Ensitrelvir for Asymptomatic and Mild Symptoms Only: COVID-19 Patients in Phase 2b/3 Part

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COI disclosure by the presenter

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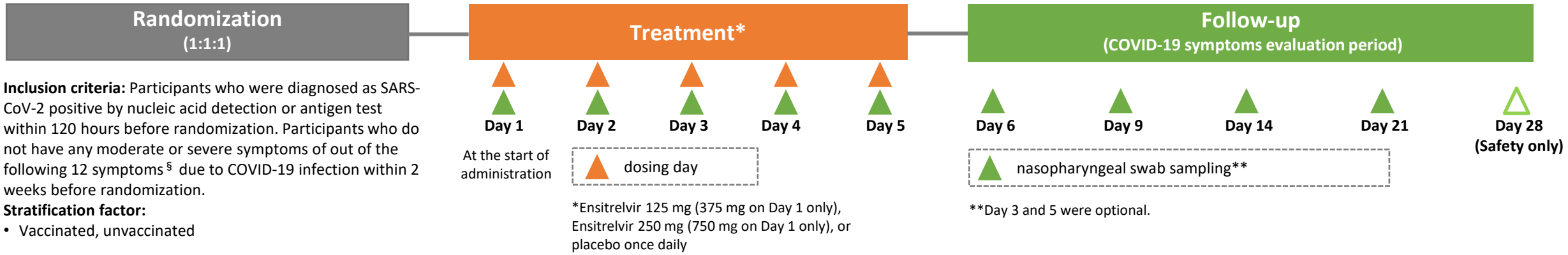
Study Design

Purpose

Exploratory evaluation of the occurrence or worsening of COVID-19 symptoms in participants who tested positive for SARS-CoV-2 but were either asymptomatic or had mild symptoms only.

Study design

A multicenter, randomized, double-blind, placebo-controlled study conducted in Japan, South Korea and Vietnam, during the Omicron variant dominant period. Patients who were asymptomatic or had mild symptoms only age 12 to <70 years and were SARS-CoV-2 positive were eligible, regardless of the SARS-CoV-2 vaccination status and presence of risk factors for severe disease.



Inclusion criteria: Participants who were diagnosed as SARS-CoV-2 positive by nucleic acid detection or antigen test within 120 hours before randomization. Participants who do not have any moderate or severe symptoms of out of the following 12 symptoms [§] due to COVID-19 infection within 2 weeks before randomization.

Stratification factor:

- Vaccinated, unvaccinated

*Ensitrelvir 125 mg (375 mg on Day 1 only), Ensitrelvir 250 mg (750 mg on Day 1 only), or placebo once daily

**Day 3 and 5 were optional.

[§] low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, stuffy or runny nose, sore throat, cough, shortness of breath (difficulty breathing), nausea, vomiting, and diarrhea.

Endpoints

- Proportion of asymptomatic participants who developed any or all of the 14 target COVID-19 symptoms or fever
- Proportion of mild-symptom-only participants who had any or all of the 14 target COVID-19 symptoms or fever worsened
- Change in SARS-CoV-2 viral RNA on Day 4 compared to baseline and time to the first negative SARS-CoV-2 viral titer
- Safety (by Day 28)

Baseline Characteristics

Patients were enrolled during the Omicron-dominant period, and 12.2% were asymptomatic and 87.8% presented with mild symptoms only; 91.8% were vaccinated.

	Ensitrelvir 125 mg (n=194)	Ensitrelvir 250 mg (n=189)	Placebo (n=189)
Gender, male (%)	56.2	58.2	54.5
Age (years), mean (SD)	37.9 (12.0)	40.9 (13.4)	38.6 (13.0)
SARS-CoV-2 vaccination history (%)	91.8	91.5	92.1
Confirmed Omicron infection (%)	67.0	66.1	56.1
Race, Asian (%)	99.5	100.0	99.5
Symptoms			
Asymptomatic (%)	11.9	13.2	11.6
Mild symptoms only[a] (%)	88.1	86.8	88.4

[a]Participants who had mild symptoms only out of the 12 symptoms due to COVID-19 infection within 2 weeks before randomization. Patients assessed 12 symptoms using a 4-point scale of 0 to 3 (0, None; 1, Mild; 2, Moderate; 3, Severe).

