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A phase 1 study of safety, tolerability and pharmacokinetics of oral single dose S-033188, a novel anti-influenza agent, in healthy adult male subjects

Akira Kawasaki, MD, PhD[1], Chisako Sato, Mpharm[2] and Toru Ishibashi, PhD[2]

1: Medical Science Department and 2: Clinical Research Department, SHIONOGI & Co., Ltd., Osaka, Japan

Contact Information:
Toru.Ishibashi@Shionogi.Co.JP
No conflicts of interests to declare

Introduction

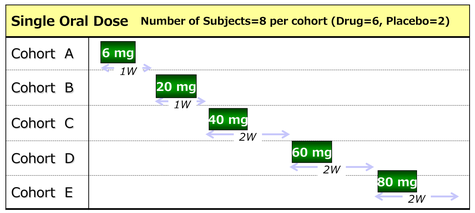
Cap-dependent endonuclease (CEN) activity of the influenza polymerase is essential for the "cap-snatching" process during influenza viral transcription. S-033188 (pro-drug form) is a novel, selective inhibitor of CEN with potent antiviral activity against Type A and Type B influenza virus in vitro and in vivo. The target plasma concentration of S-033447 (active form) at 24 hours post-dosing (C_{24}) based on the non-clinical study was 6.85 ng/mL, which provided 1-log virus reduction compared to that of oseltamivir in the lung of mice infected with influenza B virus*.

Study Objective

The aim of this study is to determine safety, tolerability of single ascending doses of S-033188 and pharmacokinetics of S-033188 and S-033447 in healthy adult male subjects.

Study Design

This was a single-center, placebo-controlled, randomized, double-blind phase 1 study. A total of 40 Japanese healthy adult male subjects were randomized into one of 5 cohorts, and received single oral dose of 6 mg, 20 mg, 40 mg, 60 mg, or 80 mg S-033188 suspension, or placebo in the fasted state.



Methods

Plasma and Urine Concentrations

Plasma and urine concentrations of S-033188 and its active form S-033447 were determined by LC/MS/MS and were summarized and plotted.

Pharmacokinetic (PK) Analysis

The following PK parameters of S-033188 and S-033447 were calculated based on the plasma and urine concentration data with the non-compartmental methods. C_{max} (ng/mL): Maximum plasma concentration. T_{max} (hr): Time to maximum plasma concentration. $AUC_{0\text{-}72}$ (ng·hr/mL): Area under the concentration-time curve from time zero to 72 hours after dosing. $AUC_{0\text{-}inf}$ (ng·hr/mL): Area under the concentration-time curve extrapolated from time zero to infinity. $t_{1/2,z}$ (hr): Terminal elimination half-life. CL/F (L/hr): Apparent total clearance. V_z/F (L): Apparent volume of distribution in the terminal elimination phase. $Feu_{0\text{-}72}$ (%): Fraction of dose excreted in urine. C_{24} (ng/mL): Plasma concentration of S-033447 24 hours post-dose.

Dose Proportionality

Dose proportionality was assessed for C_{max} and $AUC_{0\text{-}inf}$ using the power model. The power model assumed a linear relationship between the ln-transformed parameter and ln-transformed dose.

$$ln(Parameter) = \alpha + \beta \times ln(Dose) + Random\ error$$

Where Parameter is a given PK parameter, α is the intercept, β is the slope, and Random error is a random residual error.

Safety Assessments

Safety assessments included treatment-emergent adverse events (TEAEs), physical examinations, laboratory tests, vital signs, and 12-lead electrocardiograms (ECGs).

Results

Demographics of subjects are shown in Table 1. Demographic characteristics were well balanced, with no notable differences between dose groups. All subjects completed this study.

Table 1: Demographics and Baseline Characteristics

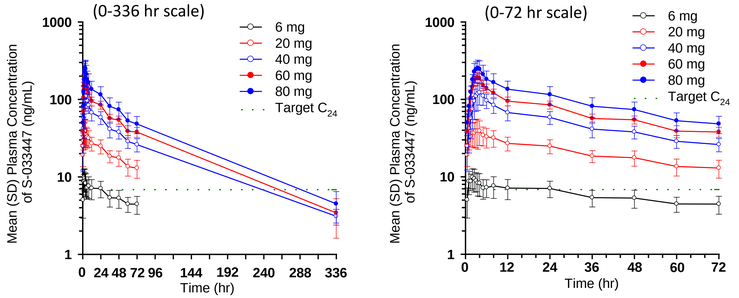
		6 mg N=6	20 mg N=6	40 mg N=6	60 mg N=6	80 mg N=6	Placebo N=10
Age (years)	Mean	23.0	25.2	28.2	26.3	29.0	30.0
	SD	3.3	4.7	4.6	4.2	5.6	7.1
Height (cm)	Mean	174.37	173.12	168.50	172.13	171.15	174.46
	SD	5.97	2.81	3.51	2.22	5.22	3.65
Weight (kg)	Mean	67.80	65.68	59.12	62.97	63.27	67.63
	SD	7.97	6.28	4.60	6.02	7.37	5.51
BMI (kg/m²)	Mean	22.23	21.92	20.82	21.23	21.60	22.20
	SD	1.32	2.04	1.40	1.63	2.41	1.35

Plasma Concentrations

Figure 1 shows mean plasma concentration-time profiles of S-033447 after single oral dose of S-033188 in the fasted state.

