Ensitrelvir Treatment of COVID-19 Across Multiple Global Phase 3 Trials Resulted in Reduced Culture Positivity and RNA Copy Number With Minimal Viral Rebound

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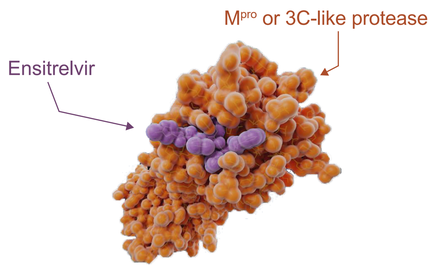
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Background

Ensitrelvir



- Ensitrelvir is an oral M^{pro} (3C-like) protease inhibitor that is administered once daily for 5 days[1-4]
- The median EC_{50} of ensitrelvir against SARS-CoV-2 Omicron sub-variants was 350 nM[5]
- Two Phase 3 studies were conducted to evaluate the efficacy and safety of ensitrelvir as a COVID-19 treatment and one Phase 3 study to evaluate its efficacy and safety as post-exposure prophylaxis (PEP; **Figure 1**)[2-4]
- Ensitrelvir is approved for the treatment and PEP of COVID-19 in Japan and is currently under review by the FDA and EMA[6,7]

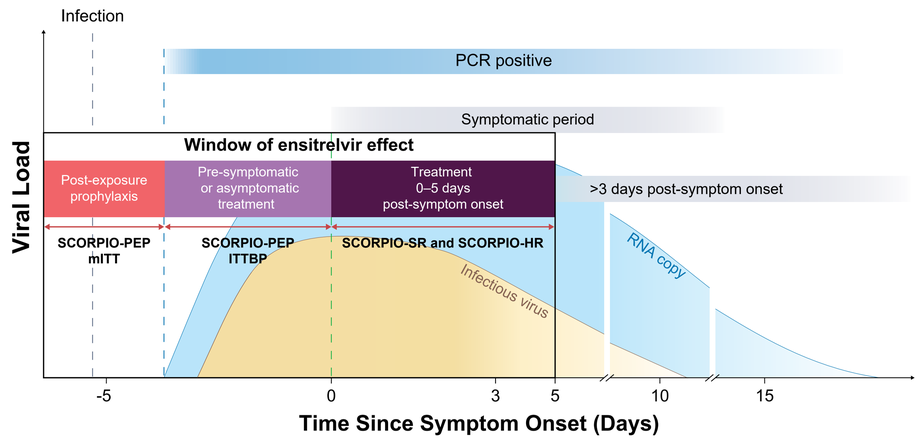
Objective

- To report outcomes of the pre-defined and post hoc analyses of infectious virus titre, RNA copy number, and viral rebound from the three Phase 3 studies

Figure 1. Phase 3 SCORPIO Studies Across the Early COVID-19 Disease Continuum[2-4]

The efficacy and safety of ensitrelvir have been evaluated across the disease continuum in:

- SCORPIO-PEP
  - mITT and ITTBP analysis populations
- SCORPIO-SR
- SCORPIO-HR



Methods

- Details of the study design, endpoints, and viral culture duration along with key results are presented in **Figure 2**
- Endpoints for pre-defined and post hoc analyses of virological potency and viral rebound included:
  - RNA copy number, determined using quantitative real-time RT-PCR (LLoQ varied between studies, ranging between <2.00 and <2.27 log_{10} RNA copies/mL)
  - Tissue culture virus titre, determined in Vero E6/TMPRSS2 cells (LLoQ: <1.00 log_{10} $TCID_{50}$)
  - Viral rebound, assessed as specified for this post hoc analysis (the criteria for each study are described in the footnotes of **Figure 2**)

Results

Figure 2. Study Design, Endpoints, and Outcomes of the Phase 3 SCORPIO Studies*

SCORPIO-PEP: Phase 3, double-blind, randomised, placebo-controlled study (NCT05897541)[4]

POST-EXPOSURE PROPHYLAXIS

ITT Population
- HHCs ≥12 years of age
- Negative local SARS-CoV-2 test
- Randomised ≤72 hours from onset of COVID-19 symptoms in the index patient
- Location: Global

R 1:1

Placebo (PBO) (n = 1193) | Ensetrilvir (ENS) (n = 1194)

mITT Population: HHCs with a negative RT-PCR — Placebo (n = 1011) | Ensitrelvir (n = 1030)

ITTBP Population†: HHCs with a positive RT-PCR — Placebo (n = 123) | Ensitrelvir (n = 114)

Treatment with ensitrelvir resulted in a 67% reduction in symptomatic infection and a 34% reduction in infection (regardless of symptoms)

