Early Pre-Symptomatic Treatment with Ensitrelvir Among PCR-Positive, SARS-CoV-2–Exposed and Infected Household Contacts: SCORPIO-PEP Subpopulation Analysis

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Session: COVID 2026: Treatment, Prevention, and the Long Game
Date and time: October 23, 2026 (Friday); 3.15 pm–3.27 pm
Session Location: Walter E. Washington Convention Center

Conflicts of Interest

- All authors are employees of the Shionogi group of companies

Background and Objectives

- Households represent a major setting for SARS-CoV-2 transmission, with secondary attack rates generally within the 32% to 47% range among household contacts (HHCs) in the Omicron era[1-3]
- Post-exposure prophylaxis (PEP) is a strategy to prevent infection after known exposure[4]
- Ensitrelvir is the first and only FDA-approved oral antiviral for PEP of COVID-19 in adults and adolescents ≥12 years in the US[5]
- Approval was based on the results of a double-blind, randomized, placebo-controlled, Phase 3 study (SCORPIO-PEP) that assessed ensitrelvir versus placebo in the prevention of symptomatic COVID-19 in HHCs of individuals with symptomatic infection (clinicaltrials.gov: NCT05897541)[5,6]

Objectives of this presentation based on subpopulation analysis of SCORPIO-PEP

- To characterize the impact of ensitrelvir on viral load and symptoms among participants with breakthrough COVID-19 despite PEP
- To explore the efficacy of early pre-symptomatic ensitrelvir treatment in RT-PCR positive, SARS-CoV-2–exposed HHCs by assessing progression to symptomatic COVID-19

COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; HHC, household contact; PEP, post-exposure prophylaxis; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; US, United States.

1. Madewell ZJ et al. *JAMA Netw Open*. 2022; 5: e229317. 2. Sumsuzzman DM et al. *BMC Infect Dis*. 2025; 25: 215. 3. Baker JM et al. *PLoS One*. 2025; 20: e0313680. 4. EBSCO Information Services. https://www.ebsco.com/blogs/health-notes/prep-and-pep-covid-can-medications-work-prevent-covid-19. Accessed September 23, 2026. 5. FDA Approval of XOCOVA® (ensitrelvir). https://www.shionogi.com/global/en/news/2026/06/20260601.html. Accessed September 23, 2026. 6. Hayden FG et al. *N Engl J Med*. 2026; 394: 1905.

SCORPIO-PEP Study

A double-blind, randomized, placebo-controlled, Phase 3 study[1]



Index patients (IP)
(SARS-CoV-2 infection)

Local test (+)
Symptom (+)

Trial dates: June 2023 to September 2024



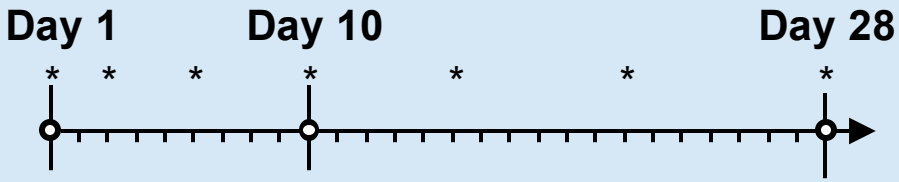
Household contacts (HHCs) ≥ 12 years

Local test (-)
Symptom (-)
Associated eligible IP (+)

Randomization ≤72 hours of index patient's symptom onset

R 1:1

Ensitrelvir (Day 1: 375 mg, Days 2–5: 125 mg)



Placebo

*Nasopharyngeal swab collection on days 1, 3, 6, 10, 15, 21, and 28

HHC, household contact; IP, index patient; R, randomized; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. Hayden FG et al. *N Engl J Med*. 2026; 394: 1905.

