E0044

Safety, tolerability, and pharmacokinetics of secutrelvir: single and multiple oral doses, and drug-drug interaction with midazolam

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Introduction and Purpose

- Secutrelvir is a new oral drug candidate to treat COVID-19.
- Secutrelvir is a second-generation 3C-like protease inhibitor designed to:
  - reduce drug–drug interactions (DDI)
  - avoid contraindications in pregnancy
- Objective
  - Evaluate safety, tolerability, and pharmacokinetics (PK) of secutrelvir in healthy volunteers after single and multiple doses in FTIH study
  - Assess DDI on CYP3A substrate (midazolam)
  - Assess relative BA (suspension vs tablet) and food effect

Key findings

- Single and multiple doses of secutrelvir were well tolerated in healthy volunteers.
  - No death, SAEs, and TEAEs leading to discontinuation.
- A linear PK profile within the planned clinical dose range.
- Single oral dose treatment is expected with the long elimination half-life.
- Did not inhibit or induce CYP3A as measured by midazolam PK.
- No clinically relevant food effect.

Single dose part

Method

- Single oral dose of secutrelvir suspension 5 to 600 mg

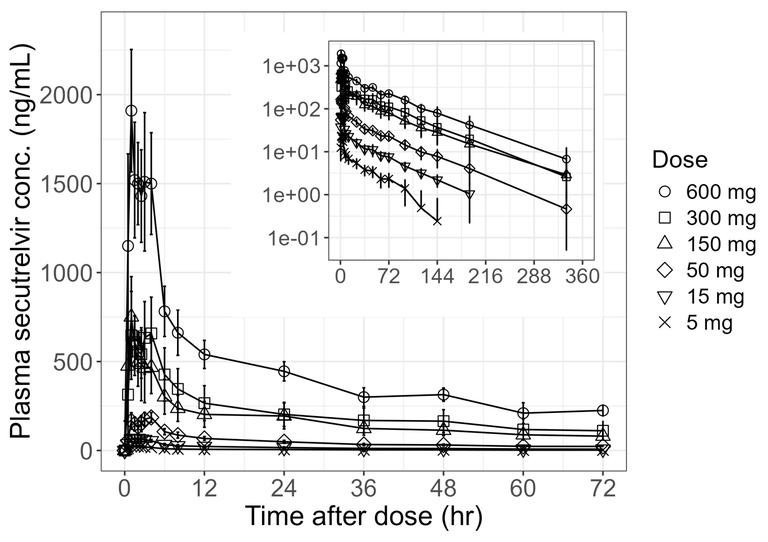


Table.1 PK parameters of secutrelvir after single dose

Parameter	5 mg	15 mg	50 mg	150 mg	300 mg	600 mg
N	6	6	6	6	6	6
C_{max} (ng/mL)	25.1 (20.4)	73.5 (21.6)	202 (16.6)	772 (23.0)	777 (28.6)	1910 (16.1)
T_{max} (hr)[a]	1.75 (1.00-2.00)	1.75 (1.00-4.00)	3.50 (1.00-4.00)	1.00 (0.50-4.00)	2.50 (1.00-4.00)	1.00 (1.00-2.00)
AUC_{0-inf} (ng·hr/mL)	549.9 (24.9)[b]	1666 (17.4)	4979 (17.2)	17160 (29.4)	21100 (50.6)	46660 (18.3)
$t_{1/2,z}$ (hr)	37.3 (31.6)	46.8 (30.2)	49.5 (18.7)	52.3 (29.9)	46.4 (19.3)	48.5 (27.0)
CL/F (L/hr)	9.09 (24.9)[b]	9.00 (17.4)	10.0 (17.2)	8.74 (29.4)	14.2 (50.6)	12.9 (18.3)

Geometric Mean (CV% Geometric Mean).
a Median (range). b N = 5.

