Efficacy and safety of ensitrelvir in non-hospitalized adults at standard or high risk of progression to severe COVID-19: the SCORPIO-HR phase 3, randomized, double-blind, placebo-controlled trial

SCORPIO-HR ACTIV-2d
Stopping COvid pRogression with early Protease InhibitOr treatment

ACTG Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections

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BACKGROUND

- Ensitrelvir has demonstrated antiviral activity against all SARS-CoV-2 variants of concern to date.[1-5]
- In the SCORPIO-SR trial, compared with placebo, ensitrelvir reduced time to resolution of 5 typical COVID-19 symptoms (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness),[6] decreased the viral load,[6-8] and was generally well tolerated.[6]
- As of March 2024, ensitrelvir obtained standard approval in Japan and has been under Fast Track review by the US Food and Drug Administration.[9,10] Since its emergency approval, more than 1 million people have been treated with ensitrelvir in Japan.[11]

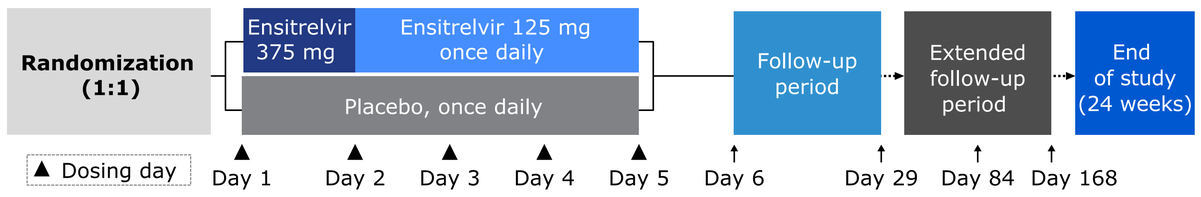
OBJECTIVE

- To evaluate the efficacy and safety of ensitrelvir vs placebo in non-hospitalized symptomatic adults with COVID-19 with or without risk factors for progression to severe disease.

METHODS

SCORPIO-HR: Study Design

A multicenter, randomized, double-blind, placebo-controlled study in 16 countries globally



Key eligibility criteria

- Age ≥18 years
- Laboratory-confirmed active SARS-CoV-2 infection
- Symptom onset ≤3 days (initially ≤5 days) before treatment initiation

Primary

- Time to sustained (≥2 days) resolution of 15 COVID-19 symptoms* through Day 29

Key secondary endpoints

- Change in quantitative nasopharyngeal SARS-CoV-2 RNA levels from Day 1 to 4
- Adjudicated COVID-19–related hospitalization or all-cause death through Day 29
- Persistent and/or late-onset symptoms of COVID-19[†]

Secondary endpoints

- Viral culture negativity at Day 4
- Viral rebound and symptomatic viral rebound
- Safety outcomes

Statistical analyses

- Primary and key secondary endpoints were tested using a fixed-sequence hierarchical approach at a two-sided significance level of 0.05. When the hierarchy was broken, the remaining tests were not considered statistically significant, were not adjusted for multiplicity, and were considered descriptive and interpreted in an exploratory manner.

*Fifteen COVID-19 symptoms: stuffy nose, runny nose, sore throat, cough, low energy or tiredness, feeling hot or feverish, shortness of breath or difficulty breathing, chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, loss of taste, and loss of smell. [†]This key secondary endpoint is not presented here.

RESULTS

- Of 2093 participants, 1888 (90%) started treatment ≤3 days after symptom onset (mITT population; **Table 1**).

Table 1. Baseline Characteristics – mITT Population

Characteristics	Ensitrelvir (N=945)	Placebo (N=943)
Age — yr, median (interquartile range)	40 (30–51)	39 (30–51)
Female sex at birth* — n (%)	540 (57)	506 (54)
BMI — kg/m^2, median (interquartile range)	26 (23–28)	26 (23–29)
Hispanic or Latino — n (%)	430 (46)	421 (45)
Race — n (%)		
American Indian or Alaska Native	9 (1)	5 (1)
Asian	387 (41)	396 (42)
Black or African American	77 (8)	92 (10)
White	403 (43)	383 (41)
Multiple races reported	5 (1)	3 (<1)
Other	40 (4)	45 (5)
Completed primary COVID-19 vaccination series — n (%)	696 (74)	732 (78)
Risk status[†] — n (%)		
High risk	301 (32)	314 (33)
Standard risk	644 (68)	629 (67)
Most common risk factors — n (%)		
BMI ≥30 kg/m^2	139 (15)	148 (16)
Hypertension	130 (14)	120 (13)
Diabetes mellitus	78 (8)	63 (7)
Age ≥65 yr	56 (6)	57 (6)
Participants with 1 risk factor only — n (%)	182 (19)	206 (22)
Participants with ≥2 risk factors — n (%)	119 (13)	108 (11)

*Gender identity not recorded; [†]High-risk participants were defined as those with at least one characteristic or comorbid condition associated with a high risk of progression to severe COVID-19. Standard-risk participants were defined as those aged between 18 and 64 years, with none of the risk factors.

