# P-1606: Clearance of Infectious Virus in COVID-19 Patients Treated With Ensitrelvir Across Vaccination Status, Age, and Risk Subgroups: Exploratory Analyses From the SCORPIO-HR Study


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## Background

- While many antiviral studies for COVID-19 have relied on molecular methods to assess viral load, these methods may detect viral RNA even after the infectious virus has been cleared[1]
- In contrast, viral culture provides a direct measure of infectious viral shedding, potentially offering more accurate insights into transmission potential[1]
- Ensitrelvir is an oral SARS-CoV-2 3C-like ($M^{pro}$) protease inhibitor approved in Japan for the treatment of mild-to-moderate SARS-CoV-2 infection[2-5]
  - It has demonstrated consistent and potent antiviral efficacy, reducing both RNA copy number and infectious virus titer in those infected with SARS-CoV-2[6-8]
- In SCORPIO-HR, a phase 3 trial in nonhospitalized symptomatic adults with COVID-19, ensitrelvir treatment led to a reduction in mean RNA copy number and infectious virus titers in a higher proportion of participants by day 4 compared with placebo[8]

## Objective

- This exploratory analysis of the SCORPIO-HR study assessed the effect of ensitrelvir vs placebo on the clearance of infectious virus on day 4 in participants with a day 1 positive viral culture across different subgroups

## Methods

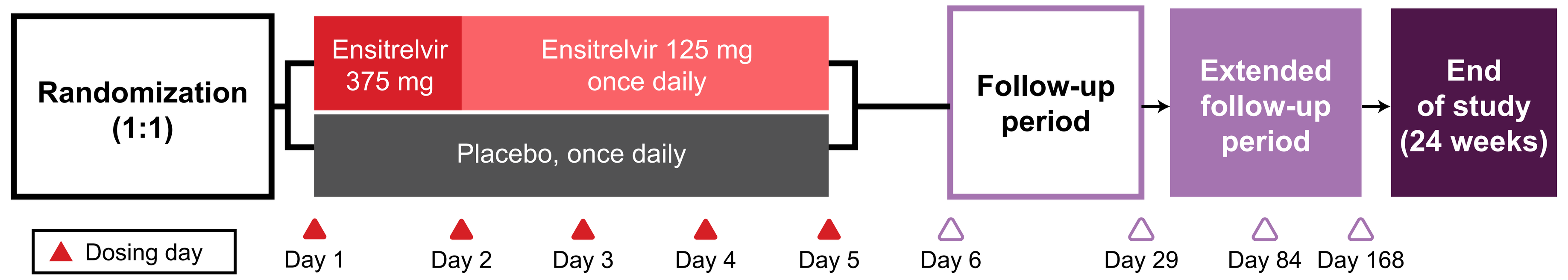
### Study design[8]

- Multicenter, randomized, double-blind, placebo-controlled, phase 3 study (NCT05305547)
- Conducted in 16 countries in Africa, Asia, Europe, North America, and South America
- Study period: August 2022 to December 2023

**Study design**

**SCORPIO-HR: Study design**

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



Randomization (1:1)
Ensitrelvir 375 mg
Ensitrelvir 125 mg once daily
Placebo, once daily
Follow-up period
Extended follow-up period
End of study (24 weeks)
Dosing day
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 29
Day 84
Day 168


### Key study eligibility criteria[8]

- Age ≥18 years
- Laboratory-confirmed SARS-CoV-2 infection
  - This post hoc analysis was limited to participants with detectable viral culture (>lower limit of quantification [LLoQ=1.0]) on day 1
- Symptom onset ≤3 days (initially ≤5 days) before randomization

### Endpoint for exploratory analysis

- Proportion of participants with a day 1 positive viral culture who had a negative viral culture (<LLoQ) on day 4
  - Subgroup results were reported by risk status for severe COVID-19 (high and standard risk), age (<65 and ≥65 years), and COVID-19 vaccination status (vaccinated and unvaccinated)
- As this was an exploratory post hoc analysis, no formal statistical testing was performed

### Viral culture procedure

- Quantitative viral culture (LLoQ=1.0) was conducted centrally at Cerba Research (formerly Viroclinics-DDL, Rotterdam, Netherlands) using nasopharyngeal swabs collected on days 1, 4, 8, and 16
- Samples were stabilized (transferred to Universal Transport Medium, aliquoted, and frozen) at designated local facilities within 48 hours of collection and shipped to the central laboratory for viral culture
- Viral titer was measured by virus-induced cytopathic effects in VeroE6/TMPRSS2 cells

## Results

- In SCORPIO-HR, 28.7% (601/2093) of participants had positive viral cultures at enrollment
- Among the 567 participants with viral culture data available at day 4, 95.5% (274/287) in the ensitrelvir group vs 75.0% (210/280) in the placebo group were viral culture negative
- Baseline characteristics were mostly similar between the two groups (**Table 1**)