Detectable Viral Load (Infectious Virus) in Participants

Viral culture positivity was not assessed

Differences in Viral Load (RNA Copy Number) (log_{10} RNA copies/mL) for Ensitrelvir versus Placebo

Through Day 6 (PEP and SR) and Day 8 (HR)

Difference in means‡

Day 3	Day 6
-1.45 (95% CI: -1.99, -0.91) ENS (n = 139); PBO (n = 210)	-1.24 (95% CI: -1.79, -0.70) ENS (n = 138); PBO (n = 206)

Difference in LS means§

Day 3	Day 6
-1.49 (95% CI: -2.02, -0.95) ENS (n = 112); PBO (n = 117)	-0.63 (95% CI: -1.14, -0.11) ENS (n = 109); PBO (n = 118)

Standard-Risk and High-Risk Populations Day 3 (PEP) or Day 4 (SR and HR)

Difference in means¶

Standard-Risk	High-Risk
-1.08 (95% CI: -1.77, -0.39) ENS (n = 81); PBO (n = 133)	-2.07 (95% CI: -2.93, -1.21) ENS (n = 58); PBO (n = 77)

Difference in LS means#

Standard-Risk	High-Risk
-1.77 (95% CI: -2.47, -1.08) ENS (n = 67); PBO (n = 66)	-1.08 (95% CI: -1.94, -0.22) ENS (n = 45); PBO (n = 51)

Time From Symptom Onset at Day 4

Time from symptom onset analysis is not applicable to the SCORPIO-PEP study

Rate of Viral RNA Rebound

Ensitrelvir**	Placebo**
0.8% (2/242) (95% CI: 0.1%, 3.0%)	1.3% (4/304) (95% CI: 0.4%, 3.3%)

Ensitrelvir††	Placebo††
15.3% (17/111) (95% CI: 9.2%, 23.4%)	6.7% (8/120) (95% CI: 2.9%, 12.7%)

SCORPIO-SR (symptomatic parts): Phase 2/3, double-blind, randomised, placebo-controlled study (jRCT2031210350)[2]

TREATMENT
- 12–69 years of age
- Mild-to-moderate COVID-19
- Positive SARS-CoV-2 test within 120 hours prior to randomisation
- ≥1 moderate or severe COVID-19 symptom
- Location: Japan, South Korea, and Vietnam

R 1:1:1‡‡

Placebo (n = 608) | Ensitrelvir (n = 607)

Culture positive on Day 4§§: Ensitrelvir 4.1% (8/197); Placebo 31.9% (66/207)

Difference in LS means¶¶

Day 4	Day 6
-1.57 (95% CI: -1.72, -1.43) ENS (n = 398); PBO (n = 395)	-1.35 (95% CI: -1.49, -1.21) ENS (n = 399); PBO (n = 391)

Difference in LS means##

Standard-Risk	High-Risk
-1.58 (95% CI: -1.74, -1.43) ENS (n = 339); PBO (n = 351)	-1.56 (95% CI: -2.00, -1.12) ENS (n = 59); PBO (n = 44)

Difference in LS means***

<72 hours	<120 hours	72–120 hours
-1.57 (95% CI: -1.72, -1.43) ENS (n = 398); PBO (n = 395)	-1.21 (95% CI: -1.32, -1.11) ENS (n = 716); PBO (n = 713)	-0.77 (95% CI: -0.93, -0.61) ENS (n = 318); PBO (n = 318)

Ensitrelvir†††	Placebo†††
9.6% (33/343) (95% CI: 6.7%, 13.2%)	4.2% (14/334) (95% CI: 2.3%, 6.9%)

SCORPIO-HR: Phase 3, double-blind, randomised, placebo-controlled study (NCT05305547)[3]

TREATMENT
- ≥18 years of age
- Mild-to-moderate COVID-19
- Positive SARS-CoV-2 test
- ≥1 COVID-19 symptom
- Symptom onset ≤5 days before treatment initiation
- Location: Global

R 1:1

Placebo (n = 1051) | Ensitrelvir (n = 1042)

Culture positive on Day 4§§§: Ensitrelvir 4.5% (13/287); Placebo 25.0% (70/280)

Difference in LS means§§§

Day 4	Day 8
-0.72 (95% CI: -0.90, -0.55) ENS (n = 798); PBO (n = 821)	-0.30 (95% CI: -0.43, -0.17) ENS (n = 840); PBO (n = 840)

Difference in LS means¶¶¶

Standard-Risk	High-Risk
-0.76 (95% CI: -0.98, -0.54) ENS (n = 557); PBO (n = 572)	-0.63 (95% CI: -0.91, -0.35) ENS (n = 241); PBO (n = 249)

