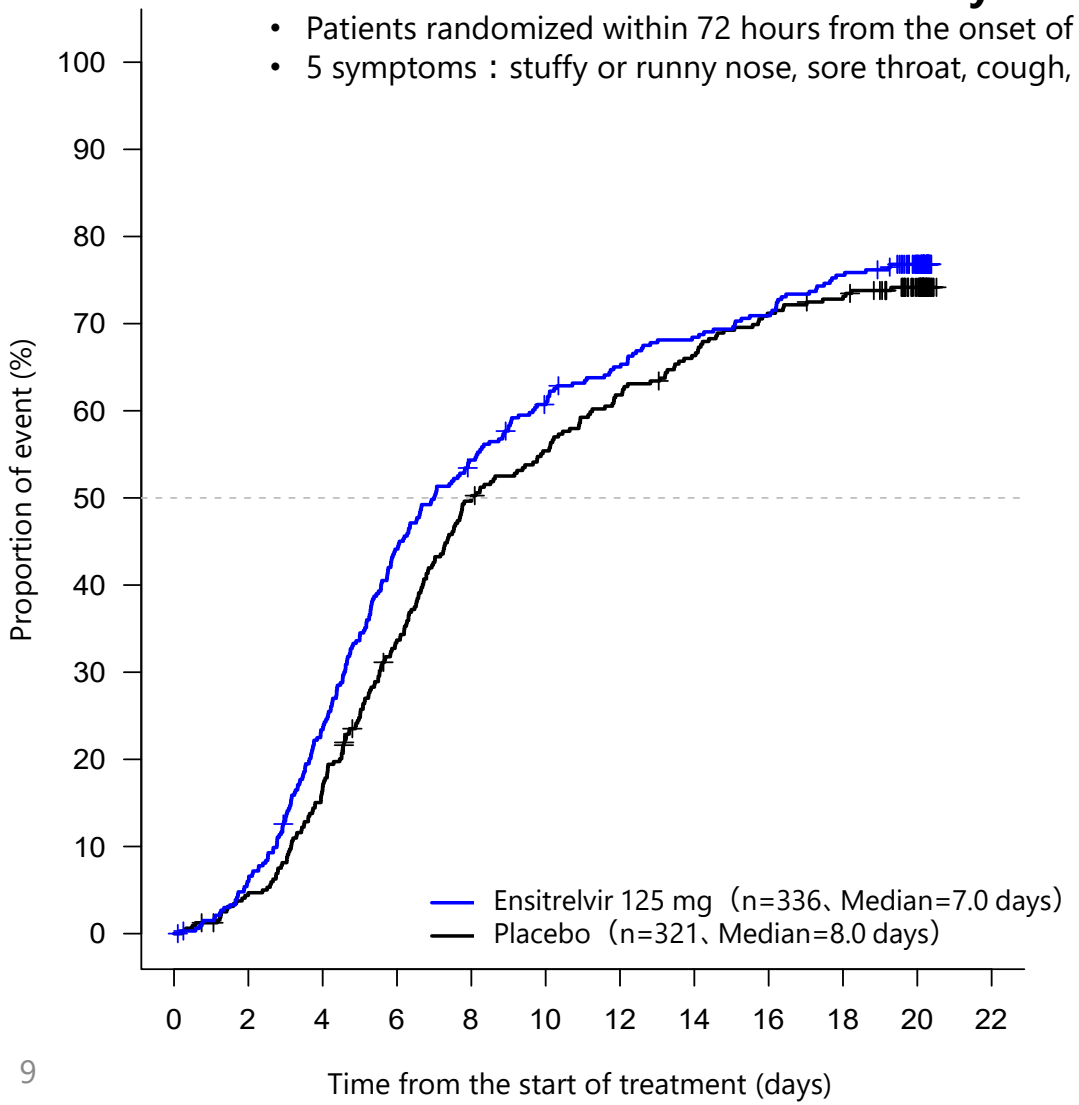
Primary endpoint: The Time to Resolution of All Five Key COVID-19 Symptoms

From the FY2022 R&D Day (Partially revised)

The time to resolution of all five key COVID-19 symptoms

- Patients randomized within 72 hours from the onset of symptoms
- 5 symptoms：stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness



Time from onset to randomization：<72 hours

		125 mg N = 347	Placebo N = 343
Median [95% CI]		167.9 [145.0, 197.6]	192.2 [174.5, 238.3]
Difference in median vs. placebo [95% CI]		**-24.3** [-78.7, 11.7]	---
Stratified Peto-Prentice's generalized Wilcoxon test vs. placebo [a]	P value	**0.0407**	---

CI = Confidence Interval
[a] Adjusted by the following stratum (SARS-CoV-2 vaccination history [Yes or No])

Significant reduction in the time to resolution of 5 symptoms of COVID-19 characteristic of Omicron strain compared to placebo (primary endpoint achieved)

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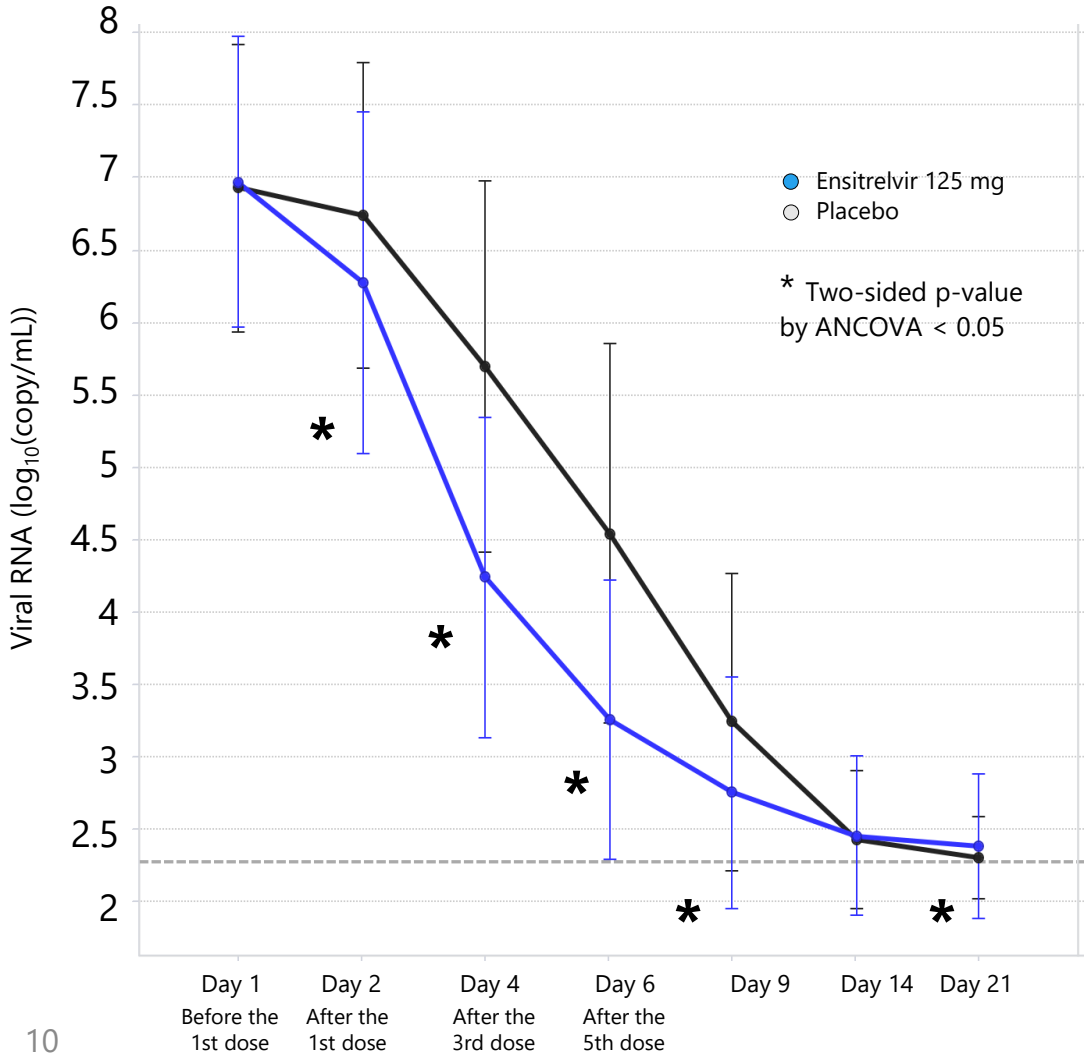
Key Secondary Endpoint①: Change in Viral RNA Amount

From the FY2022 R&D Day
(Partially revised)

Amount of viral RNA



Changes in viral RNA levels on day 4 of administration (after 3 doses)

