In the linear model, the adjusted coefficient of determination (COD) of S-033447, an active form of orally available prodrug S-033188, is a novel small molecule inhibitor of influenza virus cap-dependent endonuclease. In this study, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of S-033447 in mice infected with influenza A virus was investigated.

**Study Objective**

The objective of this study was to evaluate the relationship between pharmacokinetic (PK) parameters and pharmacodynamic (PD) effect of S-033447 in mice infected with influenza A virus.

**Methods**

Subcutaneous administration of S-033447 in mice efficacy model: Female BALB/c mice were intramuscularly inoculated with A/WSN/33 strain at 100 tissue culture infectious dose 50 (TCID₅₀)/mouse. Five days after infection, mice were subcutaneously treated with S-033447 at the dose range of 0.0625 to 8 mg/kg (QD, BID, or four times a day (QID), for 1 day).

Viral titers in the lung at 24 hours after the first administration (PD parameter) were measured in Madin-Darby canine kidney (MDCK) cells. The infected mice described above were subcutaneously treated with S-033447 (QD) and the blood was taken at each time after dosing. Plasma concentration of S-033447 were determined by LC/MS/MS.

The sigmoid maximum effect (Eₘₐₓ) model and the linear model were applied to PD and each PK parameter of S-033447: AUC₂₄ₐ₀, Cₘₚ, β⁰, (βmax, (EC₅₀, EC₇₅₀), and COD (at the time point of the dosage interval τ) after the first dosing).

Oral administration of S-033188 in mice efficacy model: Female BALB/c mice were intramuscularly inoculated with A/WSN/33 or B/Hong Kong/5/72 strain at 100 or 400 TCID₅₀/mouse. Five days after infection, mice were orally treated with S-033188 BID for 1 day. Viral titers in the lung at 24 hours after the first administration were measured in MDCK cells. The A/WSN/33 strain infected mice described above were orally treated with S-033188 and the blood was taken at each time after dosing. Plasma concentration of S-033447 were determined by LC/MS/MS.

**Results**

- In the linear model, the adjusted coefficient of determination (COD) of S-0₃₃₄₄₇ was larger than that of the other PK parameters. In the sigmoid Eₘₐₓ model, the adjusted COD of Cₘₚ and EC₅₀ were larger than those of the other PK parameters.

- S-033188 at 1.5 or 15 mg/kg BID reached approx. 1-log viral titer reduction compared to Oseltamivir phosphate 5 mg/kg BID (clinically equivalent dose) against A/WSN/33155 or B/Hong Kong/7277 mice infected.

**Conclusion**

- In order to achieve rapid reduction to more than one-log viral titer compared to oseltamivir against influenza A and B virus, target plasma Cₘₚ value of S-0₃₃₄₄₇ was set to higher than 6.85 ng/mL, which was obtained from 15 mg/kg BID for oral treatment of S-033188 in mice model.

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**Table 1:** Results from the regression models by PK parameter

**Table 2:** Plasma concentrations of S-033447 after oral administration of S-033188

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**Figure 1:** Study design for PK/PD analysis

**Figure 2:** Plasma concentrations of S-033447 after single subcutaneous administration of S-033447

**Figure 3:** Viral titers in the lungs of infected mice after subcutaneous administration of S-033447

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