COVID-19 Symptoms Occurrence in Asymptomatic Patients

Ensitrelvir 125 mg showed a non-statistically significant 77% reduction in the occurrence of COVID-19 symptoms in asymptomatic patients compared with placebo.

Definition of occurrence of symptoms

- Shortness of breath (difficulty breathing), fever: occurrence is defined as symptoms present at one-point
- Other symptoms: occurrence is defined as 2 or more symptoms present for at least 24 hours

Proportion of participants of occurrence of 14 target COVID-19 symptoms or fever (≥37.5℃) by Day 10 in asymptomatic patients and risk ratio

	Ensitrelvir 125 mg (n=23)	Ensitrelvir 250 mg (n=25)	Placebo (n=22)
Proportion of patients (%)	4.3 (1/23)	20.0 (5*/25)	18.2 (4/22)
p-value	0.1293	0.9082	---
Risk ratio [95% CI] [a]	0.23 [0.03, 1.88]	1.08 [0.31, 3.73]	---

*Among 5 patients, 2 met the definition of occurrence of symptoms because of a transient elevation of body temperature with no accompanying symptoms. The other was judged symptomatic because of a transient shortness of breath.

CI = Confidence Interval, [a] Adjusted by the stratum of SARS-CoV-2 vaccination history [Yes or No]

COVID-19 Symptoms Worsening in Mild- Symptoms-Only Patients

Ensitrelvir 125 mg showed a non-statistically significant 29% reduction in the worsening COVID-19 symptoms in patients presenting with mild symptoms only compared with placebo.

Definition of worsening

- Shortness of breath (difficulty breathing) : judged to be worsening if the symptom score increase by 1 or more
- Fever: judged to be worsening if the temperature rises by 0.5 ℃ or more
- Other symptoms: judged to be worsening if the symptom score of 2 or more symptoms increase and persist for 24 hours

Proportion of participants and risk ratio with worsening of 14 target COVID-19 symptoms or fever (≥37.5℃) by Day 10 in mild symptoms only patients

	Ensitrelvir 125 mg (n=171)	Ensitrelvir 250 mg (n=164)	Placebo (n=167)
Proportion of patients (%)	17.4 (29/167)	20.5 (33/161)	23.9 (39/163)
p-value	0.1210	0.4521	---
Risk ratio [95% CI] [a]	0.71 [0.47, 1.09]	0.86 [0.57, 1.28]	---

CI = Confidence Interval
[a] Adjusted by the following stratum (SARS-CoV-2 vaccination history [Yes or No])

Virological Endpoint: SARS-CoV-2 Viral RNA in Asymptomatic and Mild-Symptoms-Only Patients