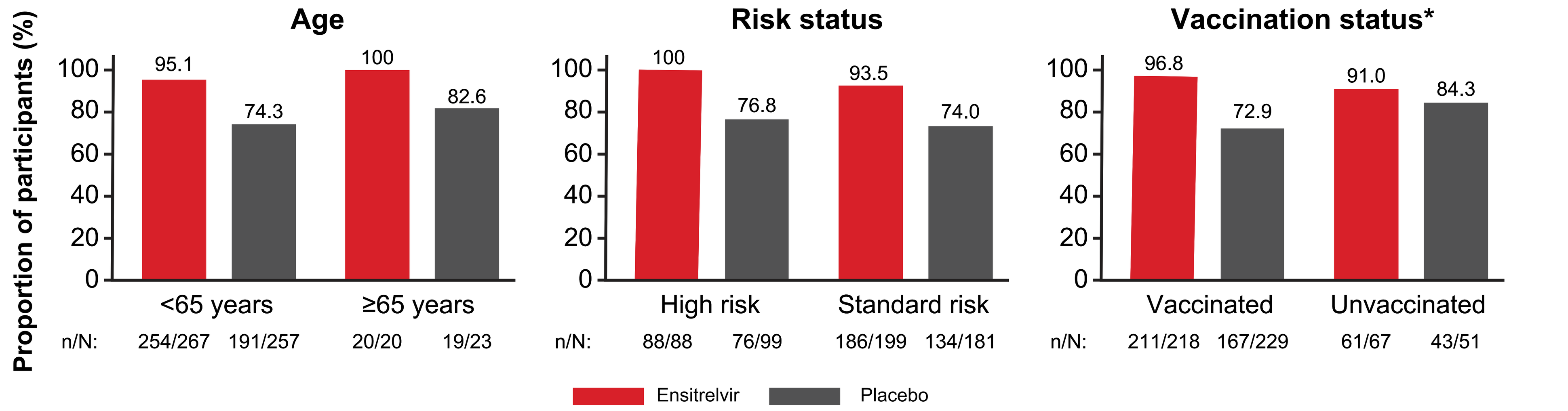
**Table 1. Characteristics of participants with day 1 positive viral culture and available day 4 viral culture data**

| | Ensitrelvir* (N=287) | Placebo* (N=280) |
|---|---|---|
| **Age, n (%)** | | |
| <65 years | 267 (93.0) | 257 (91.8) |
| ≥65 years | 20 (7.0) | 23 (8.2) |
| **Sex, n (%)** | | |
| Male | 104 (36.2) | 114 (40.7) |
| Female | 183 (63.8) | 166 (59.3) |
| **Risk status†, n (%)** | | |
| High risk | 88 (30.7) | 99 (35.4) |
| Standard risk | 199 (69.3) | 181 (64.6) |
| **COVID-19 vaccination‡, n (%)** | | |
| Yes | 218 (76.5)§ | 229 (81.8) |
| No | 67 (23.5)§ | 51 (18.2) |

*Among the 601 participants enrolled with positive viral cultures on day 1 (ensitrelvir: n=309; placebo: n=292), 34 participants without viral culture data on day 4 were excluded from this summary. These participants were excluded from the analysis assuming that they were completely missing at random.[8] †High-risk participants were defined as individuals aged ≥65 years or aged ≥18 years with ≥1 of the following: obesity (BMI ≥30 kg/m²), diabetes mellitus, hypertension or cardiovascular/lung/kidney disease requiring daily therapy, congenital heart disease, Down syndrome, sickle cell disease, or immunocompromising conditions/immunosuppressive treatments (e.g., cancer therapy, hematologic malignancy, transplant history, HIV with CD4+ <200 cells/mm³, primary immunodeficiency, immunosuppressive medications). Standard-risk participants were defined as those aged 18–64 years with none of these risk factors. ‡Participants were classified as unvaccinated if they responded "No" to the question "Has the subject taken COVID-19 vaccines?" or if they had received vaccination but had not completed the primary series of COVID-19 vaccinations. §Vaccination status was missing in two enistrelvir-treated participants.

