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Reduction of Infectious SARS-CoV-2 and Viral Titer with Ensitrelvir: A Pooled Analysis of SCORPIO-SR and SCORPIO-HR Trials

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INTRODUCTION

- Ensitrelvir is an oral 3CL^{pro} inhibitor of SARS-CoV-2[1]
- Previous studies have demonstrated the clinical and virologic efficacy of ensitrelvir, with reduction in both RNA copy number and infectious virus titer in those infected with SARS-CoV-2[2–4]
- Ensitrelvir is approved in Japan for both the treatment and PEP of COVID-19,[5,6] and in the United States and Europe for COVID-19 PEP[7,8]

OBJECTIVE

To evaluate the effect of ensitrelvir on infectious virus in participants with confirmed COVID-19 infection using pooled virology data from two Phase 3 treatment studies (SCORPIO-SR[3] and SCORPIO-HR[4])

METHODS

- This post hoc exploratory analysis was conducted using pooled data from the SCORPIO-SR and SCORPIO-HR studies[3,4]
- In both studies, the presence of infectious virus, as measured by viral culture ($TCID_{50}$), was assessed centrally using nasopharyngeal swab samples
- No formal statistical testing was performed

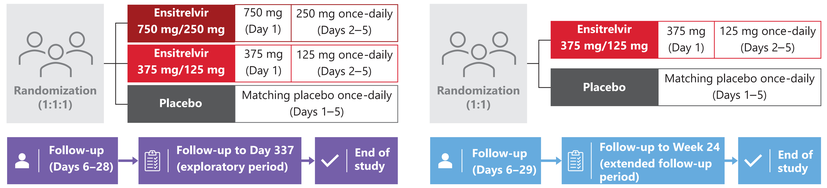
SCORPIO-SR[3] (jRCT2031210350)

Phase 3 (of the Phase 2/3 trial), multicenter, randomized, double-blind, placebo-controlled study conducted in Japan, Vietnam, and South Korea

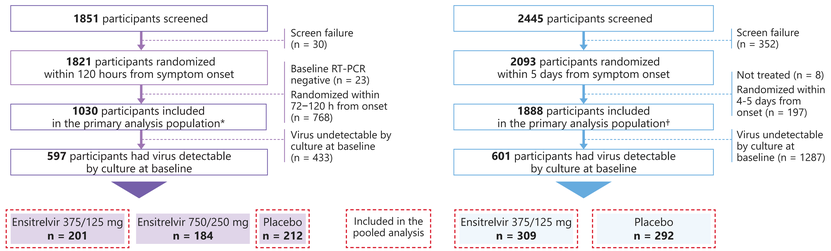
SCORPIO-HR[4] (NCT05305547)

Phase 3, multicenter, randomized, double-blind, placebo-controlled study conducted in 16 countries globally

Study design



Participant disposition



*The primary analysis population of the SCORPIO-SR (Phase 3 part) study was the intention-to-treat (ITT) population, which was defined as all randomized participants who were RT-PCR positive at baseline and randomized less than 72 hours from symptom onset.[3] †The primary analysis population of the SCORPIO-HR study was the modified ITT (mITT) population, which was defined as all randomized participants who received at least one dose of the study drug and started the intervention within 3 days from symptom onset.[4]

RESULTS

Overall, 1014 participants with detectable infectious virus at baseline (ensitrelvir, n = 510; placebo, n = 504) were pooled from the SCORPIO-SR and SCORPIO-HR studies. Baseline demographic characteristics were comparable across study groups (**Table 1**)

Table 1 Baseline demographic characteristics of the pooled SCORPIO-SR and SCORPIO-HR studies