Time from onset to randomization : <72 hours

		125 mg N = 347	Placebo N = 343
Mean (SD)		-2.737 (1.085)	-1.235 (1.528)
ANCOVA vs. placebo [a]	LS mean (SE)	-2.48 (0.08)	-1.01 (0.08)
	Difference in LS mean (SE) [95% CI]	**-1.47 (0.08)** [-1.63, -1.31]	---
	P value	**<0.0001**	---

UNIT: log_{10} copies/mL
ANCOVA = Analysis of Covariance; SD = Standard Deviation; SE = Standard Error; LS = Least Squares; CI = Confidence Interval
Lower limit of quantification of viral RNA is 2.08 log_{10} copies/mL.
If viral RNA is negative and less than the lower limit of quantification, the viral RNA was imputed 2.27 and 2.08 log_{10} copies/mL, respectively.
[a] Covariate: SARS-CoV-2 viral RNA at baseline, SARS-CoV-2 vaccination history [Yes or No]

Ensitrelvir 125 mg group reduced viral RNA level to 1/300 of the level before administration by day 4 of administration (after the 3rd dose) (placebo decreased to 1/10)

Significantly reduced viral RNA levels on day 4 of administration (after 3 doses), confirming antiviral efficacy

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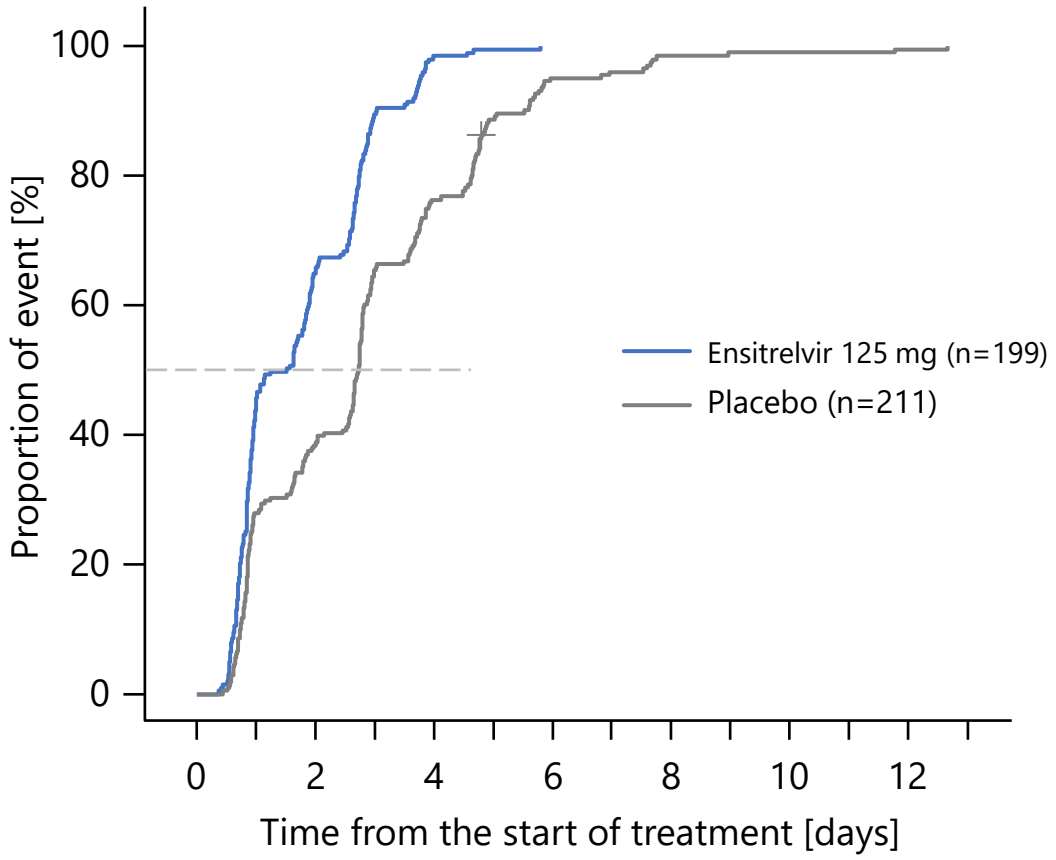
Key Secondary Endpoint②: Virus Titer

Time to first confirmed negative virus titer for SARS-CoV-2



		125 mg N = 203	Placebo N = 214
Median [95% CI]		36.2 [23.4, 43.2]	65.3 [62.0, 66.8]
Difference in median vs. placebo [95% CI]		**-29.1** [-42.3, -21.1]	---
Stratified log-rank test [a]	P value	**<0.0001**	---

Analysis in the Modified Intention-to-Treat Population (All Pretreatment RT-PCR-Positive Patients with Detectable SARS-CoV-2 Viral Titers at Baseline), CI = Confidence Interval
[a] Adjusted for SARS-CoV-2 vaccination status

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

Ensitrelvir 125 mg significantly reduced time to viral titer negative compared to placebo

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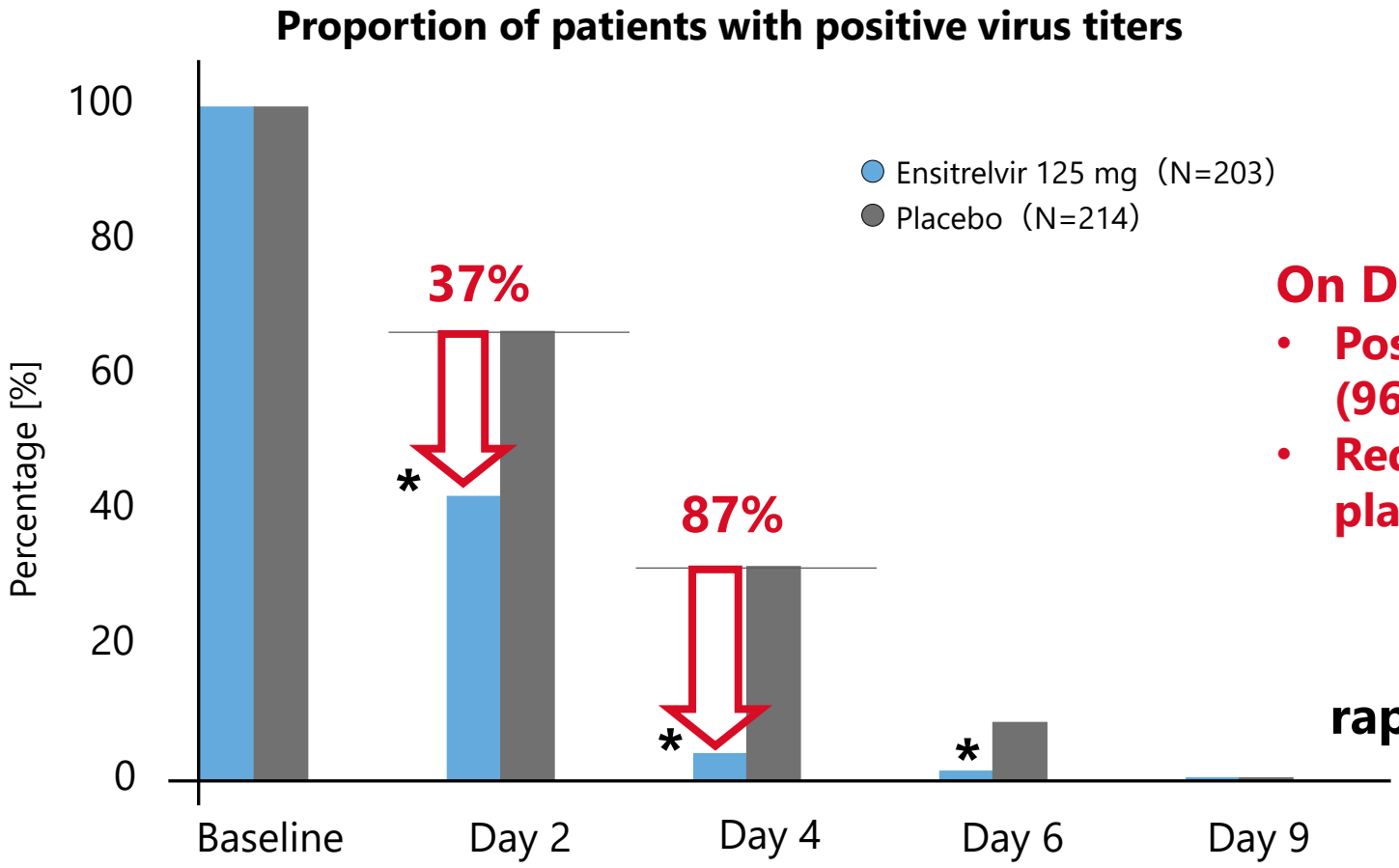
Key Secondary Endpoint②: Virus Titer