- Across all subgroups, a greater proportion of participants in the ensitrelvir vs placebo group achieved a negative viral culture on day 4 (**Figure 1**)

**Figure 1. Proportion of participants with negative SARS-CoV-2 viral culture on day 4**

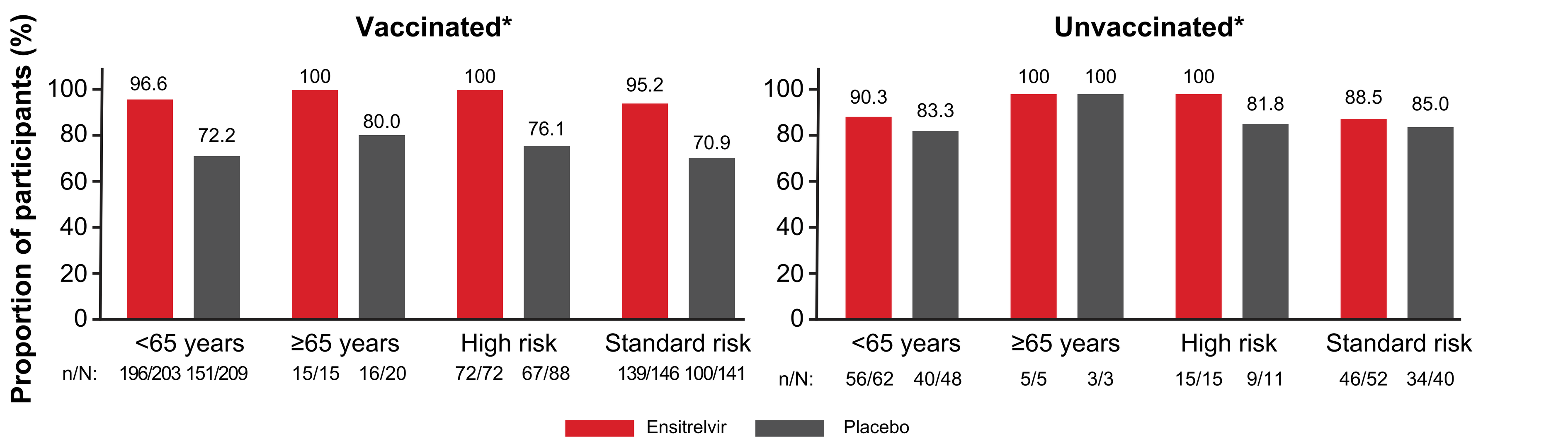


Proportion of participants (%)
Age
Risk status
Vaccination status*
100
80
60
40
20
0
95.1
74.3
100
82.6
<65 years
≥65 years
n/N:
254/267
191/257
20/20
19/23
100
76.8
93.5
74.0
High risk
Standard risk
88/88
76/99
186/199
134/181
96.8
72.9
91.0
84.3
Vaccinated
Unvaccinated
211/218
167/229
61/67
43/51
Ensitrelvir
Placebo


*Participants were classified as unvaccinated if they responded "No" to the question "Has the subject taken COVID-19 vaccines?" or if they had received vaccination but had not completed the primary series of COVID-19 vaccinations. n=number of participants with viral clearance on day 4; N=total number of participants in the group.

- Among vaccinated participants, clearance of infectious virus was consistently higher with ensitrelvir than with placebo, regardless of risk status and age (**Figure 2**)

**Figure 2. Proportion of participants with negative SARS-CoV-2 viral culture on day 4 by vaccination status in combination with age and risk status**