Fig.1 PK profile of secutrelvir after single dose



- **Three mild or moderate TEAEs, but not treatment-related.**
- **Secutrelvir exposure increased in a dose-proportional manner including planned clinical doses (120 mg).**
- **Long elimination half-life enough to maintain the target concentration[1] from nonclinical study with a single oral dose treatment.**

Multiple dose/DDI part

Method

- Once-daily multiple oral doses of secutrelvir tablet with loading dose on Day 1/maintenance doses on Days 2 to 14 (40/20 mg or 80/40 mg)
- The effect of secutrelvir on the PK of CYP3A substrate, midazolam (MDZ)

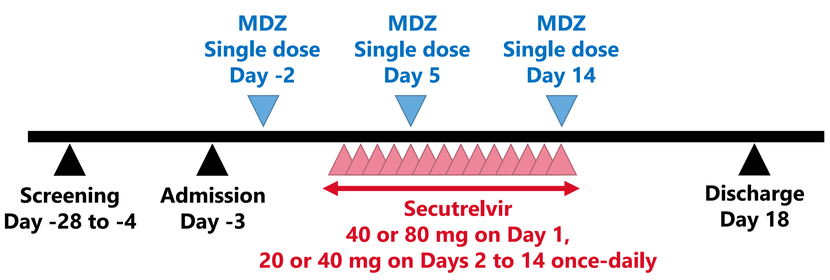
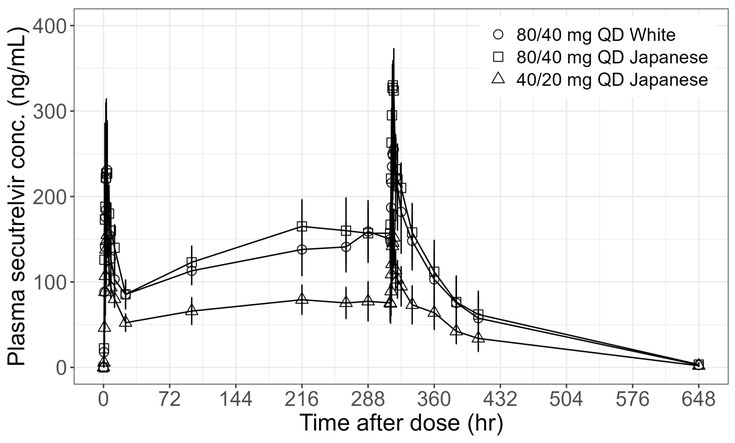


Table.2 PK parameters of secutrelvir after multiple dose

Parameter	40/20 mg QD Japanese		80/40 mg QD Japanese		80/40 mg QD White	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
N	8	8	8	8	8	8
C_{max} (ng/mL)	169 (21/7)	155 (22.0)	270 (20.2)	347 (10.9)	239 (26.3)	270 (20.2)
T_{max} (hr)[a]	3.00 (2.00-4.00)	3.50 (2.50-6.00)	2.75 (1.00-6.00)	2.75 (2.00-4.00)	4.00 (1.50-6.00)	2.75 (2.00-4.00)
$AUC_{0-\tau}$ (ng·hr/mL)	1955 (14.4)	2293 (23.3)	3237 (20.7)	5104 (12.6)	2752 (22.8)	4424 (23.6)
C_{24} (ng/mL)	51.3 (22.1)	70.2 (30.9)	84.2 (18.4)	155 (22.1)	83.7 (21.6)	144 (25.0)
$t_{1/2,z}$ (hr)	NC	52.0 (32.9)	NC	50.2 (38.2)	NC	47.3 (26.8)

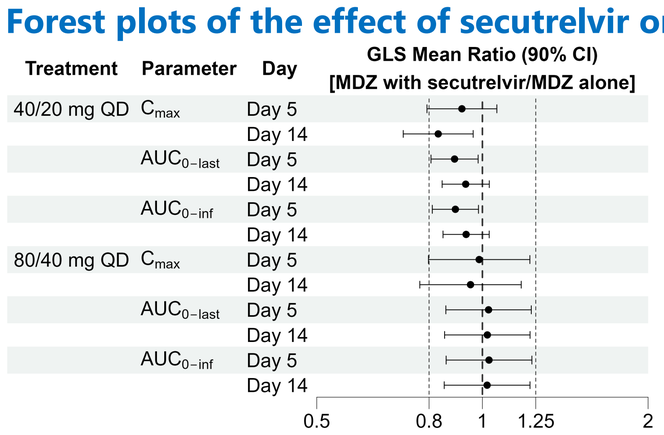
Geometric Mean (CV% Geometric Mean).
NC = Not calculated.
a Median (range).