On Day 4 (after 3 doses)

- **Positive viral titers have almost disappeared (96% negative)**
- **Reduced by about 90% compared to the placebo group**

Proportion of patients with the potential to shed infectious virus rapidly decrease after taking ensitrelvir

vs Placebo group *< 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))

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Long COVID Symptoms and Definitions

Follow-up questionnaires obtained after 3 to 6 months for patients enrolled in the Phase 3 part (Time from Onset to Randomization：<120 Hours)

Long COVID symptoms

1 14 COVID-19 symptoms

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

Definition of Long COVID symptoms

- **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**

2 PASC* （neurological symptoms）

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

Definition of Long COVID symptoms

- **One mild or more severe symptom at Day 85 OR Day 169**

Evaluate the effect of ensitrelvir on Long COVID based on the above definitions

* post-acute sequelae of SARS-CoV-2

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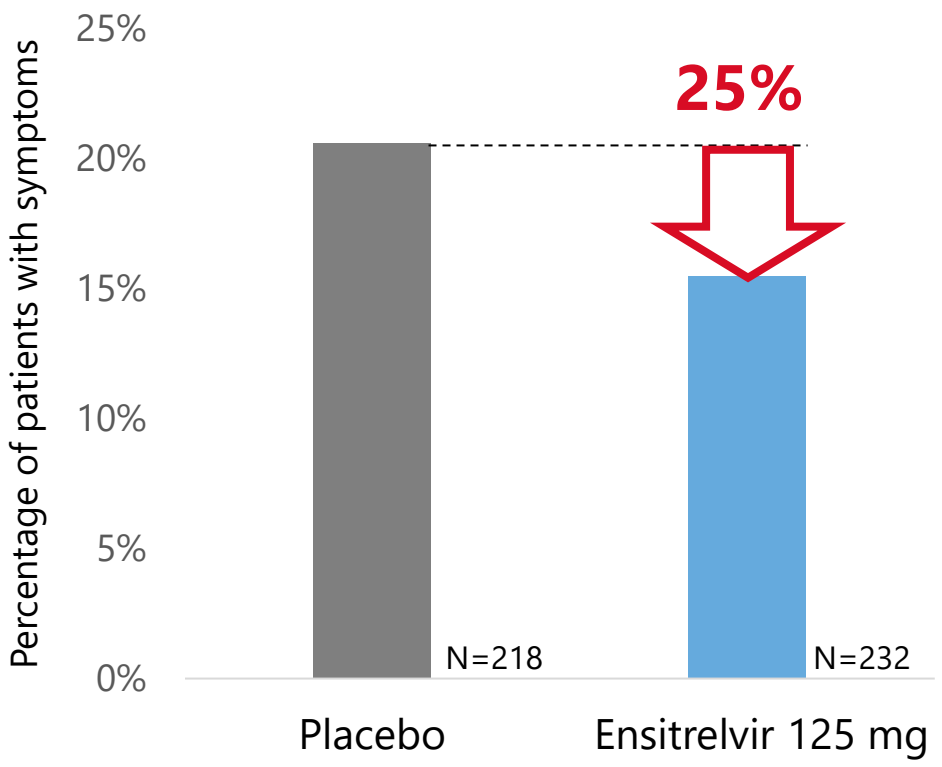
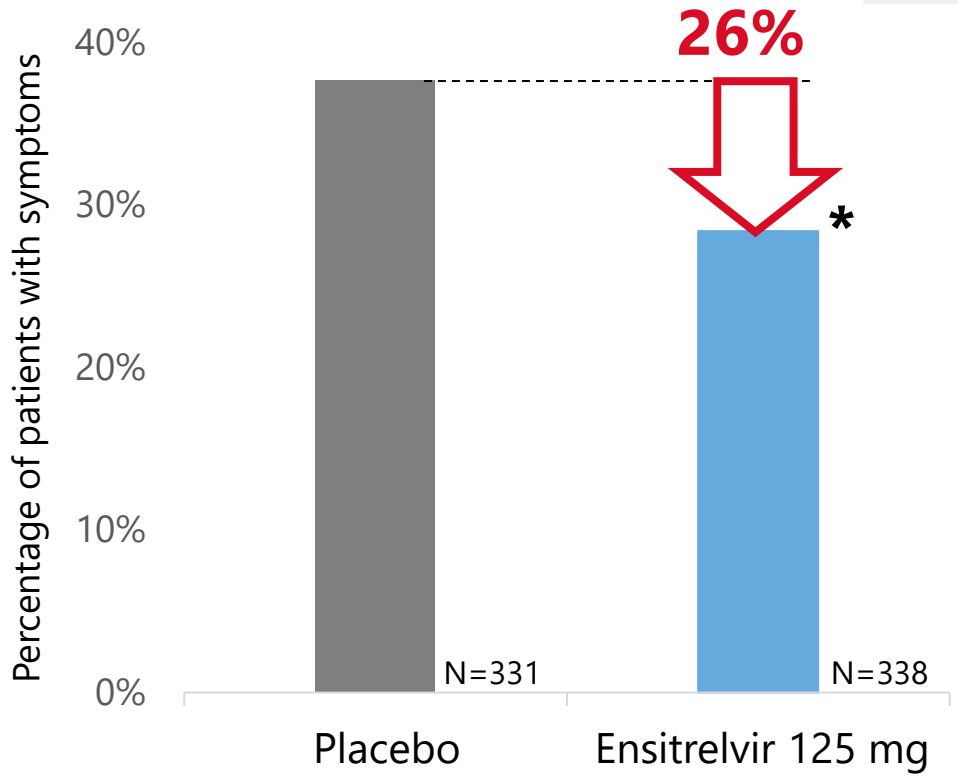
Effect on Long COVID Symptoms（All Patients）

Percentage of patients with 14 symptoms



Percentage of patients with neurological symptoms



Approximately 25% reduction in Long COVID onset/persistence risk

P value by Fisher's exact test *<0.05

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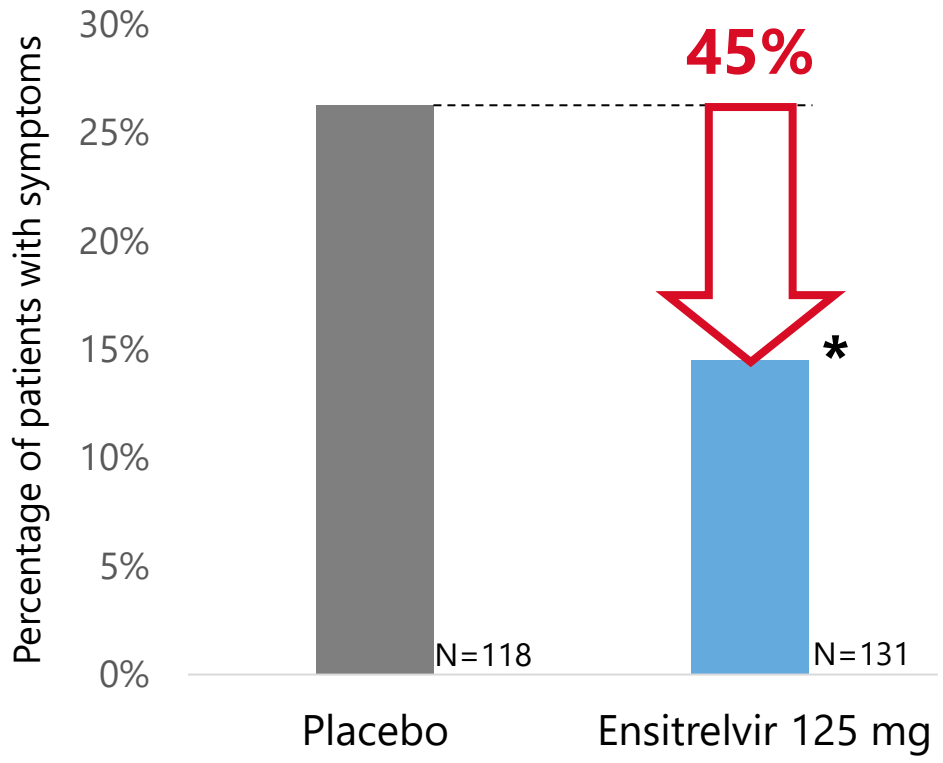
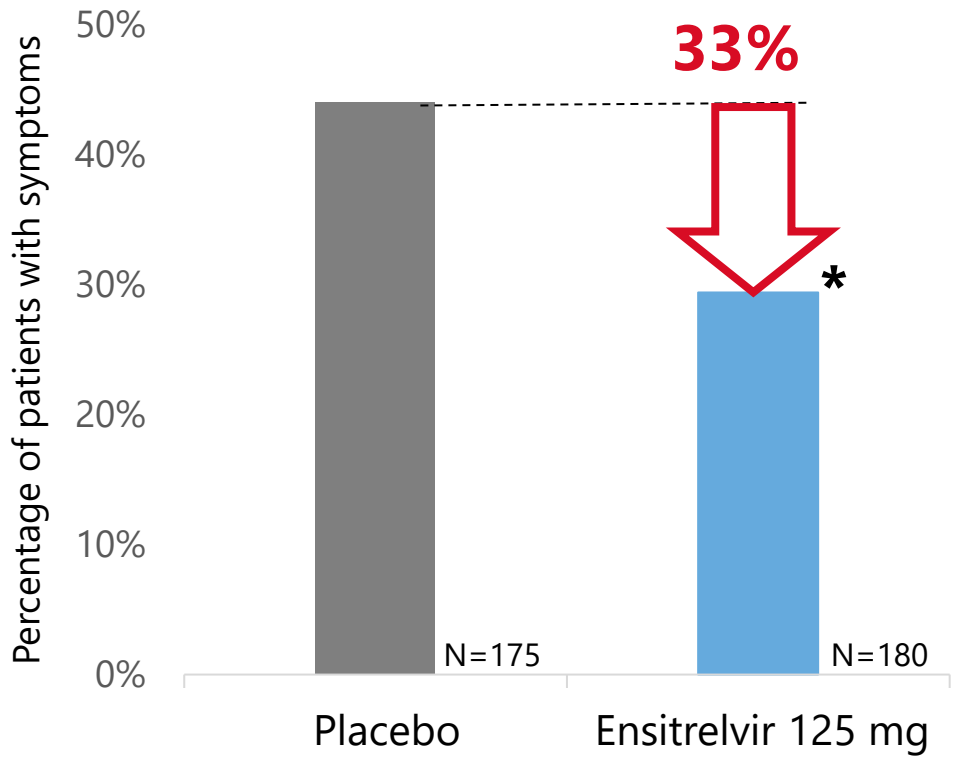
Effect on Long COVID Symptoms（Patients who Have High Symptom Score**）