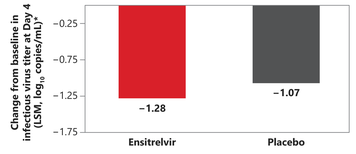
	Ensitrelvir (n = 510)	Placebo (n = 504)	Total (n = 1014)
Mean age, years (SD)	39.0 (14.1)	39.3 (14.6)	39.2 (14.4)
Age categories, years			
<18	1 (0.2)	9 (1.8)	10 (1.0)
18–64	486 (95.3)	469 (93.1)	955 (94.2)
≥65	23 (4.5)	26 (5.2)	49 (4.8)
Female	274 (53.7)	273 (54.2)	547 (53.9)
BMI (kg/m^2), mean (SD)	25.2 (4.9)	25.0 (4.6)	25.1 (4.8)
Geographic region			
North America	114 (22.4)	101 (20.0)	215 (21.2)
South America	64 (12.5)	69 (13.7)	133 (13.1)
Africa	33 (6.5)	25 (5.0)	58 (5.7)
Asia	280 (54.9)	289 (57.3)	569 (56.1)
Europe	19 (3.7)	20 (4.0)	39 (3.8)
High-risk factors for severe illness*	127 (24.9)	125 (24.8)	252 (24.9)

Data are presented as n (%) unless otherwise stated.
*Participants with at least one risk factor associated with severe COVID-19. Risk factors present in ≥5% of participants in at least one treatment group were smoking, dyslipidemia, obesity (BMI ≥30 kg/m^2), and hypertension in the SCORPIO-SR study;[3] and age ≥65 years, obesity (BMI ≥30 kg/m^2), hypertension, and diabetes mellitus in the SCORPIO-HR study.[4]

On Day 4, ensitrelvir showed greater reductions in infectious virus titer (**Figure 1A**) and a lower proportion of ensitrelvir-treated participants had positive viral culture at baseline (**Figure 1B**) compared with placebo

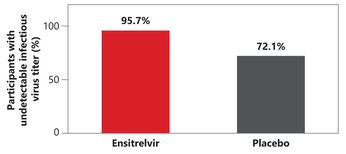
Figure 1 (A) Infectious virus titer and (B) proportion of participants with undetectable virus titer on Day 4 among participants with positive viral culture at baseline: Pooled subgroup analysis of the SCORPIO-SR and SCORPIO-HR studies

A. Change from baseline in infectious virus titer at Day 4



	Ensitrelvir	Placebo
n	484	487
Mean (SD)	−1.335 (1.078)	−1.059 (1.104)
Difference in LSM vs placebo* (95% CI)	−0.21 (−0.27, −0.16)	

B. Participants with undetectable infectious virus titer at Day 4



	Ensitrelvir	Placebo
n/N	463/484	351/487
Risk difference (%) (95% CI)†	23.5 (19.1, 27.9)	

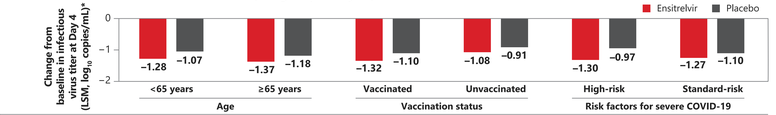
*Mean represents the arithmetic mean. LSM, the difference in LSM, and the corresponding 95% CI were calculated using ANCOVA with covariates of baseline infectious virus titer and study (SCORPIO-SR/SCORPIO-HR). †Calculated by Mantel-Haenszel method adjusted by stratum of the study (SCORPIO-SR/SCORPIO-HR).
Values were imputed as follows: SCORPIO-SR: Viral culture values <LLOQ (1.0 log_{10} $TCID_{50}$/mL) and detected sample values were imputed as 1.0, whereas values <LLOD (0.75 log_{10} $TCID_{50}$/mL) were imputed as 0.75;[3] Viral culture values <LLOQ (1.0 log_{10} $TCID_{50}$/mL) and detected sample values were imputed as 0.75, whereas values <LLOD (0.75 log_{10} $TCID_{50}$/mL) were imputed as 0.5.[4]

CONCLUSION

Regardless of vaccination status, age, and risk for severe disease, ensitrelvir was consistently associated with a greater reduction in quantitative viral culture and higher proportion of participants with infectious viral clearance compared with placebo, confirming its potent antiviral activity.