Fig.2 PK profile of secutrelvir after multiple dose



- **22 mild or moderate TEAEs, but not treatment-related except for ALT increase.**
- **Plasma concentrations after multiple doses of secutrelvir with Phase 2 study dosages well exceeded the target concentration[1].**
- **No notable PK differences between Japanese and White participants.**

Fig.3 Forest plots of the effect of secutrelvir on the PK of midazolam



GLS Mean Ratio = geometric least squares mean ratio
CI = confidence interval

- **Secutrelvir did not alter the PK of midazolam, a CYP3A substrate.**

BA/FE part

Method

- 3-period, 3-sequence cross-over fashion
- Suspension 20 mg vs. one 20-mg tablet in the fasted state
- One 20-mg tablet in the fasted state vs. fed state (high-fat, high-calorie food)

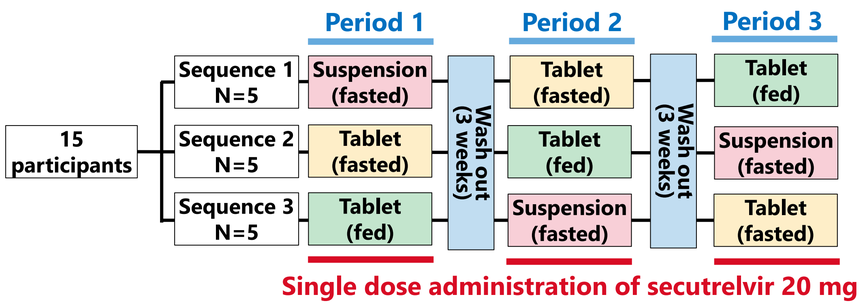
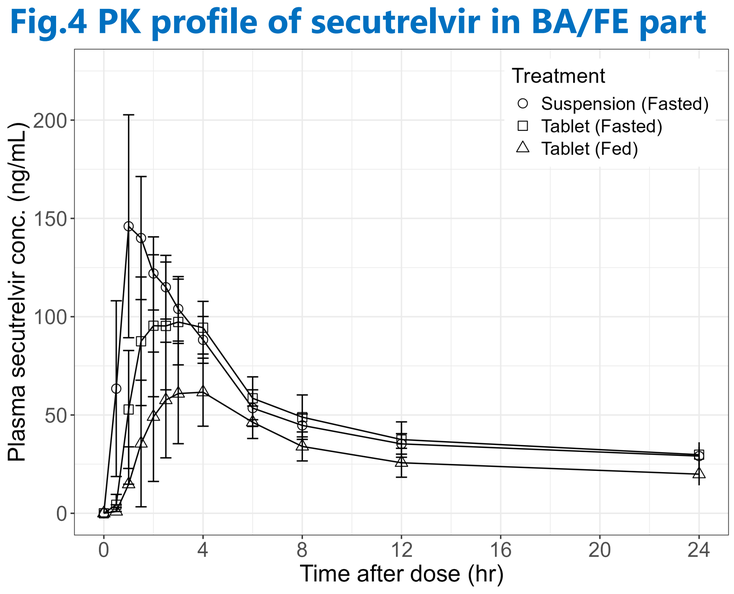


Fig.4 PK profile of secutrelvir in BA/FE part



- **Six mild or moderate TEAEs, but not treatment-related.**
- **The C_{max} was 27% lower for tablet. The AUCs were comparable between suspension and tablet.**
- **The C_{max}, AUC_{0-last}, and AUC_{0-inf} decreased by 42%, 33%, and 30%, respectively, in the fed state.**
- **Secutrelvir can be administered irrespective of meals in Phase 2 or Phase 3 studies.**

Reference

[1] Ueno Y, et al. J. Med. Chem. 2025, 68, 20, 21099–21119.

Conflict of Interest

This study was funded by Shionogi & Co., Ltd. H. Koshimichi, T. Sonoyama, R. Yonemoto, and R. Kubota are employees of Shionogi & Co. Ltd.