Percentage of patients with 14 symptoms



Percentage of patients with neurological symptoms



Significant reduction of the risk of developing Long COVID versus placebo in patients with a high symptom score

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

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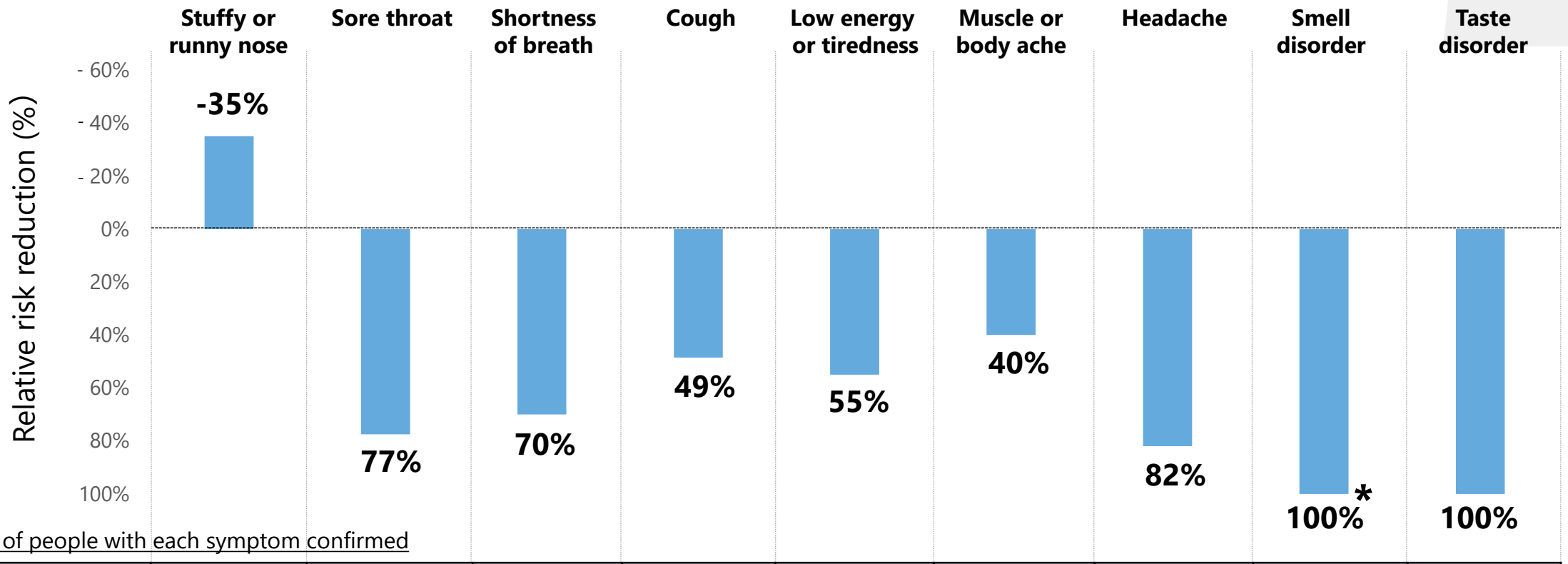
Effect on Long COVID Symptoms（Patients who Have High Symptom Score）- 14 Symptoms -

Only symptoms with 3 or more cases in the placebo group are displayed



Number of people with each symptom confirmed

	Stuffy or runny nose	Sore throat	Shortness of breath	Cough	Low energy or tiredness	Muscle or body ache	Headache	Smell disorder	Taste disorder
Ensitrelvir 125 mg (N=131)	6 (4.6%)	1 (0.8%)	1 (0.8%)	8 (6.1%)	7 (5.3%)	2 (1.5%)	1 (0.8%)	0 (0%)	0 (0%)
Placebo (N=118)	4 (3.4%)	4 (3.4%)	3 (2.5%)	14 (11.9%)	14 (11.9%)	3 (2.5%)	5 (4.2%)	5 (4.2%)	3 (2.5%)

Confirmed risk reduction for almost all of the 14 symptoms

P value by Fisher's exact test *<0.05

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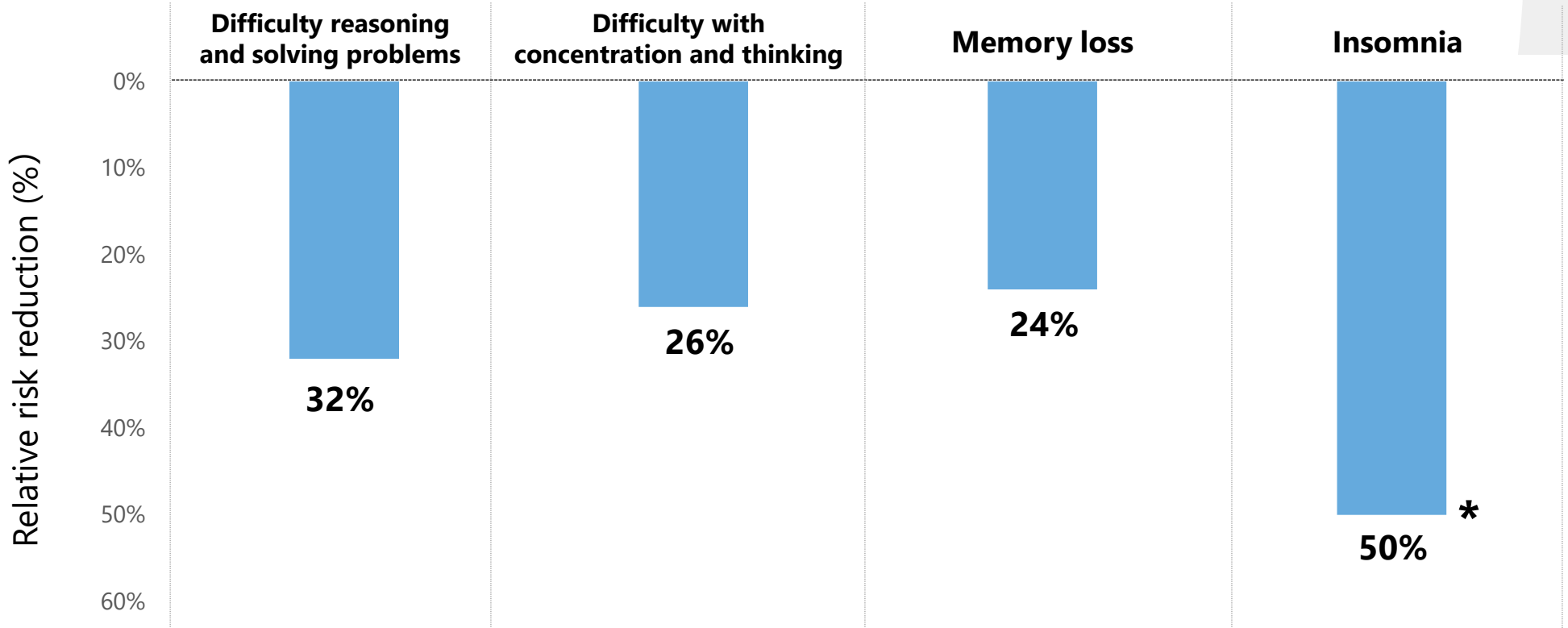
Effect on Long COVID Symptoms（Patients who Have High Symptom Score）- Neurological Symptoms -