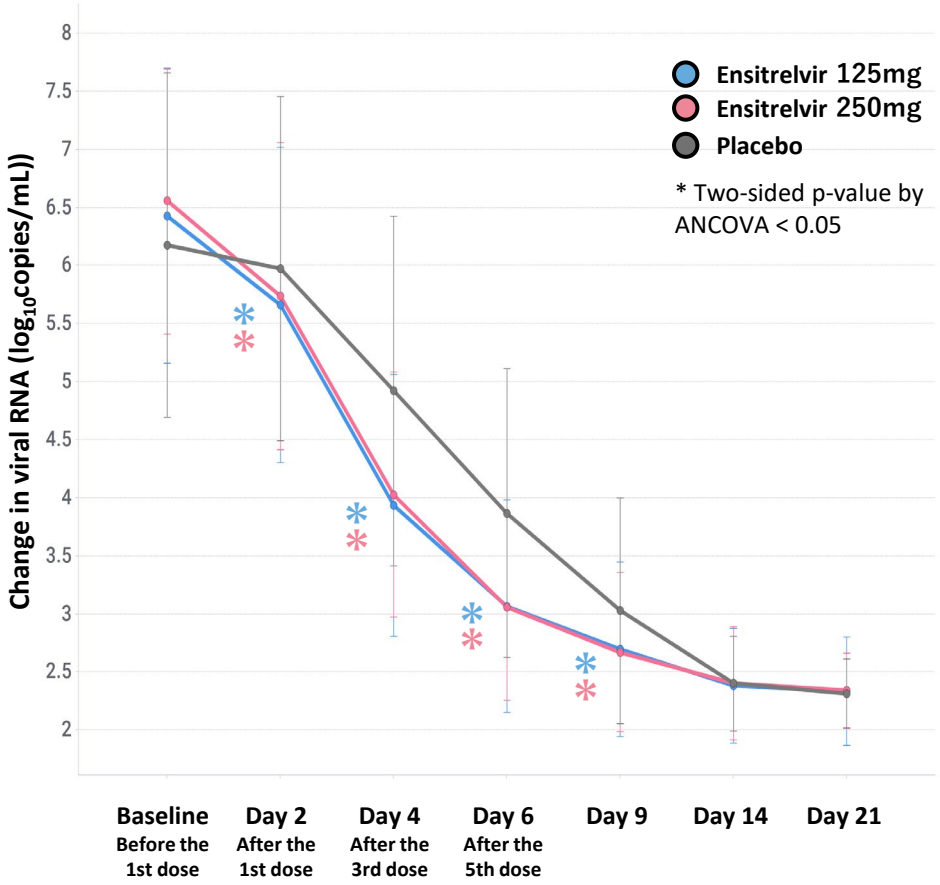
Both ensitrelvir 125 mg and 250 mg showed significantly greater reduction in viral RNA from baseline to Day 4 compared with placebo.

Changes in viral RNA on Day 4 of administration

	Ensitrelvir 125 mg (n=191)	Ensitrelvir 250 mg (n=183)	Placebo (n=185)
Change in viral RNA (log_{10} copies/mL), Mean (SD)	-2.491 (1.107)	-2.539 (0.941)	-1.245 (1.540)
ANCOVA vs. placebo [a]			
LS mean (SE)	-2.19 (0.10)	-2.18 (0.10)	-1.07 (0.10)
Difference in LS mean (SE) [95% CI]	-1.12 (0.11) [-1.33, -0.91]	-1.10 (0.11) [-1.32, -0.89]	---
p-value	<.0001	<.0001	---

ANCOVA = Analysis of Covariance; SD = Standard Deviation; SE = Standard Error; Min = Minimum; Max = Maximum; LS = Least Squares; CI = Confidence Interval
Lower limit of quantification of viral RNA is 2.08 log_{10} copies/mL.
If viral RNA is negative and/or less than the lower limit of quantification, the viral RNA was imputed to be 2.27 and 2.08 log_{10} copies/mL, respectively.
[a] Covariate: SARS-CoV-2 viral RNA at baseline, SARS-CoV-2 vaccination history [Yes or No]