Study Population and Assessments in this Presentation

Study population

ITT population

All randomized HHCs with a **negative local** SARS-CoV-2 test at baseline[1,*]

mITT population

ITT with a **negative Central** SARS-CoV-2 RT-PCR test at baseline[1]

ITTBP population

ITT with a **positive Central** SARS-CoV-2 RT-PCR test at baseline[1]

Assessments

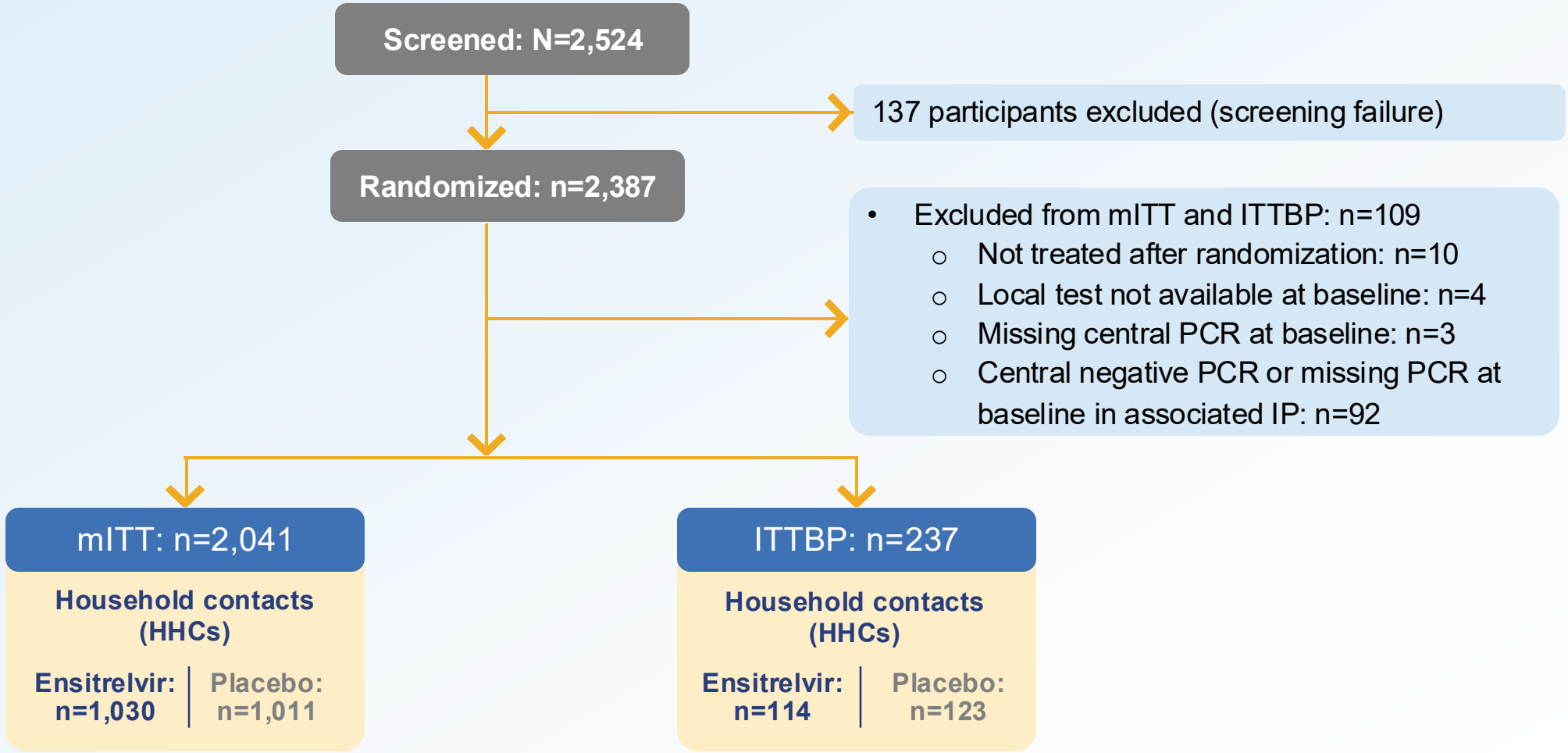
- **Virological outcomes, symptom scores, and symptom severity upon PEP with ensitrelvir versus placebo** in breakthrough infection cases in the following populations of the SCORPIO-PEP study:
  - mITT population
  - ITTBP population
- **Efficacy of PEP with ensitrelvir versus placebo** against symptomatic COVID-19 in the mITT and ITTBP populations of the SCORPIO-PEP study

*Index patients need to have a positive SARS-CoV-2 RT-PCR (central laboratory–confirmed) at baseline.