Number of people with each symptom confirmed

Ensitrelvir 125 mg (N=180)	19（10.6%）	35（19.4%）	40（22.2%）	16（8.9%）
Placebo (N=175)	27（15.4%）	46（26.3%）	51（29.1%）	31（17.7%）

Confirmed risk reduction for each neurological symptom

P value by Fisher's exact test *<0.05

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Summary of Results

- **Phase 3 part of Phase 2/3 trial was conducted in patients with mild/moderate COVID-19**
  - ✓ Approximately 90% of patients were vaccinated against SARS-CoV-2 and infected with Omicron
  - ✓ With or without high-risk factors
- **Early improvement of COVID-19 symptoms by administration of ensitrelvir**
- **Confirmed potent antiviral activity**
  - ✓ Significantly reduced time to infectious virus negativity compared to placebo
  - ✓ Nearly all patients (96%) had negative viral titers on Day 4 (after 3 doses) compared to placebo
- **Reduction of the risk of Long COVID manifestation**
  - ✓ Significantly reduced risk of Long COVID manifestation in severely symptomatic patients versus placebo
    - 45% reduction in the proportion of patients with long-lasting any of the 14 symptoms characteristic of COVID-19
    - 33% reduction in the proportion of patients presenting with the four most commonly reported post-acute neurological symptoms
- **No safety concerns were identified; ensitrelvir was well tolerated**

Note) The figures in red are newly announced results

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Appendix

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CROI 2023 Presentation

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

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

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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#)

CROI 2023 Presentation

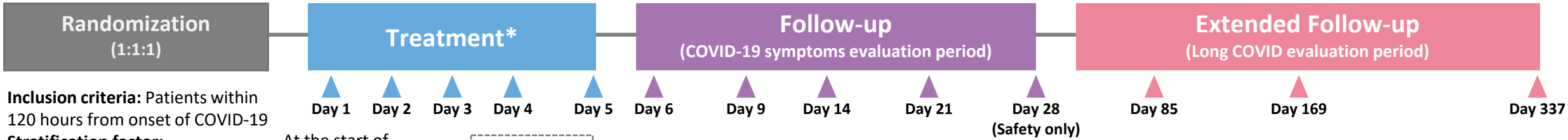
#: ClinicalTrials.gov Identifier: NCT05305547

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)

At the start of administration

dosing day

*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)

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Baseline Characteristics

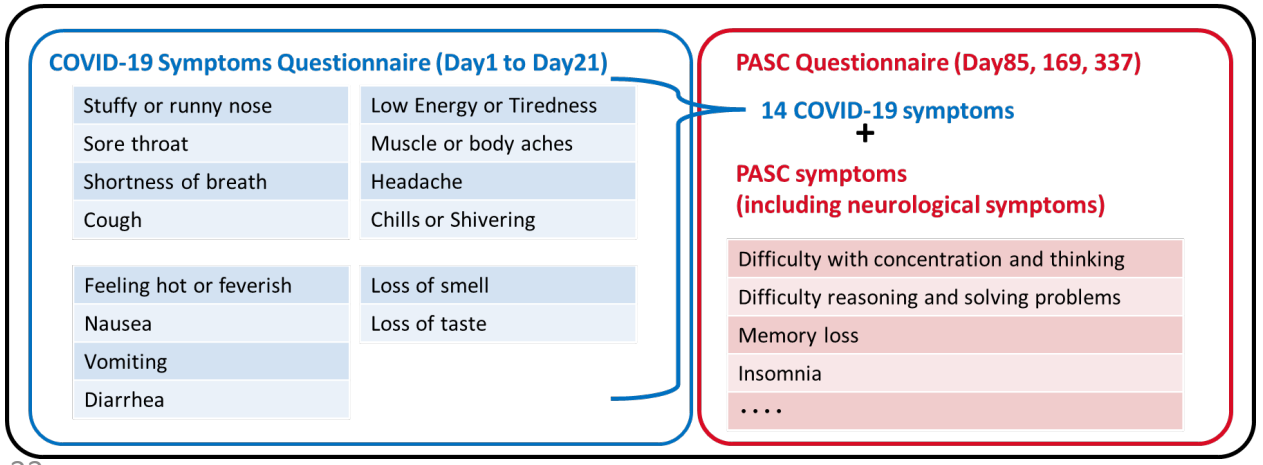
	COVID-19 onset to randomization : **<72 hours**			COVID-19 onset to randomization : **≤120 hours**		
	Ensitrelvir 125 mg (n=347)	Ensitrelvir 250 mg (n=340)	Placebo (n=343)	Ensitrelvir 125 mg (n=603)	Ensitrelvir 250 mg (n=595)	Placebo (n=600)
Gender, Male (%)	55.6%	54.4%	50.7%	52.7%	54.3%	51.8%
Age (years), 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

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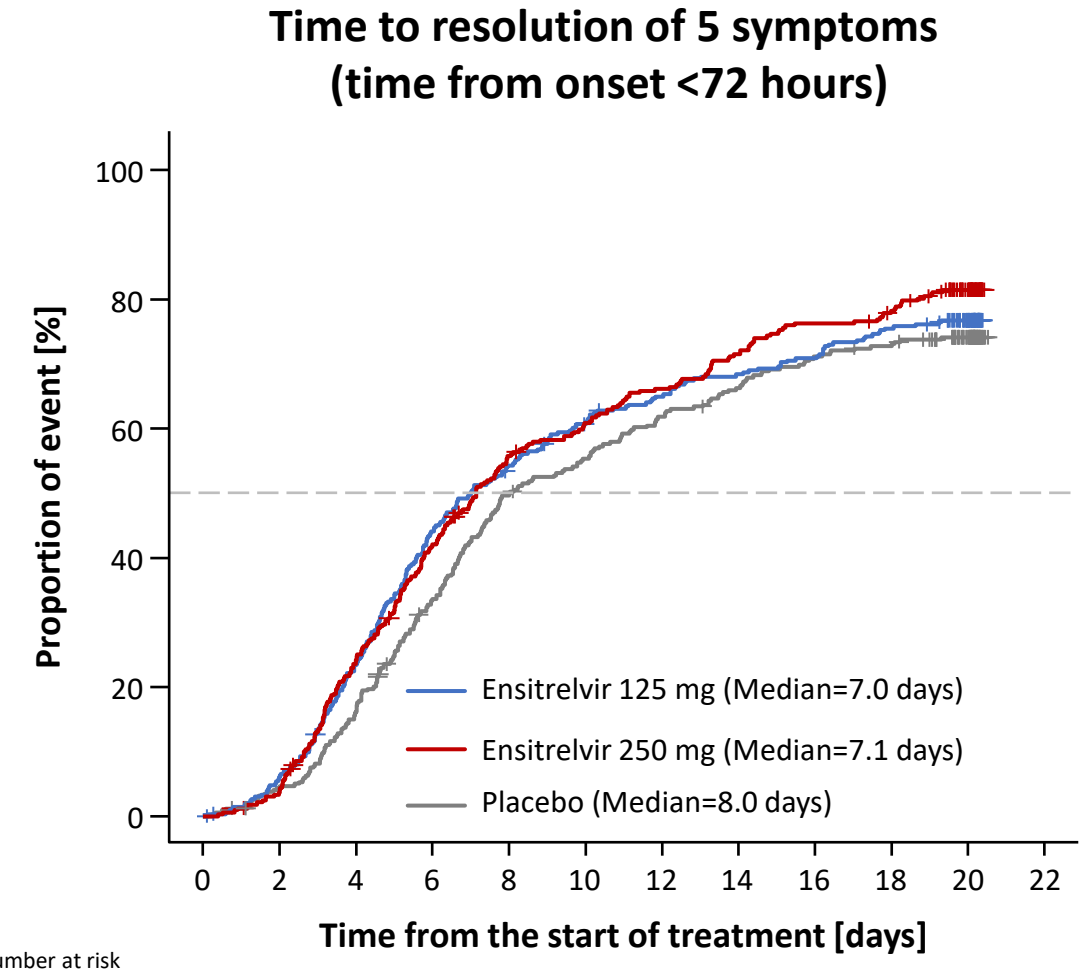
Ensitrelvir 125 mg demonstrated the earlier (1 day) resolution of 5 COVID-19 symptoms than placebo.