Difference in LS means###

<72 hours	<120 hours	72–120 hours
-0.72 (95% CI: -0.90, -0.55) ENS (n = 798); PBO (n = 821)	-0.65 (95% CI: -0.82, -0.49) ENS (n = 877); PBO (n = 909)	0.01 (95% CI: -0.50, 0.51) ENS (n = 79); PBO (n = 88)

Ensitrelvir****	Placebo****
2.4% (23/945) (95% CI: 1.5%, 3.6%)	2.2% (21/943) (95% CI: 1.4%, 3.4%)

*The ensitrelvir group comprises of participants receiving ensitrelvir 375 mg on Day 1 and 125 mg on Days 2–5. †The ITTBP population comprises of asymptomatic participants with a negative rapid antigen test who were subsequently found to be RT-PCR positive at baseline by central laboratory testing. ‡For viral reduction analysis in the SCORPIO-PEP mITT population, participant numbers were placebo n = 217 and ensitrelvir n = 144. The baseline RNA value was negative; therefore, LS means and their difference adjusted by the baseline value using ANCOVA could not be calculated. §For viral reduction analysis in the SCORPIO-PEP ITTBP population, participant numbers were placebo n = 123 and ensitrelvir n = 114. ¶For the mITT population, participant numbers were placebo n = 137 and ensitrelvir n = 85 in the SR subgroup and placebo n = 80 and ensitrelvir n = 59 in the HR subgroup. The baseline RNA value was negative; therefore, LS means and their difference adjusted by the baseline value using ANCOVA could not be calculated.Data reported are difference in means of ensitrelvir and placebo. #For the ITTBP population, participant numbers were placebo n = 70 and ensitrelvir n = 67 in the SR subgroup and placebo n = 53 and ensitrelvir n = 47 in the HR subgroup. **For the SCORPIO-PEP mITT population, the proportion of participants with viral RNA rebound through Day 28 was assessed. Viral RNA rebound through Day 28 was defined as ≥1.0 log_{10} RNA copies/mL increase with ≥3.27 log_{10} RNA copies/mL observed, compared with the lowest viral RNA with ≥1.0 log_{10} RNA copies/mL decrease from the peak viral RNA within all time points after the peak viral RNA visit (defined as the earliest visit at which a larger viral RNA value was observed than both of the previous non-missing visit and the next non-missing visit where the viral RNA was ≥3.27 log_{10} RNA copies/mL). If the viral RNA value was negative and <LLoQ, the viral RNA was imputed as 0 and 1.97 (= log_{10} [$10^{2.27}$/2]) log_{10} RNA copies/mL, respectively. ††For the SCORPIO-PEP ITTBP population, the proportion of participants with viral RNA rebound from Days 6 to 28 was assessed. Viral RNA rebound was defined as (a) viral RNA on Day 6 <LLoQ and ≥LLoQ at any subsequent visit through Day 28 or viral RNA on Day 6 ≥LLoQ and ≥0.5 log_{10} RNA copies/mL increase at any subsequent visit through Day 28, (b) viral RNA on Day 10 <LLoQ and ≥LLoQ at any subsequent visit through Day 28 or viral RNA on Day 10 ≥LLoQ and ≥0.5 log_{10} RNA copies/mL increase at any subsequent visit through Day 28. If the viral RNA value was negative and <LLoQ, the viral RNA was imputed as 0 and 1.97 (= log_{10} [$10^{2.27}$/2]) log_{10} RNA copies/mL, respectively. ‡‡Participants were randomised 1:1:1 in the SCORPIO-SR study, and the third group receiving ensitrelvir 750 mg/250 mg (n = 606) was not included in the current viral load and rebound analysis. §§For viral culture analysis, only the data for Phase 3 were analysed. On the other hand, viral load analysis was performed for symptomatic participants in the Phase 2a, 2b, and 3 symptomatic parts. ¶¶For viral reduction analysis in SCORPIO-SR, participant numbers for placebo were n = 402 and ensitrelvir n = 407 (participants randomised within <72 hours of symptom onset). ##Participant numbers were placebo n = 357 and ensitrelvir n = 347 in the SR subgroup and placebo n = 45 and ensitrelvir n = 60 in the HR subgroup (participants randomised within <72 hours of symptom onset). LS mean (log_{10} RNA copies/mL) was calculated by ANCOVA with the following covariates: time from symptom onset 0 to 72 hours–SARS-CoV-2 viral RNA at baseline and SARS-CoV-2 vaccination history (Yes or No). ***Participant numbers were placebo n = 402 and ensitrelvir n = 407 in the <72 hours subgroup, placebo n = 725 and ensitrelvir n = 731 in the <120 hours subgroup, and placebo n = 323 and ensitrelvir n = 324 in the 72–120 hours subgroup. LS mean (log_{10} RNA copies/mL) calculated by ANCOVA with the following covariates: (a) time from symptom onset 0 to 72 hours and 72 to 120 hours–SARS-CoV-2 viral RNA at baseline and SARS-CoV-2 vaccination history (Yes or No), (b) time from symptom onset 0 to 120 hours– SARS-CoV-2 viral RNA at baseline and SARS-CoV-2 vaccination history (Yes or No); and (c) time from symptom onset to randomisation (<72 hours or ≥72 hours). †††For SCORPIO-SR, viral RNA rebound through Days 6 to 21 was defined as ≥ 1.0 log_{10} RNA copies/mL with ≥3.27 log_{10} RNA copies/mL observed at any visit after Day 9 compared to the previous nonmissing visit (i.e. Day 6 or after) at which viral RNA was detected or ≥3.27 log_{10} RNA copies/mL (2.27 + 1 log_{10} RNA copies/mL) observed at any visit after Day 9 compared to the previous non-missing visit (i.e. Day 6 or after) at which viral RNA was below LLoQ or undetected. If the viral RNA value was negative and <LLoQ, the viral RNA was imputed as 0 and 1.97 (=log_{10} [$10^{2.27}$/2]) log_{10} RNA copies/mL, respectively. ‡‡‡Analysis population is the full mITT set (randomised and administered within ≤3 days from onset) with baseline viral culture detected. §§§For viral reduction analysis in SCORPIO-HR, participant numbers for placebo were n = 943 and ensitrelvir n = 945 (participants randomised within <72 hours of symptom onset). ¶¶¶Participant numbers were placebo n = 651 and ensitrelvir n = 654 in the SR subgroup and placebo n = 292 and ensitrelvir n = 291 in the HR subgroup (participants randomised within <72 hours of symptom onset). LS mean (log_{10} RNA copies/mL) calculated by ANCOVA with covariate: if the viral RNA value was <LLoQ (<2.0 log_{10}) and undetected, (10^{LLoQ}/2) log_{10} (=1.7) and 0 log_{10} were imputed, respectively. ###Participant numbers were placebo n = 943 and ensitrelvir n = 945 in the <72 hours subgroup, placebo n = 1047 and ensitrelvir n = 1038 in the <120 hours subgroup, and placebo n = 104 and ensitrelvir n = 93 in the 72–120 hours subgroup. LS mean (log_{10} RNA copies/mL) calculated by ANCOVA with covariate: if viral RNA was <LLoQ (<2.0 log_{10}) and undetected, (10^{LLoQ}/2) log_{10} (=1.7) and 0 log_{10} were imputed, respectively. ****For SCORPIO-HR, viral RNA rebound was defined as an increase of ≥1.0 log_{10} from the previous non-missing visit value when the previous visit was detected or an increase to ≥LLoQ + 1.0 log_{10} when the previous non-missing visit value was below LLoQ or an increase to ≥LoD + 1.0 log_{10} when the previous non-missing visit was undetected (2.0 log_{10} was used as LLoQ and LoD for viral RNA rebound assessment).