COVID-19, coronavirus disease 2019; HHC, household contact; ITT, intention-to-treat; ITTBP, intention-to-treat baseline RT-PCR positive; mITT, modified intention-to-treat; PEP, post-exposure prophylaxis; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. Hayden FG et al. *N Engl J Med*. 2026; 394: 1905.

Participant Disposition



The proportions of participants in the mITT and ITTBP groups were similar between the ensitrelvir and placebo arms

HHC, household contact; IP, index patient; ITTBP, intention-to-treat baseline RT-PCR positive; mITT, modified intention-to-treat; PCR, polymerase chain reaction.

Demographics and Baseline Characteristics

	Household contacts (HHCs); mITT population[1]			Household contacts (HHCs); ITTBP population		
	Ensitrelvir (n=1,030)	Placebo (n=1,011)	Total (n=2,041)	Ensitrelvir (n=114)	Placebo (n=123)	Total (n=237)
Age, years, mean (SD)	41.8 (16.9)	43.0 (16.1)	42.4 (16.6)	44.0 (18.0)	42.5 (18.9)	43.2 (18.4)
Age categories, n (%)						
<18 years	64 (6.2)	54 (5.3)	118 (5.8)	7 (6.1)	10 (8.1)	17 (7.2)
18-64 years	867 (84.2)	867 (85.8)	1,734 (85.0)	95 (83.3)	92 (74.8)	187 (78.9)
≥65 years	99 (9.6)	90 (8.9)	189 (9.3)	12 (10.5)	21 (17.1)	33 (13.9)
Female, n (%)	584 (56.7)	627 (62.0)	1,211 (59.3)	65 (57.0)	67 (54.5)	132 (55.7)
BMI, kg/m^2, mean (SD)	26.4 (5.7)	26.5 (5.3)	26.4 (5.5)	26.2 (5.7)	25.6 (5.9)	25.9 (5.8)
Hispanic or Latino, n (%)	620 (60.2)	623 (61.6)	1,243 (60.9)	55 (48.2)	62 (50.4)	117 (49.4)
Geographic Region, n (%)						
North America	692 (67.2)	683 (67.6)	1,375 (67.4)	62 (54.4)	68 (55.3)	130 (54.9)
Japan	266 (25.8)	270 (26.7)	536 (26.3)	40 (35.1)	36 (29.3)	76 (32.1)
Asia (except Japan)	59 (5.7)	49 (4.8)	108 (5.3)	9 (7.9)	15 (12.2)	24 (10.1)
South America and Africa	13 (1.3)	9 (0.9)	22 (1.1)	3 (2.6)	4 (3.3)	7 (3.0)
High-risk factors for severe illness,* n (%)	382 (37.1)	374 (37.0)	756 (37.0)	47 (41.2)	53 (43.1)	100 (42.2)
Viral RNA level at baseline, log_{10} copies/mL, mean (SD)	NA	NA	NA	3.3 (1.5)	3.1 (1.2)	3.2 (1.3)
Index patient antiviral treatment, n (%)	140 (13.6)	134 (13.3)	274 (13.4)	18 (15.8)	17 (13.8)	35 (14.8)

Demographics and baseline characteristics were well balanced between the ensitrelvir and placebo arms in the mITT/ITTBP population

*Some high-risk factors for severe illness are obesity, cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, Down syndrome, sickle-cell disease, immunocompromise conditions or treatment for immunocompromised conditions, dementia, diabetes mellitus, smoking, and history of stroke or cerebrovascular disease.

BMI, body mass index; HHC, household contact; ITTBP, intention-to-treat baseline RT-PCR positive; mITT, modified intention-to-treat; NA, not applicable; RNA, ribonucleic acid; RT-PCR, reverse transcriptase–polymerase chain reaction; SD, standard deviation.