	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.



Number at risk											
Ensitrelvir 125 mg	336	314	255	186	151	128	113	102	94	79	55
Ensitrelvir 250 mg	329	315	247	188	141	124	107	90	75	67	37
Placebo	321	304	265	208	158	139	119	104	89	83	52

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Key Secondary Endpoint: SARS-CoV-2 Viral Titer

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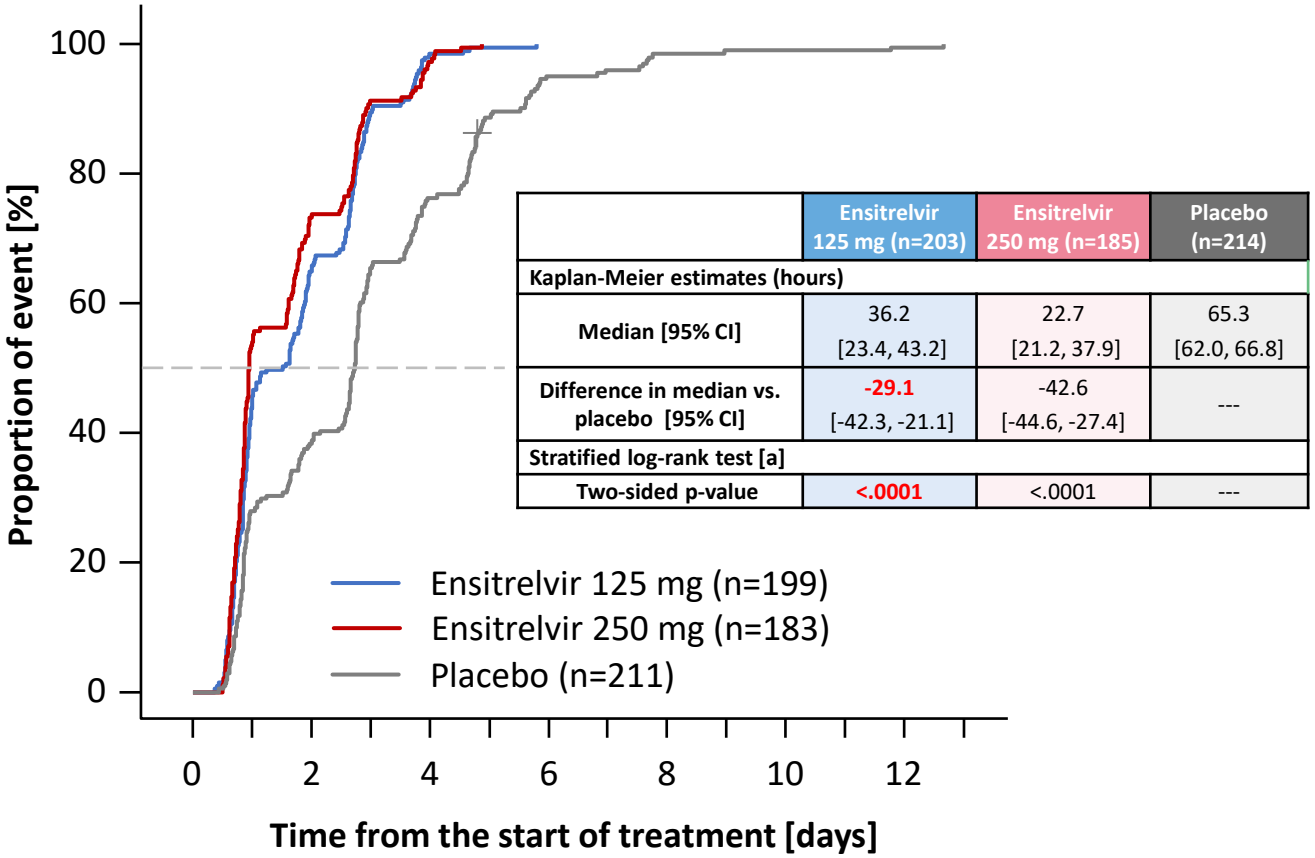
Ensitrelvir 125 mg significantly shorten the time to cessation of SARS-CoV-2 viral shedding compared with placebo.
Ensitrelvir 125 mg showed 87% reduction of patient with positive viral titer at Day 4 compared with placebo.

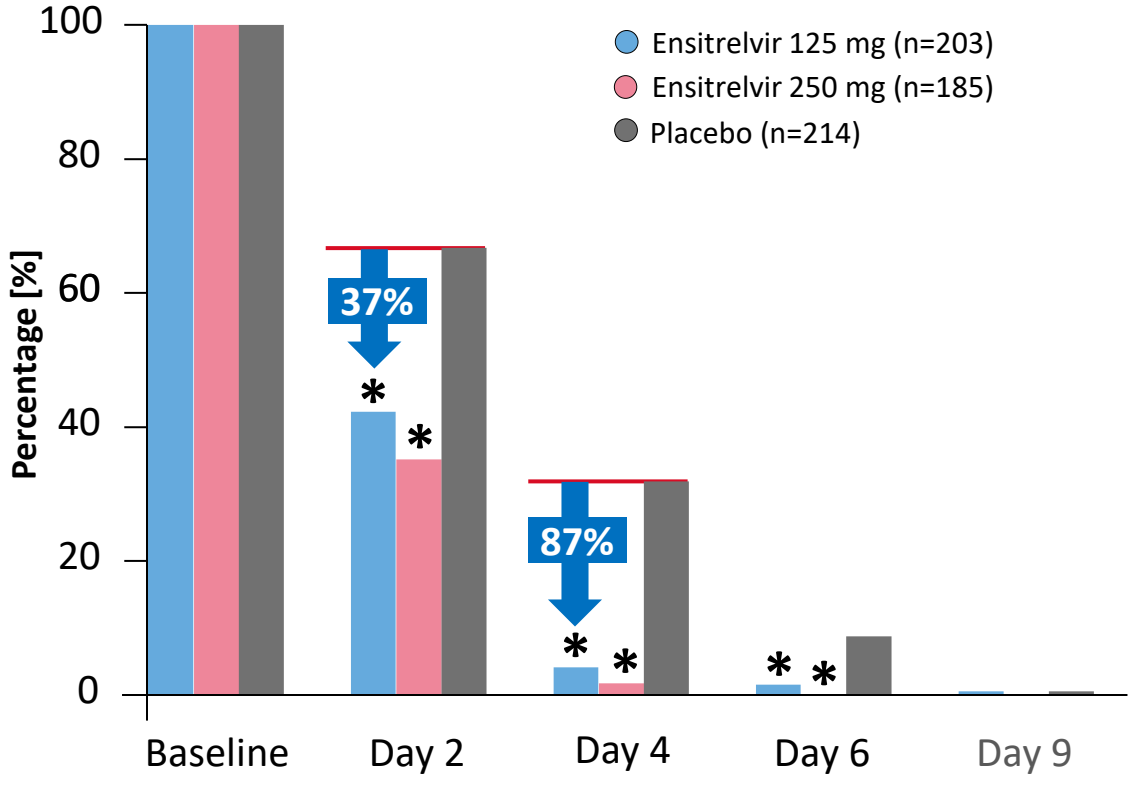
Time to first confirmed negative SARS-CoV-2 viral titer



	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

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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%)

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Long COVID Symptoms, ≤120 hours

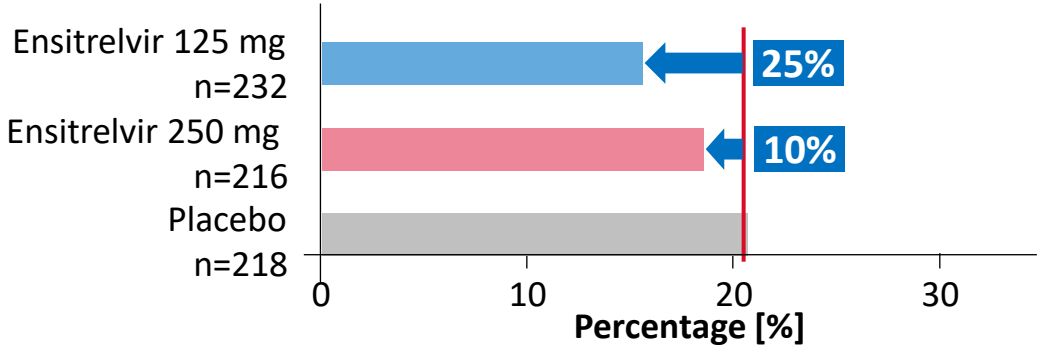
Definition for presence of Long COVID symptoms in post-hoc analysis

