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Combined results of the Phase 2a/2b/3 randomized controlled trials of ensitrelvir for the treatment of COVID-19 infection

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Introduction

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- Ensitrelvir, a selective SARS-CoV-2 3CL protease inhibitor, is being developed as a once-daily oral therapy for the treatment of COVID-19 infection.[1]
- Ensitrelvir 125 mg (with 375 mg loading dose on Day 1) and 250 mg (with 750 mg loading dose on Day 1), once-daily, oral treatment for 5 days significantly shortened the time to resolution of five key COVID-19 symptoms vs placebo in the Phase 3 part of the SCORPIO-SR study.[2]
- Of note, the 125 mg was selected as the clinical dose as there was no difference of exposure and dose for anti-viral effect in PK/PD analysis.[3]

Objective

- To investigate the integrated efficacy and safety of ensitrelvir vs placebo in the Phase 2a, 2b, and 3 parts of the SCORPIO-SR clinical study (jRCT2031210350; NCT05305547)[4,5]

Methods

- Multicenter, randomized, double-blind, placebo-controlled study in Japan, South Korea, and Vietnam
- Treatment arms: ensitrelvir 125 mg oral (PO), once daily (QD) [375 mg loading dose on Day 1], 250 mg PO QD [750 mg loading dose on Day 1], and placebo PO QD for 5 days

Stratification:
Vaccination status
Time from onset to treatment
(<3 days, ≥3 days)

Symptoms assessment

Primary endpoint: time to resolution of five main symptoms (runny or stuffy nose, cough, shortness of breath, fever or feeling hot, fatigue)

- **Inclusion criteria**: patients (aged 12–70 years) with mild/moderate symptoms occurring within 5 days, regardless of vaccination status or risk factors for severe disease
- **Exclusion criteria**: patients requiring hospitalization, mechanical ventilation, or oxygen supplementation

Results

Baseline parameters	COVID-19 onset to randomization <72 hours		
	Ensitrelvir 125 mg N=407	Ensitrelvir 250 mg N=398	Placebo N=402
Sex, male, %	**56.0**	**54.3**	**52.5**
Age, mean (SD), years	35.8 (12.7)	35.1 (12.3)	34.9 (12.3)
Vaccination status, %	**91.4**	**91.2**	**91.3**
Virus strain, %			
Delta	0.7	1.0	1.2
Omicron	90.4	88.3	88.5
BA.1	29.0	27.9	26.6
BA.2	**59.5**	**58.3**	**60.2**

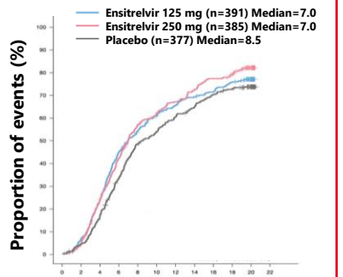
Safety cohort: N=2288
Efficacy cohort: N=1207

- **>50% were male**
- **>90% were vaccinated**
- **Dominant variant: omicron BA.2**

Enrollment period:
- Phase 2a: 09/2021–01/2022
- Phase 2b: 01/2022–02/2022
- Phase 3: 02/2022–07/2022

Ensitrelvir 125 mg and 250 mg significantly reduced the time to resolution vs placebo.

Outcomes	COVID-19 onset to randomization <72 hours		
	Ensitrelvir 125 mg N=407	Ensitrelvir 250 mg N=398	Placebo N=402
Estimator by Kaplan–Meier method (hours)			
Median [95% CI]	**167.9** [144.5; 194.5]	**167.8** [150.6; 183.9]	**204.4** [176.9; 244.5]
Difference vs placebo [95% CI]	**–36.4** [–85.9; 5.0]	**–36.5** [–82.8; –5.2]	-
Generalized Wilcoxon test with stratified Peto–Prentice			
***P* value (two sided)**	**0.0120**	**0.0035**	-



Safety

- Ensitrelvir was well tolerated, and no new safety concerns emerged.
- Main adverse events: ↓ in high-density lipoprotein (HDL), ↑ in triglycerides, ↑ in bilirubin, all of which were temporary.

Number of occurrences (%)[a]	Ensitrelvir 125 mg (N=763)	Ensitrelvir 250 mg (N=759)	Placebo (N=766)
Adverse events	**325 (42.6)**	**395 (52.0)**	**205 (26.8)**
Events leading to death	0 (0)	0 (0)	0 (0)
Serious adverse events	1 (0.1)	0 (0)	3 (0.4)
Adverse events leading to trial discontinuation	6 (0.8)	6 (0.8)	2 (0.3)
Incidence >2% in any of the groups			
Headache	17 (2.2)	26 (3.4)	14 (1.8)
Reduced HDL	222 (29.1)	281 (37.0)	30 (3.9)
Increased blood triglycerides	50 (6.6)	85 (11.2)	33 (4.3)
Increased blood bilirubin	37 (4.8)	59 (7.8)	7 (0.9)
Reduced blood cholesterol	20 (2.6)	30 (4.0)	3 (0.4)
Treatment-related adverse events	**172 (22.5)**	**255 (33.6)**	**67 (8.7)**
Events leading to death	0 (0)	0 (0)	0 (0)
Serious side effects	0 (0)	0 (0)	3 (0.4)
Adverse reactions that led to discontinuation of the study	4 (0.5)	2 (0.3)	1 (0.1)
Incidence >2% in any of the groups			
Reduced HDL	127 (16.6)	185 (24.4)	9 (1.2)
Increased blood triglycerides	17 (2.2)	39 (5.1)	17 (2.2)
Increased blood bilirubin	18 (2.4)	36 (4.7)	4 (0.5)

[a]All patients randomized within 120 hours of COVID-19 onset were included.

Conclusions

- The integrated efficacy results of the Phase 2a, Phase 2b, and Phase 3 randomized clinical trials show that ensitrelvir treatment initiated within 72 hours statistically significantly shortened the time to resolution of the main symptoms of COVID-19 in an outpatient setting.
- Ensitrelvir was well tolerated with mild or moderate adverse events, and no significant differences from placebo were observed.

References

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Conflict of interest

These clinical trials were funded by Shionogi & Co., Ltd., Osaka, Japan. YT, TI, TSo, and TSa are employees of Shionogi & Co. HY, NO, YD, MY, and HM are study medical experts, principal investigators, or coordinating investigators, and members of the Ensitrelvir Advisory Board.

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