SYMPTOM RESOLUTION

- Restricted mean time to symptom resolution was numerically shorter with ensitrelvir than with placebo but not statistically significant (**Table 2**).
- Prespecified and post hoc supportive analyses similarly demonstrated numerically shorter time to symptom resolution with ensitrelvir than with placebo (**Table 2**).

Table 2. Time to Resolution of COVID-19 Symptoms Through Day 29

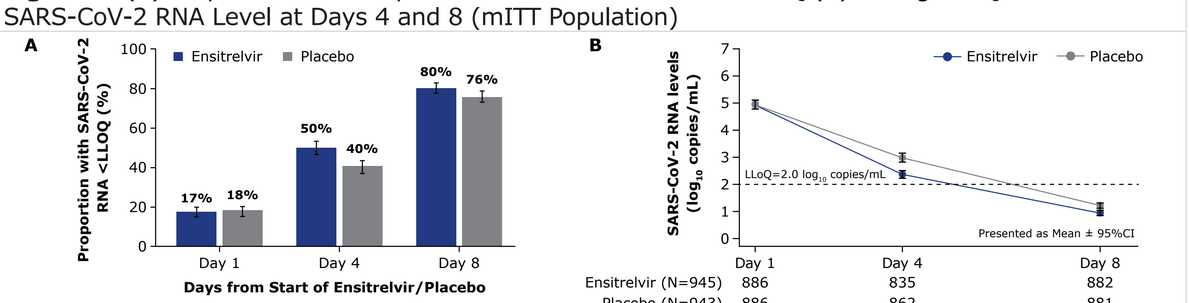
Endpoint	Number of COVID-19 symptoms evaluated	Analysis population	Symptom resolution definition	Restricted mean days to symptom resolution: Ensitrelvir	Placebo	Difference (95% CI)	P value	Peto-Prentice's generalized Wilcoxon test (P value)
Primary endpoint	15	mITT (N=1888)	≥2 consecutive days	12.5	13.1	-0.6 (-1.38, 0.19)	0.14	0.07
Prespecified supportive analyses*	15	mITT2[†] (N=1535)	≥2 consecutive days	12.3	13.0	-0.7 (-1.56, 0.16)	0.11	-
	15	mITT (N=1888)	≥1 day	11.4	12.2	-0.8 (-1.54, 0.01)	0.05	-
	6[‡]	mITT (N=1888)	≥1 day	10.3	11.0	-0.7 (-1.48, 0.02)	0.06	0.02
Post hoc supportive analyses*	15	mITT2[†] (N=1535)	≥2 consecutive days	-	-	-	-	0.08
	15	mITT (N=1888)	≥1 day	-	-	-	-	0.02

*Supportive analyses were not part of the statistical hierarchy, were not adjusted for multiplicity, and should be interpreted in an exploratory manner. [†]mITT2 population included the mITT population with positive PCR test results (>LoD) on Day 1. [‡]The six targeted COVID-19 symptoms, the same as those in the primary endpoint of the SCORPIO-SR study,[6] were stuffy nose, runny nose, sore throat, cough, low energy or tiredness, and feeling hot or feverish.

VIRAL EFFICACY

- At Day 4, in the mITT population, SARS-CoV-2 RNA was <LLoQ in more ensitrelvir-treated vs placebo-treated participants (**Figure 1A**), with a 0.72 $\log_{10}$ copies/mL greater reduction in least-squares mean RNA with ensitrelvir vs placebo (**Figure 1B**).

Figure 1. (A) Proportion of Participants With SARS-CoV-2 RNA<LLoQ (B) Change in Quantitative SARS-CoV-2 RNA Level at Days 4 and 8 (mITT Population)



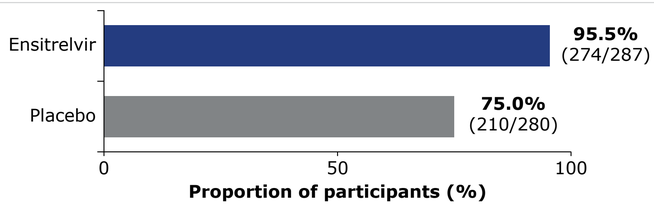
	Day 1	Day 4	Day 8
Ensitrelvir (x/n)	151/886	415/835	707/882
Placebo (x/n)	156/886	345/862	666/881
LSM change (95% CI) from Day 1 vs placebo		-0.72 (-0.90, -0.55)	-0.30 (-0.43, -0.17)