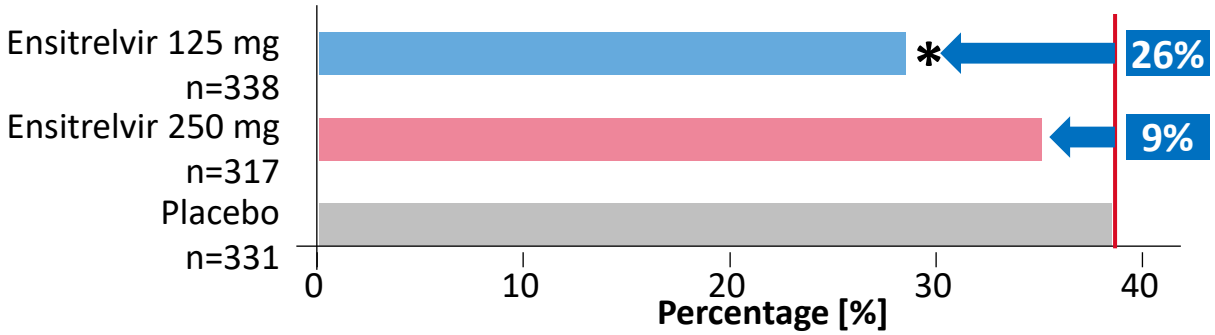
- Symptoms listed in 14 COVID-19 symptom questionnaire
  - ✓At least 2 consecutive time points with a mild or more severe symptom continuing from the last observation in the follow up (e.g., Day 21) to Day 169
- Symptoms listed only in PASC questionnaire
  - ✓One mild or more severe symptom at Day 85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

Proportion with ongoing symptoms (14 COVID-19 symptoms)

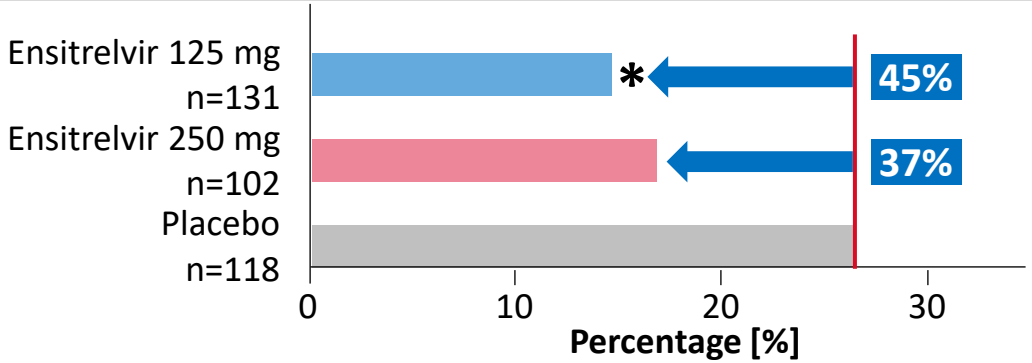
Proportion of 4 neurological symptoms in PASC Questionnaire

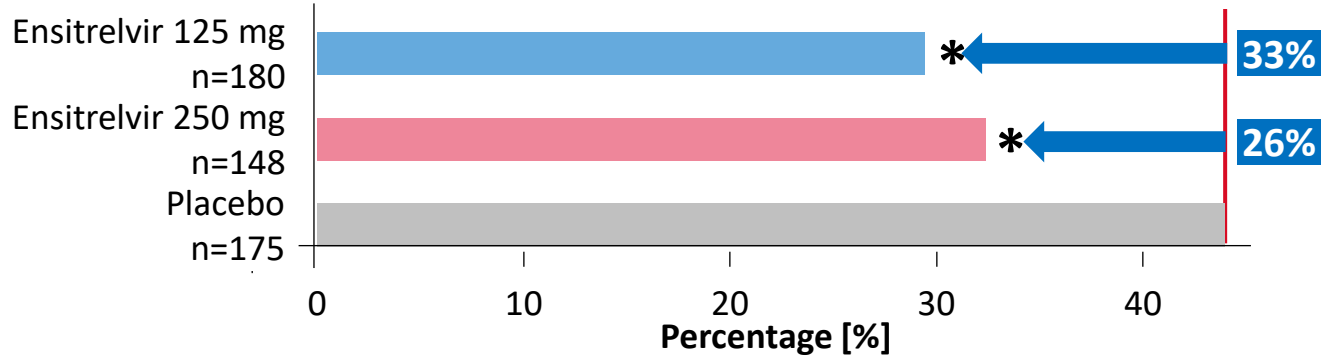
Overall population





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

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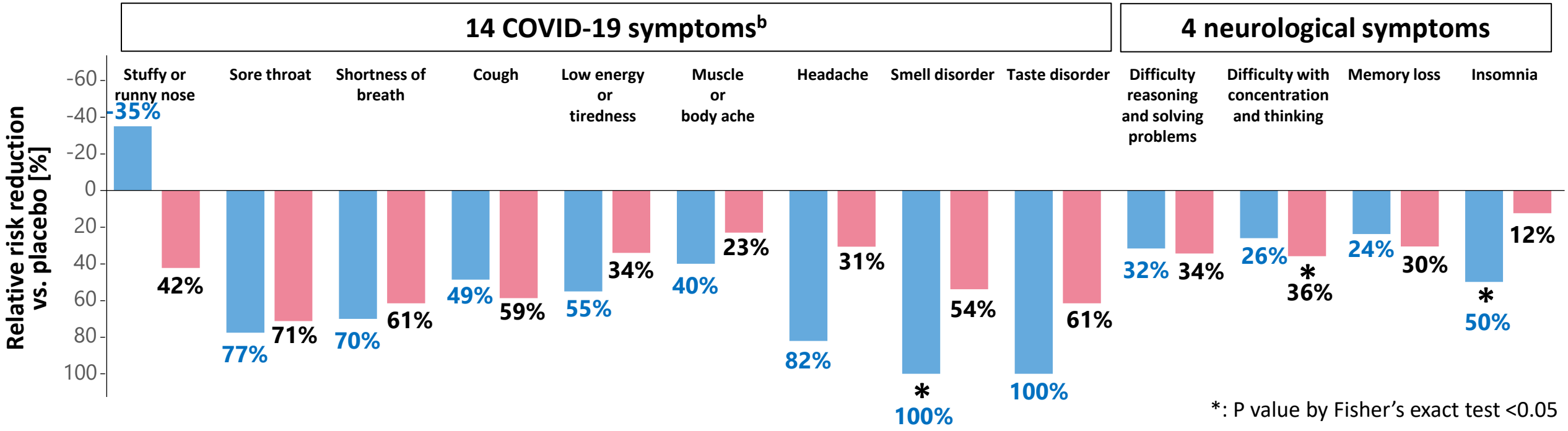
[a]high symptom score is defined as the total score of 14 symptoms at baseline ≥ 9
[b]symptoms presented in 3 or more cases in placebo were shown



*: 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.