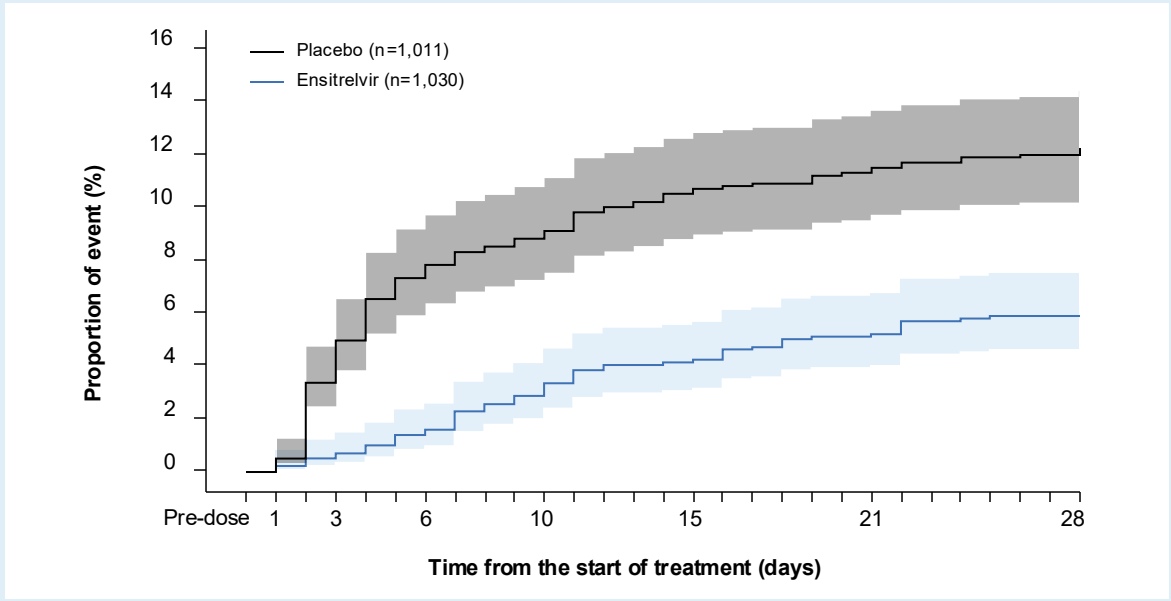
1. Hayden FG et al. *N Engl J Med*. 2026; 394: 1905.



mITT Population

mITT, modified intention-to-treat.

Symptomatic Infection Through Day 10 in the mITT Population



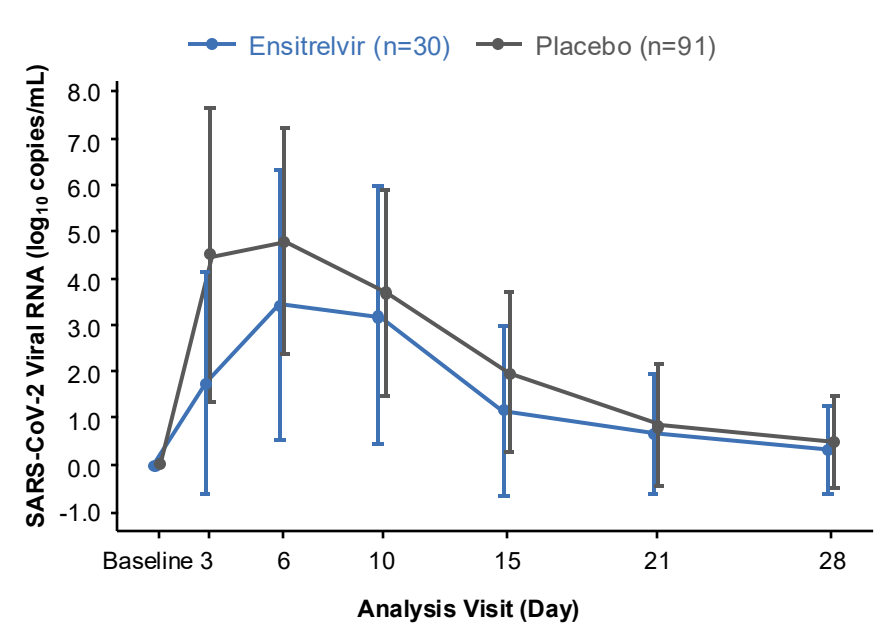
	Ensitrelvir		Placebo		Risk Ratio (95% CI)*
	HHCs with Endpoint No./Total No.	Proportion of events, % (95% CI)	HHCs with Endpoint No./Total No.	Proportion of events, % (95% CI)	
Risk for COVID-19 through Day 10 (primary endpoint)	30/1,030	**2.9** (1.97, 4.13)	91/1,011	**9.0** (7.31, 10.94)	**0.33** (0.22, 0.49; p<0.001)