- Plasma concentrations of S-033188 were very low (maximum 0.363 ng/mL) and S-033188 was eliminated rapidly from plasma in all subjects [Not shown].
- Plasma concentrations of S-033447 increased as dose of S-033188 increased.
- Mean plasma S-033447 concentration at 24 hours after 6 mg single oral administration exceeded the target C_{24} (6.85 ng/mL) based on the non-clinical study*.

Figure 1: Plasma S-033447 Concentration-Time Profiles after Single Oral Dose of S-033188 in the Fasted State

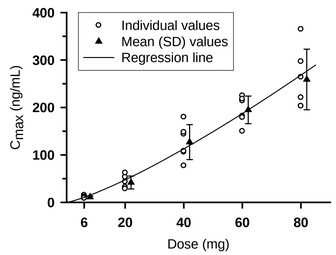


Dose Proportionality

Figure 2 shows the relationship between the S-033447 exposures (C_{max} and $AUC_{0\text{-}inf}$) and Dose.

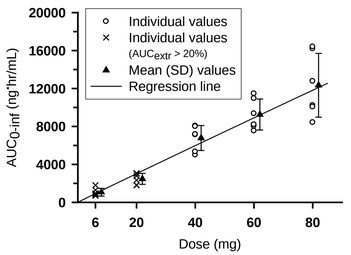
- The S-033447 exposures (C_{max} and $AUC_{0\text{-}inf}$) increased in an almost dose-proportional manner across the dose range from 6 to 80 mg.

Figure 2: Relationship between S-033447 C_{max} (left) and $AUC_{0\text{-}inf}$ (right) and Dose



$$\ln(C_{max}) = 0.114 + 1.25 \times \ln(Dose)$$

[95% Confidence Interval of slope: 1.14-1.35]



$$\ln(AUC_{0-inf}) = 5.07 + 0.983 \times \ln(Dose)$$

[95% Confidence Interval of slope: 0.873-1.09]

PK Analysis

Table 2 shows the pharmacokinetic parameters of S-033447 after single oral dose of S-033188 in the fasted state.

- The C_{max} of S-033447 was attained generally within 3.5 hours post dose.
- The long $t_{1/2,z}$ of S-033447 ranged from 48.9 to 90.9 hours.
- The C_{24} of S-033447 exceeded the target C_{24} after 6 mg oral single dose.
- The renal excretion of S-033447 was minimal.

Table 2: Summary of Pharmacokinetic Parameters of Plasma S-033447 after Single Oral Dose of S-033188 in the Fasted State

Parameters	6 mg N=6	20 mg N=6	40 mg N=6	60 mg N=6	80 mg N=6
C_{max} (ng/mL)	11.0 (22.3)	40.2 (32.5)	123 (31.0)	193 (15.7)	253 (23.9)
T_{max}# (hr)	2.00 (1.00, 2.50)	3.50 (1.50, 4.00)	3.50 (3.50, 5.00)	3.25 (2.50, 4.00)	3.50 (2.50, 4.00)
$AUC_{0\text{-}72}$ (ng·hr/mL)	417.4 (22.1)	1484 (21.5)	3475 (22.5)	5073 (11.8)	6795 (25.5)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	1018 (35.7)	2419 (24.8)	6669 (20.8)	9141 (17.5)	11970 (27.8)
$t_{1/2,z}$ (hr)	90.9 (55.7)	48.9 (30.1)	85.9 (8.2)	75.2 (15.3)	75.9 (11.1)
CL/F (L/hr)	4.99 (35.7)	6.99 (24.8)	5.07 (20.8)	5.55 (17.5)	5.65 (27.8)
V_z/F (L)	655 (33.0)	494 (28.4)	629 (22.3)	603 (10.3)	619 (23.3)
C_{24} (ng/mL)	6.92 (22.1)	24.4 (22.5)	57.6 (20.1)	84.4 (12.7)	112 (27.2)
$Feu_{0\text{-}72}$ (%)	1.7 (14.8)	1.9 (22.8)	2.1 (23.7)	2.1 (9.3)	2.3 (25.7)

Geometric mean (coefficient of variation for geometric mean, %). #: Median (Minimum, Maximum)

Safety Assessment

- There were no deaths, serious TEAEs (SAEs), or TEAEs leading to withdrawal of study drug during the study.
- One subject receiving 6 mg S-033188 experienced headache that was considered by the investigator to be related to the study drug. The event was mild and resolved without any treatment.
- One subject receiving 40 mg S-033188 experienced abnormal elevation of ALT on Day 6 (45 IU/L) and Day 8 (45 IU/L).

Conclusion

- **Single oral doses of S-033188 at the doses of 6-80 mg were generally safe and well tolerated in healthy adult male subjects.**
- **Single oral dose of S-033188 showed linear pharmacokinetics of the active drug form S-033447, with long elimination half-life.**
- **Single oral dose of 6 mg S-033188 achieved mean plasma concentration at 24 hours (C_{24}) that exceeded the target C_{24} estimated from non-clinical study*.**

** Reference: T.Uehara et al. S-033188, a Small Molecule Inhibitor of Cap-dependent Endonuclease of Influenza A and B Virus, Leads to Rapid and Profound Viral Load Reduction. OPTIONS IX. Chicago, IL, August 24-28, 2016.*