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Conclusion

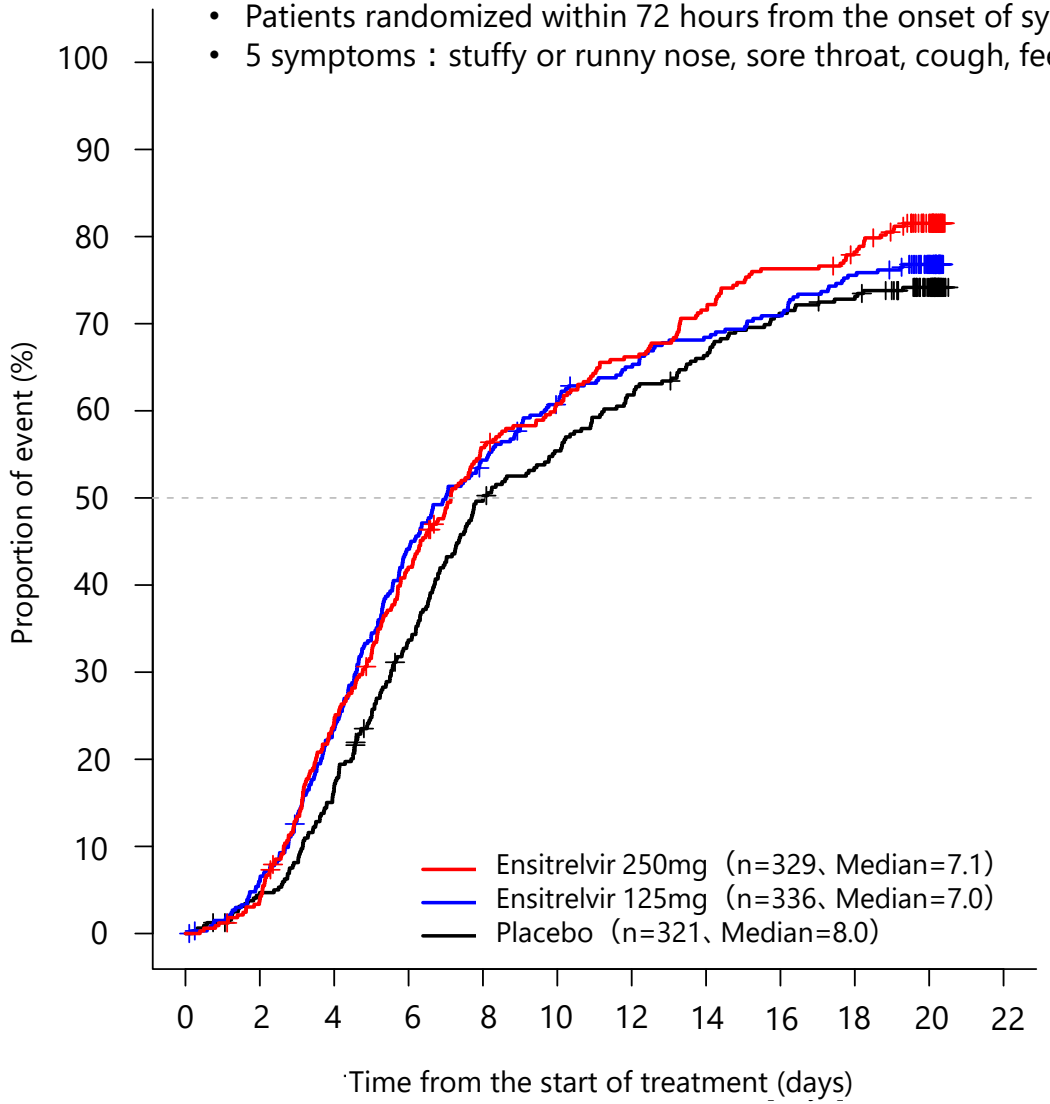
- SCORPIO-SR enrolled mild/moderate COVID-19 patients
  - ✓Approximately 90% were SARS-CoV-2 vaccinated, Omicron infected
  - ✓With and without risk factors for severe disease
- Ensitrelvir demonstrated earlier COVID-19 symptoms resolution
- Ensitrelvir demonstrated potent antiviral activity
  - ✓Significantly 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

Primary Endpoint: The Time to Resolution of All Five Key COVID-19 Symptoms

From the FY2022 R&D Day
(Partially revised)

The time to resolution of all five key COVID-19 symptoms

- Patients randomized within 72 hours from the onset of symptoms
- 5 symptoms：stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness



		Time from onset to randomization : <72 hours		
		125 mg N = 347	**250 mg** N = 340	**プラセボ群** N = 343
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 vs. placebo [a]	P value	**0.0407**	0.0203	---

CI = Confidence Interval
[a] Adjusted by the following stratum (SARS-CoV-2 vaccination history [Yes or No])

Significant reduction in the time to resolution of 5 symptoms of COVID-19 characteristic of Omicron strain compared to placebo (primary endpoint achieved)

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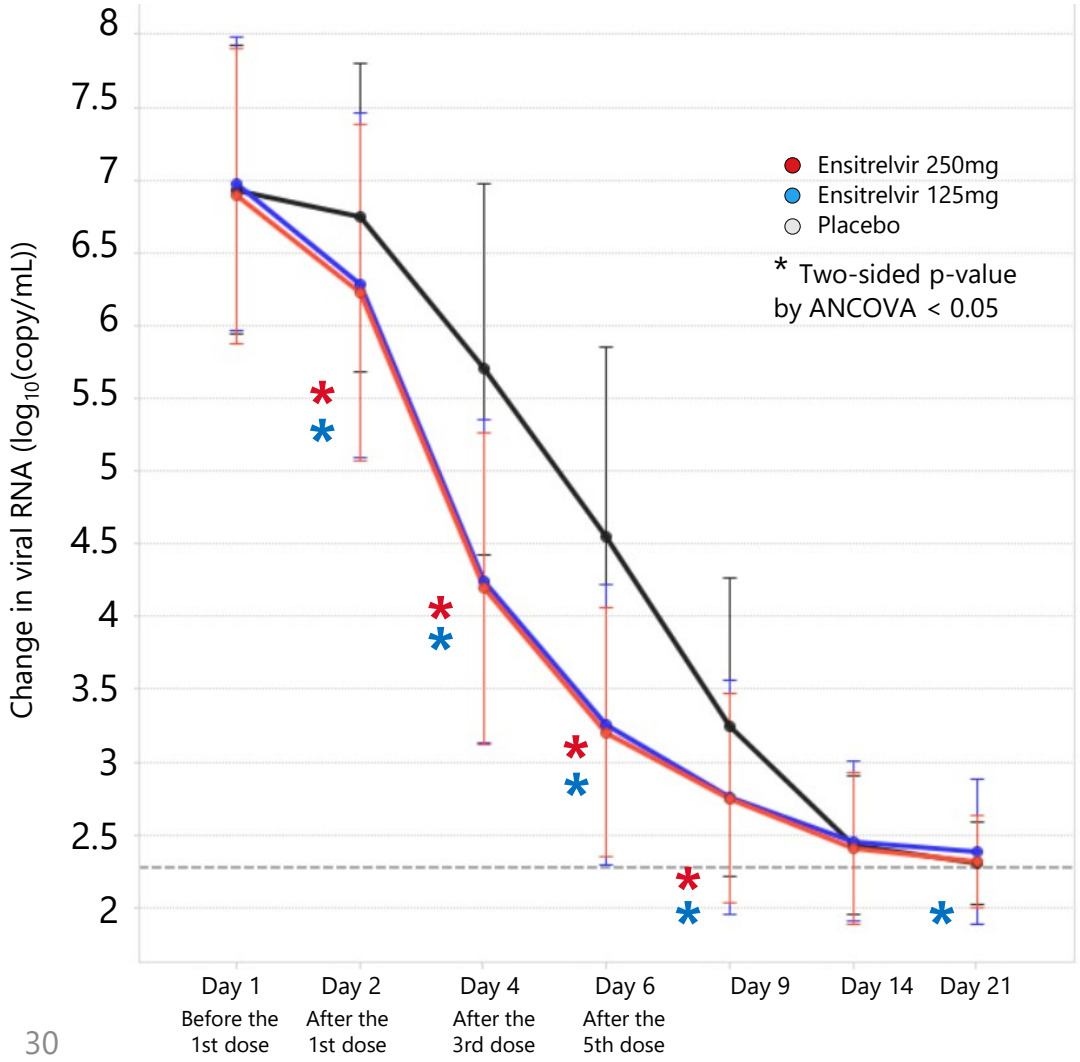
Key Secondary Endpoint①: Change in Viral RNA Amount

From the FY2022 R&D Day (Partially revised)

Mean change in amount of viral RNA



【Population within 72 hours from the onset of symptoms】
Changes in viral RNA levels on day 4 of administration (after 3 doses)

		Time from onset to randomization : <72 hours		
		125 mg N = 347	**250 mg** N = 340	**プラセボ群** N = 343
Mean (SD)		-2.737 (1.085)	-2.690 (0.974)	-1.235 (1.528)
ANCOVA vs. placebo [a]	LS mean (SE)	-2.48 (0.08)	-2.49 (0.08)	-1.01 (0.08)
	Difference in LS mean (SE) [95% CI]	**-1.47 (0.08)** [-1.63, -1.31]	-1.48 (0.08) [-1.64, -1.32]	---
	P value	**<0.0001**	<0.0001	---

UNIT: log_{10} copies/mL
ANCOVA = Analysis of Covariance; SD = Standard Deviation; SE = Standard Error; LS = Least Squares; CI = Confidence Interval
Lower limit of quantification of viral RNA is 2.08 log_{10} copies/mL.
If viral RNA is negative and less than the lower limit of quantification, the viral RNA was imputed 2.27 and 2.08 log_{10} copies/mL, respectively.
[a] Covariate: SARS-CoV-2 viral RNA at baseline, SARS-CoV-2 vaccination history [Yes or No]

Ensitrelvir 125mg group reduced viral RNA level to 1/300 compared to before administration on day 4 of administration (after the 3rd dose) (placebo decreased to 1/10)

Significantly reduced viral RNA levels on day 4 of administration (after 3 doses), confirming superior antiviral effects

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