Ensitrelvir significantly reduced symptomatic infection versus placebo by 67% through Day 10 in the mITT population

*Estimated by GEE Poisson model with exchangeable correlation structure and with following covariates: Geographic region (North America/Japan/RoW), Time from index patients onset to enrollment (<48 hours/≥48 hours).
CI, confidence interval; COVID-19, coronavirus disease 2019; GEE, Generalized Estimating Equations; HHC, household contact;mITT, modified intention-to-treat.

Viral RNA Levels Among *Symptomatic* Breakthrough Infection Cases in the mITT Population

Mean viral load*,†



Maximum viral load‡

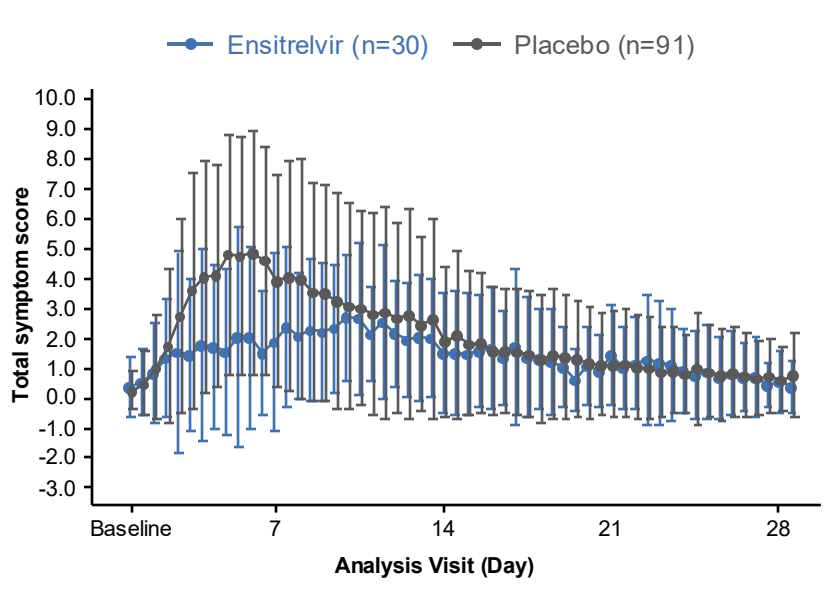
	Ensitrelvir n=1,030	Placebo n=1,011
Breakthrough infection cases	30	91
n	26	86
Mean (95% CI)	**5.004** (4.182, 5.826)	**6.293** (5.885, 6.700)
SD	2.035	1.901
Median (min, max)	**5.445** (1.97, 8.03)	**7.025** (1.97, 8.55)

Among **symptomatic breakthrough infection cases** in the mITT population, the **mean and maximum viral RNA levels were lower in participants receiving ensitrelvir compared to those receiving placebo**

*The error bars in the mean plot shows SD. †Average of log-transformed SARS-CoV-2 viral RNA quantity in body fluids (log_{10} copies/mL). ‡Defined as the largest viral RNA load in the range between the central PCR positive by Day 10 and the last observation time point.
CI, confidence interval; mITT, modified intention-to-treat; PCR, polymerase chain reaction; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

Total Symptom Score and Severity Among *Symptomatic* Breakthrough Infection Cases in the mITT Population