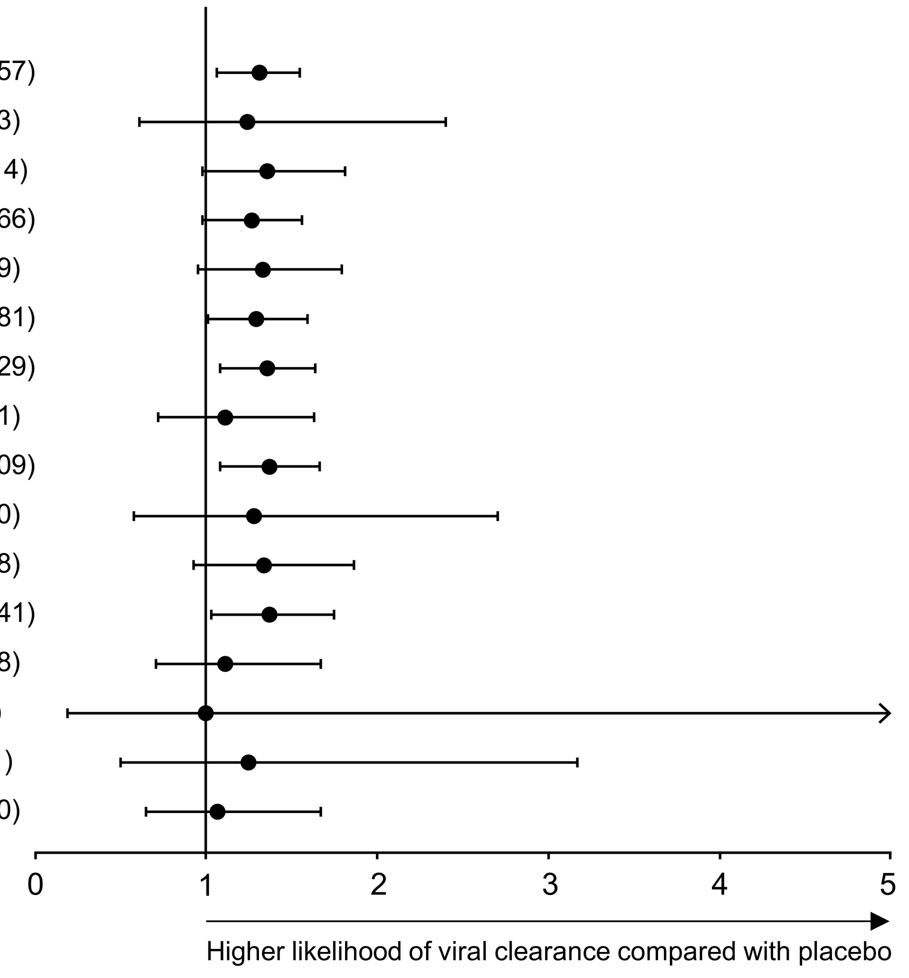


Proportion of participants (%)
Vaccinated*
Unvaccinated*
100
80
60
40
20
0
96.6
72.2
100
80.0
100
76.1
95.2
70.9
<65 years
≥65 years
High risk
Standard risk
n/N:
196/203 151/209
15/15 16/20
72/72 67/88
139/146 100/141
90.3
83.3
100
100
100
81.8
88.5
85.0
56/62 40/48
5/5 3/3
15/15 9/11
46/52 34/40
Ensitrelvir
Placebo


*Participants were classified as unvaccinated if they responded "No" to the question "Has the subject taken COVID-19 vaccines?" or if they had received vaccination but had not completed the primary series of COVID-19 vaccinations. n=number of participants with viral clearance on day 4; N=total number of participants in the group.

**Figure 3. Forest plot of risk ratios for SARS-CoV-2 viral culture negativity on day 4**

| Subgroups | Ensitrelvir, % (n/N) | Placebo, % (n/N) | Risk ratio (95% CI)* |
|---|---|---|---|
| <65 yrs | 95.1 (254/267) | 74.3 (191/257) | 1.28 (1.06, 1.55) |
| ≥65 yrs | 100 (20/20) | 82.6 (19/23) | 1.21 (0.61, 2.40) |
| Male | 93.3 (97/104) | 70.2 (80/114) | 1.33 (0.98, 1.81) |
| Female | 96.7 (177/183) | 78.3 (130/166) | 1.24 (0.98, 1.56) |
| HR | 100 (88/88) | 76.8 (76/99) | 1.30 (0.95, 1.79) |
| SR | 93.5 (186/199) | 74.0 (134/181) | 1.26 (1.01, 1.59) |
| Vaccinated | 96.8 (211/218) | 72.9 (167/229) | 1.33 (1.08, 1.64) |
| Unvaccinated | 91.0 (61/67) | 84.3 (43/51) | 1.08 (0.72, 1.63) |
| Vaccinated <65 yrs | 96.6 (196/203) | 72.2 (151/209) | 1.34 (1.08, 1.66) |
| Vaccinated ≥65 yrs | 100 (15/15) | 80.0 (16/20) | 1.25 (0.58, 2.70) |
| Vaccinated HR | 100 (72/72) | 76.1 (67/88) | 1.31 (0.93, 1.86) |
| Vaccinated SR | 95.2 (139/146) | 70.9 (100/141) | 1.34 (1.03, 1.75) |
| Unvaccinated <65 yrs | 90.3 (56/62) | 83.3 (40/48) | 1.08 (0.71, 1.67) |
| Unvaccinated ≥65 yrs | 100 (5/5) | 100 (3/3) | 1.00 (0.19, 6.44) |
| Unvaccinated HR | 100 (15/15) | 81.8 (9/11) | 1.22 (0.50, 3.17) |
| Unvaccinated SR | 88.5 (46/52) | 85.0 (34/40) | 1.04 (0.65, 1.67) |



0
1
2
3
4
5
Higher likelihood of viral clearance compared with placebo


*The 95% CI of the risk ratio was obtained using the exact method.
CI, confidence interval; HR, high risk; SR, standard risk; yrs, years.

- By day 4, the following groups showed a numerically higher likelihood of achieving a negative viral culture when treated with ensitrelvir compared with placebo **(Figure 3)**: <65 years, standard risk, vaccinated, vaccinated <65 years, and vaccinated standard risk

## Conclusion

- Ensitrelvir demonstrated consistent antiviral efficacy, as measured by clearance of infectious virus, across participant characteristics of vaccination status, age, and risk for severe disease

### References


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### Abbreviations

BMI, body mass index; CD4, cluster of differentiation 4; CI, confidence interval; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; HR, high risk; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SR, standard risk; yrs, years

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