Ensitrelvir showed larger reductions in infectious virus titer compared with placebo, regardless of age, vaccination status, and risk factors for severe COVID-19 (**Figure 2**)

Figure 2 Infectious virus titer on Day 4 among participants with positive viral culture at baseline, based on pooled data from the SCORPIO-SR and SCORPIO-HR studies (subgroup analysis)

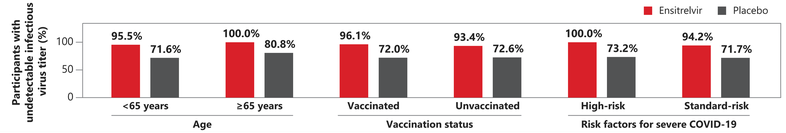


	Age				Vaccination status				Risk factors for severe COVID-19			
	<65 years		≥65 years		Vaccinated		Unvaccinated		High-risk		Standard-risk	
	Ensitrelvir	Placebo	Ensitrelvir	Placebo	Ensitrelvir	Placebo	Ensitrelvir	Placebo	Ensitrelvir	Placebo	Ensitrelvir	Placebo
n	462	461	22	26	406	425	76	62	120	123	364	364
Mean (SD)	−1.332 (1.072)	−1.047 (1.110)	−1.409 (1.224)	−1.279 (0.965)	−1.367 (1.101)	−1.076 (1.093)	−1.191 (0.942)	−0.944 (1.174)	−1.485 (1.068)	−0.961 (1.116)	−1.286 (1.078)	−1.092 (1.099)
Difference in LSM vs placebo* (95% CI)	−0.21 (−0.27, −0.16)		−0.19 (−0.43, 0.05)		−0.22 (−0.28, −0.16)		−0.17 (−0.33, −0.01)		−0.33 (−0.46, −0.21)		−0.17 (−0.24, −0.11)	

*Arithmetic mean is presented. LSM, the difference in LSM, and the corresponding 95% CI were calculated using ANCOVA with covariates of baseline infectious virus titer and study (SCORPIO-SR/SCORPIO-HR). The values for samples with concentrations below the LLOQ and for undetected samples were imputed according to the imputation rules defined and applied in each study.

Compared with placebo, a lower proportion of ensitrelvir-treated participants had positive viral culture on Day 4, regardless of age, vaccination status, and risk factors for severe COVID-19 (**Figure 3**)

Figure 3 Proportion of participants with undetectable virus titer on Day 4 among participants with positive viral culture at baseline, based on pooled data from the SCORPIO-SR and SCORPIO-HR studies (subgroup analysis)



	Age				Vaccination status				Risk factors for severe COVID-19			
	<65 years		≥65 years		Vaccinated		Unvaccinated		High-risk		Standard-risk	
	Ensitrelvir	Placebo	Ensitrelvir	Placebo	Ensitrelvir	Placebo	Ensitrelvir	Placebo	Ensitrelvir	Placebo	Ensitrelvir	Placebo
n/N	441/462	330/461	22/22	21/26	390/406	306/425	71/76	45/62	120/120	90/123	343/364	261/364
Risk difference (%) (95% CI)*	23.8 (19.3, 28.3)		19.2 (4.0, 34.3)		24.1 (19.4, 28.7)		18.1 (5.6, 30.5)		27.4 (19.6, 35.3)		22.5 (17.2, 27.7)	

*Calculated by Mantel-Haenszel method adjusted by stratum of study (SCORPIO-SR/SCORPIO-HR). The values for samples with concentrations below the LLOQ and for undetected samples were imputed according to the imputation rules defined and applied in each study.

STRENGTHS

- Diverse population in terms of racial/ethnic backgrounds and geographic regions included during the Omicron era

LIMITATIONS

- All analyses were post hoc and exploratory
- Unable to assess efficacy of those with elevated risk of disease progression
- Objective measure of treatment adherence was not evaluated
- Impact of adherence on treatment outcomes was not evaluated

References

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Abbreviations

3CL^{pro}, 3C-like protease; ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; EMA, European Medicines Agency; ITT, intention-to-treat; LLOD, lower limit of detection; LLOQ, lower limit of quantification; LSM, least squares mean; mITT, modified ITT; NIAID, National Institute of Allergy and Infectious Diseases; NIH, National Institute of Health; PEP, post-exposure prophylaxis; RNA, ribonucleic acid; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; $TCID_{50}$, 50% tissue culture infectious dose.

Disclosures

ACH, HN, HS, QND, DV, SP, and FD are employees of the Shionogi group of companies. AFL received research grant support from the NIH and unrelated research grant support from Gilead, GSK/ViiV, and Merck.