Mean total symptom score*



Maximum total symptom score†

	Ensitrelvir n=1,030	Placebo n=1,011
Breakthrough infection cases	30	91
n	28	89
Mean (SD)	**6.643** (4.731)	**8.888** (4.881)
Median (min, max)	**6.0** (0, 18)	**8.0** (0, 24)

Symptom severity

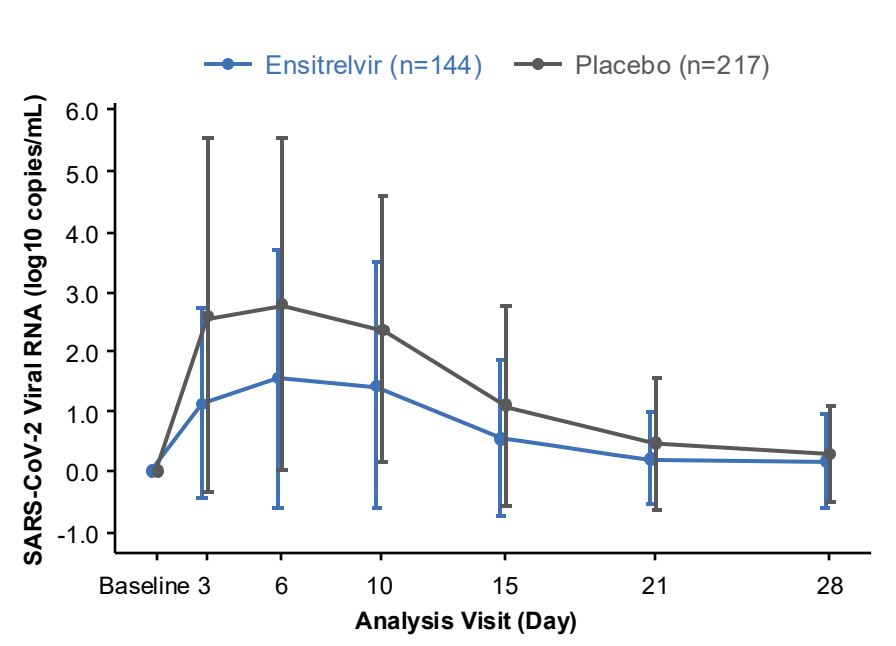
	Ensitrelvir n=1,030	Placebo n=1,011
Breakthrough infection cases	30	91
n	28	89
Participants with severe symptoms	**8/28 (28.6%)** (95% CI: 13.2, 48.7)	**48/89 (53.9%)** (95% CI: 43.0, 64.6)

Among **symptomatic breakthrough infection cases** in the mITT population, the **mean and maximum total symptom scores and symptom severity were numerically lower in participants receiving ensitrelvir compared to those receiving placebo**

*The error bars in the mean plot shows SD. †Defined as the largest total symptom within 18 days from the day of symptom onset for the primary endpoint.
CI, confidence interval; mITT, modified intention-to-treat; SD, standard deviation.

Viral RNA Levels Among Breakthrough Infection Cases *Regardless of Symptoms* in the mITT Population

Mean viral load*,†



Maximum viral load‡

	Ensitrelvir n=1,030	Placebo n=1,011
Breakthrough infection cases	144	217
n	140	212
Mean (95% CI)	**3.072** (2.780, 3.364)	**4.345** (4.015, 4.675)
SD	1.747	2.435
Median (min, max)	**2.125** (0.00, 8.03)	**3.610** (0.00, 8.55)

- A majority of **breakthrough infection cases** in the mITT population were **asymptomatic**
- Among **breakthrough infection cases (based on RT-PCR positivity regardless of symptoms)** in the mITT population, **the mean and maximum viral RNA levels were lower in participants receiving ensitrelvir compared to those receiving placebo**

