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Pharmacokinetic and pharmacodynamic analysis of S-033188/S-033447, a novel inhibitor of influenza virus Cap-dependent endonuclease, in mice infected with influenza A virus

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Background: 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) profile of S-033447 in mice infected with influenza A virus was investigated.

Material/methods: Female BALB/c mice were intranasally inoculated with A/WSN/33 strain at 100 tissue culture infectious dose 50 ($TCID_{50}$)/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, 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 sigmoid maximum effect (E_{max}) model and the linear model were applied to PD and each PK parameter of S-033447: $AUC_{0\text{-}24hr}$, C_{max}, C_{24hr}, and C_{τ} (plasma concentration at the time point of the dosage interval ($_{\tau}$) after the first dosing).

Results: In the linear model, the adjusted coefficient of determination (COD) of C_{τ} was larger than that of the other PK parameters (Table 1). In the sigmoid E_{max} model, the adjusted COD of C_{τ} and C_{24hr} were larger than those of the other PK parameters.

Conclusions: C_{τ} was the best PK parameter predicting viral load at 24 hours after the first administration of S-033447. In order to achieve the rapid reduction to more than one-tenth viral load compared to oseltamivir against influenza A and B virus, the nonclinical target plasma C_{τ} 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.

Table 1 Coefficient of determination (COD) of PK parameters in the linear Model

PK Parameter	Model parameter	Estimate	SE	P value	COD [adjusted COD]
AUC_{0-24}	E_0	5.705	0.326	<0.0001	0.399
(ng·hr/mL)	β	0.400	0.052	<0.0001	[0.392]
C_{max}	E_0	4.542	0.248	<0.0001	0.249
(ng/mL)	β	0.335	0.062	<0.0001	[0.241]
C_{24}	E_0	3.624	0.066	<0.0001	0.527
(ng/mL)	β	0.303	0.031	<0.0001	[0.522]
C_{τ}	E_0	3.603	0.064	<0.0001	0.532
(ng/mL)	β	0.318	0.032	<0.0001	[0.527]