ANCOVA was used to obtain the estimate of difference in mean change in SARS-CoV-2 RNA (95% CI) adjusted for Day 1. Participants who were alive and not hospitalized on Day 4 or Day 8 but who had missing RNA values at Day 4 or Day 8, respectively, were excluded.
Day 1, Day 4 and Day 8 values detected and <LLoQ were imputed as 1.7 $\log_{10}$ SARS-CoV-2 RNA; <LoD as 0.0; and >ULoQ as 8.3 $\log_{10}$ SARS-CoV-2 RNA.
As the primary efficacy endpoint was not statistically significant, secondary endpoint results are descriptive.

- Among participants with positive viral cultures at enrollment, a greater number were culture-negative on Day 4 with ensitrelvir than with placebo (**Figure 2**).
- Viral rebound* occurred in 0.6% of ensitrelvir-treated and 1.4% of placebo-treated participants by Day 29; no symptomatic viral rebound was observed.

*Viral rebound after treatment completion through Day 29 was defined as an increase in quantitative viral RNA by at least 1.0 $\log_{10}$ from the previous quantifiable value or increase to at least 1.0 $\log_{10}$ above LoD or LLoQ if the previous value was <LoD or <LLoQ. Symptomatic viral rebound was defined as viral rebound in the setting of new or worsening clinical symptoms. The analysis was performed in the mITT population.

Figure 2. Viral Culture Negativity on Day 4*



*The analysis was performed on the viral culture set (all participants in the mITT population with detectable viral cultures [>LLoQ] on Day 1). Missing data were excluded from the analysis, assuming that they were missing completely at random.

SAFETY

- Treatment with ensitrelvir was well tolerated, with a similar adverse event profile as placebo (**Table 3**).
- COVID-19–related hospitalization was observed in three (0.3%) ensitrelvir-treated and one (0.1%) placebo-treated participants; there were no deaths (safety analysis population).

Table 3. Safety Outcomes (Safety Analysis Population)

	Ensitrelvir (N=1037)	Placebo (N=1048)	Total (N=2085)
Events that emerged during the treatment period — n (%)			
Any adverse event	638 (61.5)	635 (60.6)	1273 (61.1)
Serious adverse event	5 (0.5)	6 (0.6)	11 (0.5)
Events related to ensitrelvir or placebo — n (%)			
Any adverse event	86 (8.3)	74 (7.1)	160 (7.7)
Serious adverse event	0	0	0

The safety analysis population included participants who received ≥1 dose of ensitrelvir/placebo and analyzed by study intervention received. The severity of adverse events was graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).[12]

CONCLUSIONS

- The primary endpoint of time to 2-day sustained resolution of 15 COVID-19 symptoms was not met.
- Ensitrelvir did demonstrate a numeric reduction in time to symptom resolution compared with placebo in the primary analysis and several prespecified supportive analyses.
- Ensitrelvir demonstrated potent antiviral efficacy and a low incidence of viral rebound, with no symptomatic viral rebound in either arm.
- Ensitrelvir was well tolerated, with no new safety concerns.
- These findings highlight the difficulty of relating antiviral activity to symptom-based endpoints of treatment response when evaluating novel COVID-19 therapeutics.

References

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Abbreviations

ANCOVA, analysis of covariance; **BMI**, body mass index; **CI**, confidence interval; **COVID-19**, coronavirus disease 2019; **FDA**, Food and Drug Administration; **LLoQ**, lower limit of quantification; **LoD,** limit of detection; **LSM**, least-squares mean; **mITT**, modified intention-to-treat; **mITT2**, modified intention-to-treat 2; **PCR**, polymerase chain reaction; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus-2; **ULoQ**, upper limit of quantification; **US**, United States.

Presented at AIDS 2024, the 25th International AIDS Conference

Acknowledgements

We thank all participants involved in this study. Medical writing support was provided by Neha Shrestha, PhD, of Cactus Life Sciences (part of Cactus Communications) and funded by Shionogi.

Funding

This study was largely funded by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Numbers UM1AI068636, UM1AI068634, and UM1AI106701. The content is the sole responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The study was partly funded and sponsored by Shionogi & Co., Ltd., who provided the study agent.

Disclosures

KC has served as a consultant for Pardes Biosciences. The potential effects of relevant financial relationships with ineligible companies have been mitigated. Any clinical recommendations are based on evidence and free of commercial bias.

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AIDS 2024 22–26 July