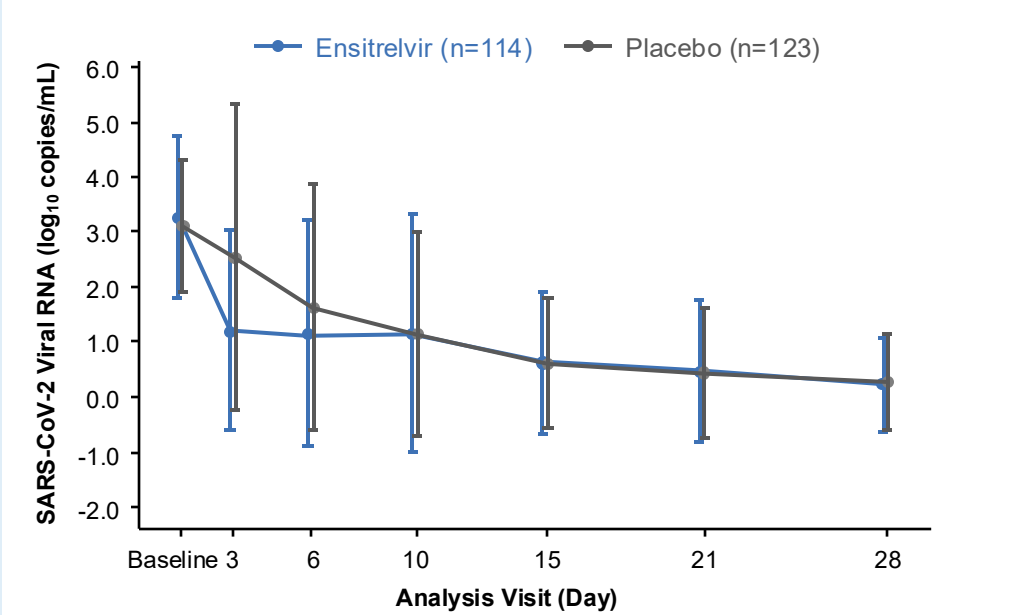
*The error bars in the mean plot shows SD (standard deviation). †Average of log-transformed SARS-CoV-2 viral RNA quantity in body fluids (log_{10} copies/mL). ‡Defined as the largest viral RNA load in the range between the central PCR positive by Day 10 and the last observation time point.
CI, confidence interval; mITT, modified intention-to-treat; PCR, polymerase chain reaction; RNA, ribonucleic acid; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

ITTBP Population

ITTBP, intention-to-treat baseline reverse transcriptase–polymerase chain reaction positive.

Viral RNA Levels in the ITTBP Population *(Central RT-PCR Positive at Baseline)*

Mean viral load*,†

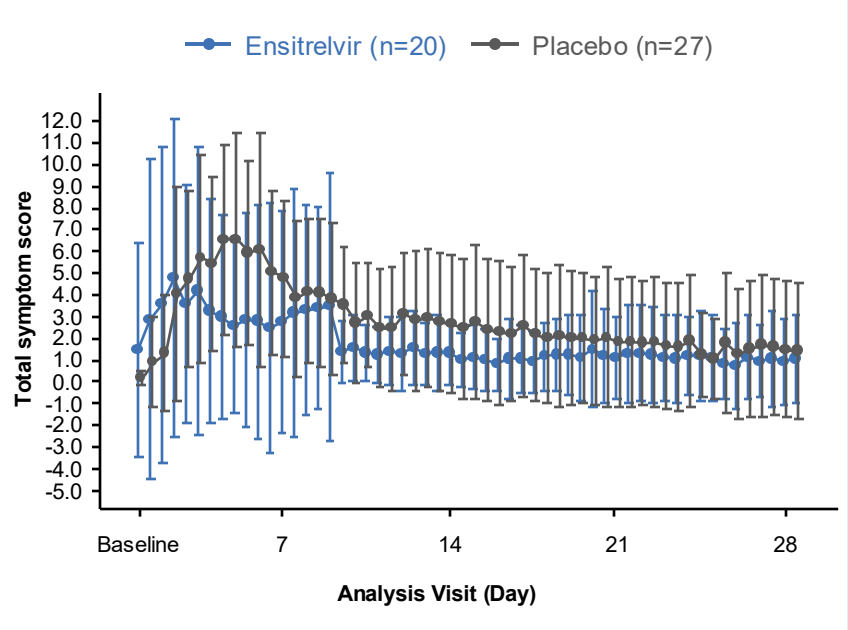


Ensitrelvir was associated with **numerically lower mean viral RNA levels** compared to placebo in the ITTBP population (central RT-PCR positive at baseline) **on Days 3 and 6**