Conclusions

Virological Potency

- Across the disease continuum, ensitrelvir demonstrated significant virological potency against SARS-CoV-2 compared with placebo
- Ensitrelvir was associated with substantially reduced viral culture positivity and lower viral load compared with placebo at Day 4
- Ensitrelvir treatment resulted in lower viral load (RNA) compared with placebo irrespective of the risk status or time of symptom onset



Viral Rebound

- Viral RNA rebound rates were variable, but generally low across studies, and rarely associated with the presence of cell culture infectious virus
- Cell culture infectious virus was detected in only 8% (7/87) of viral RNA rebound cases in both ensitrelvir (375 mg and 125 mg) and placebo arms in SCORPIO-SR Phase 3 and SCORPIO-HR
- Viral rebound was not associated with the recurrence of symptoms

References

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Abbreviations

ANCOVA, analysis of covariance; CI, confidence interval; COVID-19, coronavirus disease 2019; EC_{50}, 50% of maximal effective concentration; EMA, European Medicines Agency; ENS, ensitrelvir; FDA, Food and Drug Administration; HHC, household contact; HR, high risk; ITT, intention-to-treat; ITTBP, intention-to-treat baseline positive; LoD, limit of detection; LLoQ, lower limit of quantitation; LS, least squares; mITT, modified intention-to-treat; M^{pro}, main protease; PBO, placebo; PCR, polymerase chain reaction; PEP, post-exposure prophylaxis; R, randomisation; RNA, ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCORPIO, Stopping COVID-19 pRogression with early Protease InhibitOr; SR, standard risk; $TCID_{50}$, 50% tissue culture infectious dose.

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