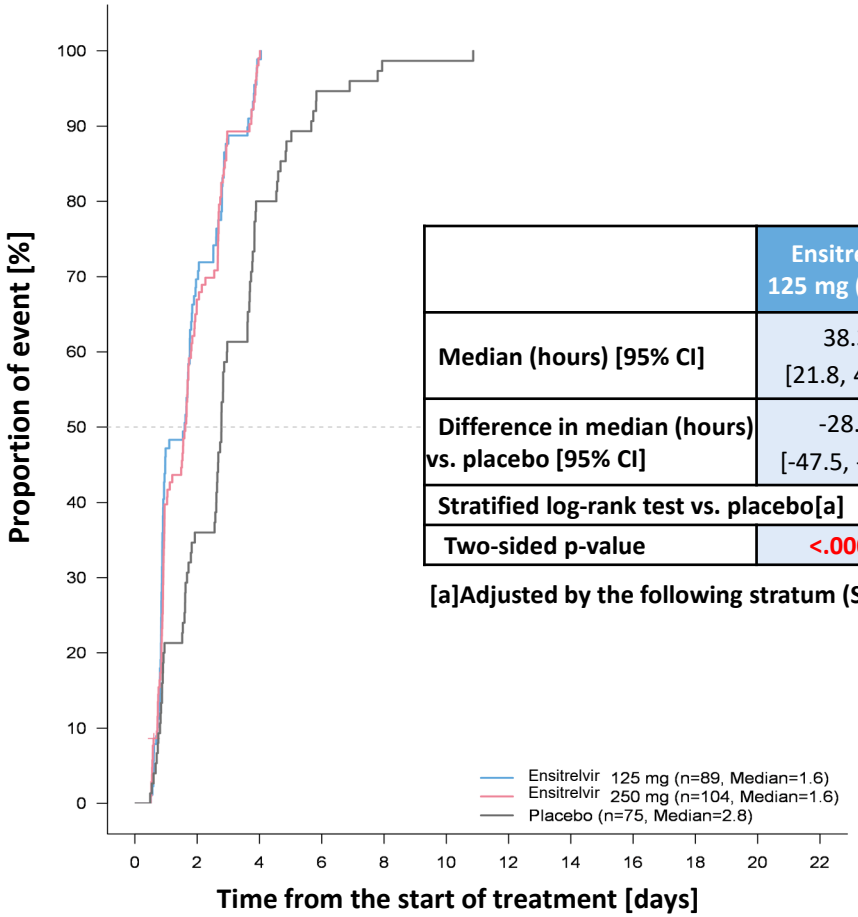
Mean change in viral RNA



Virological Endpoint: SARS-CoV-2 Viral Titer in Asymptomatic and Mild-Symptom-Only Patients

Both ensitrelvir 125 mg and 250 mg significantly shorten the time to cessation of SARS-CoV-2 viral shedding compared with placebo.

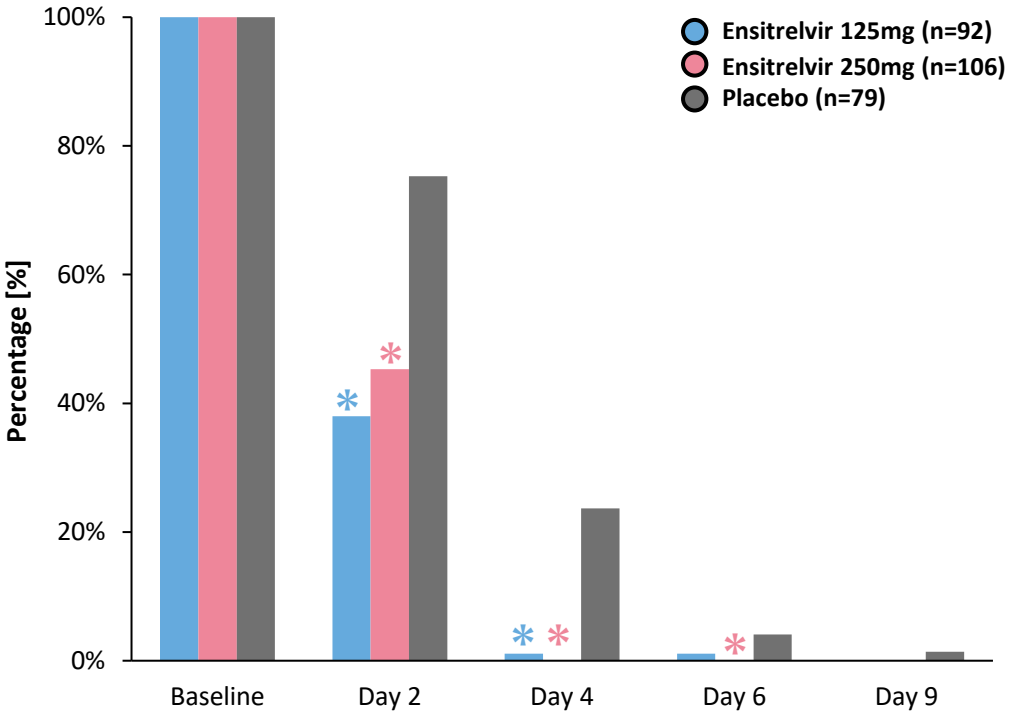
Time to first confirmed negative SARS-CoV-2 viral titer