*The error bars in the mean plot shows SD. †Average of log-transformed SARS-CoV-2 viral RNA quantity in body fluids (log_{10} copies/mL).
ITTBP, intention-to-treat baseline RT-PCR positive; RNA, ribonucleic acid; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

Total Symptom Score and Severity in the ITTBP Population that Developed Symptoms

Mean total symptom score*



Maximum total symptom score†

	Ensitrelvir n=114	Placebo n=123
Symptomatic cases	20	27
n	18	24
Mean (SD)	**6.222** (6.709)	**10.292** (4.535)
Median (min, max)	**4.5** (1, 31)	**10.5** (1, 22)

Symptom severity

	Ensitrelvir n=114	Placebo n=123
Symptomatic cases	20	27
n	18	24
Participants with severe symptoms	**2/18 (11.1%)** (95% CI: 1.4, 34.7)	**9/24 (37.5%)** (95% CI: 18.8, 59.4)

In the **ITTBP population that developed symptoms**, the **mean and maximum total symptom scores and symptom severity were numerically lower in participants receiving ensitrelvir compared to those receiving placebo**

*The error bars in the mean plot shows SD. †Defined as the largest total symptom within 18 days from the day of symptom onset for the primary endpoint.
CI, confidence interval; ITTBP, intention-to-treat baseline RT-PCR positive; RT-PCR, reverse transcriptase–polymerase chain reaction; SD, standard deviation.

Safety: Overall TEAEs

Number of participants with – n (%) (95% CI)*	Ensitrelvir n=1,190	Placebo n=1,187
Any TEAEs	180 (15.1) (13.1, 17.3)	184 (15.5) (13.5, 17.7)
Any serious TEAEs	2 (0.2) (0.0, 0.6)	2 (0.2) (0.0, 0.6)
Any study drug-related TEAEs	19 (1.6) (1.0, 2.5)	21 (1.8) (1.1, 2.7)
Any study drug-related serious TEAEs	0 (0.0, 0.3)	0 (0.0, 0.3)
Any TEAEs leading to treatment discontinuation	1 (<0.1) (0.0, 0.5)	1 (<0.1) (0.0, 0.5)
Any TEAEs leading to study discontinuation	0 (0.0, 0.3)	1 (<0.1) (0.0, 0.5)
Any adverse events leading to death	0 (0.0, 0.3)	0 (0.0, 0.3)

Adverse events were balanced across arms, with no new concerns identified

*n represents the number of participants with treatment-emergent adverse event; Percentages are based on the number of participants in the Safety Analysis Set within each treatment arm; Two-sided 95% CI is based on the Clopper-Pearson method.
CI, confidence interval; TEAE, Treatment-emergent adverse event.

Conclusions

In SCORPIO-PEP, ensitrelvir significantly reduced symptomatic infection versus placebo by 67% through Day 10 in household contacts

Importantly, among participants with breakthrough infections in mITT, ensitrelvir was associated with lower viral RNA levels, lower symptom burden, and fewer severe symptoms compared to placebo

A similar trend was observed among participants who were SARS-CoV-2 RT-PCR positive at baseline (ITTBP), with numerically lower viral RNA levels and symptom severity in the ensitrelvir arm

Early ensitrelvir administration may provide benefit in both breakthrough infection cases and in those participants who were already infected, **reducing progression to COVID-19 symptom severity and viral replication**

COVID-19, coronavirus disease 2019; RNA, ribonucleic acid; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Funding and Acknowledgements

- We thank the investigators and the participants involved in this study
- This study was funded by Shionogi Inc.
- Medical writing support was provided by Advait A. Joshi, PhD, of Cactus Life Sciences (part of Cactus Communications) and was funded by Shionogi Inc.

Thank you!



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