	Ensitrelvir 125 mg (n=89)	Ensitrelvir 250 mg (n=104)	Placebo (n=75)
Median (hours) [95% CI]	38.3 [21.8, 42.3]	38.9 [24.8, 43.2]	66.7 [62.0, 71.2]
Difference in median (hours) vs. placebo [95% CI]	-28.3 [-47.5, -22.0]	-27.8 [-45.5, -21.6]	---
Stratified log-rank test vs. placebo[a]			
Two-sided p-value	<.0001	<.0001	---

[a]Adjusted by the following stratum (SARS-CoV-2 vaccination history [Yes or No])

Patients with positive virus titer



vs. Placebo *< 0.05
Mantel-Haenszel test stratified by SARS-CoV-2 vaccination history
Viral titer negative (< 0.75 $\log_{10}$ ($TCID_{50}$/mL))
Viral titer positive (≥ 0.75 $\log_{10}$ ($TCID_{50}$/mL))

Safety Endpoint: Summary of Treatment-Emergent Adverse Events in Asymptomatic and Mild-Symptoms-Only Patients

Ensitrelvir was well tolerated and no new safety concerns were identified.

Safety population	Ensitrelvir 125 mg n=201 (%)	Ensitrelvir 250 mg n=202 (%)	Placebo n=201 (%)
Treatment-Emergent adverse events (TEAEs)	**88 (43.8%)**	**115 (56.9%)**	**43 (21.4%)**
Death	**0**	**0**	**0**
Serious TEAEs other than death	**0**	**2 (1.0%)**	**0**
TEAEs leading to discontinuation	**1 (0.5%)**	**2 (1.0%)**	**0**
TEAE occurring in ≥2% of patients in either group			
- Headache	5 (2.5)	11 (5.4)	3 (1.5)
- Nausea	1 (0.5)	7 (3.5)	0
- Diarrhea	1 (0.5)	6 (3.0)	4 (2.0)
- High density lipoprotein decreased	61 (30.3)	91 (45.0)	4 (2.0)
- Blood triglycerides increased	14 (7.0)	22 (10.9)	9 (4.5)
- Blood bilirubin increased	7 (3.5)	15 (7.4)	0
- Blood cholesterol decreased	8 (4.0)	7 (3.5)	0
- Bilirubin conjugated increased	3 (1.5)	7 (3.5)	0
Treatment-related adverse event (AE)	**47 (23.4%)**	**75 (37.1%)**	**14 (7.0%)**
Treatment-related AEs in ≥2% of patients in either group			
- Blood bilirubin increased	2 (1.0)	5 (2.5)	0
- Blood triglycerides increased	0	5 (2.5)	1 (0.5)

Summary

- Ensitrelvir 125 mg showed a non-statistically significant 77% reduction in the occurrence of COVID-19 symptoms in asymptomatic patients and 29% reduction in the worsening of COVID-19 symptoms in patients presented mild symptoms only compared with placebo.
- Time to first negative SARS-CoV-2 culture was significantly shorter in both ensitrelvir arms compared with placebo.
- Ensitrelvir was well tolerated and no new safety concerns were identified.

Conclusion

- The reduction in viral RNA and the faster time to a negative viral culture may be predictive factors for shortening the infection period which may lead to reducing the risk of transmission. Further investigation on Ensitrelvir for post exposure prophylaxis is planned.

Thank you for your attention