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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no conflicts of interest to declare

Introduction

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.

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 A/WSN/33 strain of influenza virus.

Methods

Subcutaneous administration of S-033447 in mice efficacy model: 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 (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 (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 (τ) after the first dosing).

Oral administration of S-033188 in mice efficacy model: Female BALB/c mice were intranasally inoculated with A/WSN/33 or B/Hong Kong/5/72 strain at 100 or 400 $TCID_{50}$/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.

Figure 1: Study design for PK/PD analysis

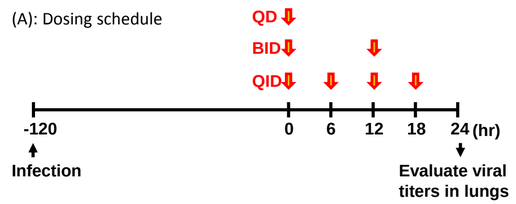
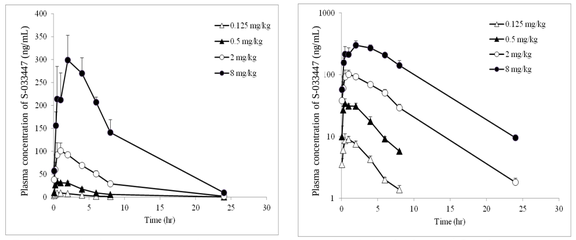


Figure 2: Plasma concentrations of S-033447 after single subcutaneous administration of S-033447

(A): Normal plot (B): Semi-log plot



Each symbol represents the mean and standard deviation of 3 mice.
When the error bar was not seen, the error was smaller than the symbol.

(C): Image of PK parameters

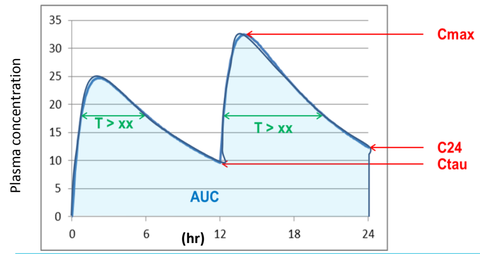


Figure 3: Virus titers in the lungs of infected mice after subcutaneous administration of S-033447

Viral titers ($TCID_{50}$/mL) in the lung at 24 hours after the first administration were measured in MDCK cells. Control substance (Oseltamivir phosphate: OTV) was administrated orally at 5mg/kg BID for 1 day.

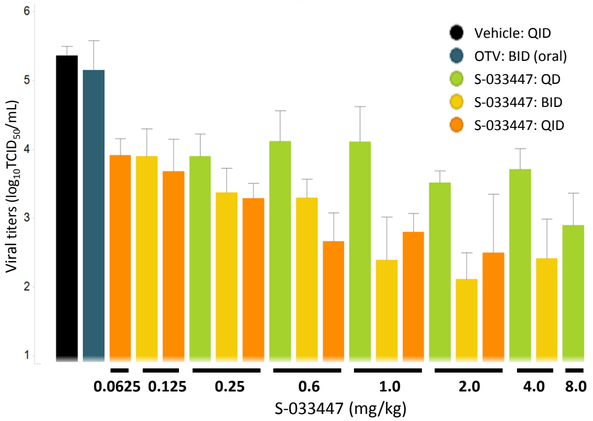


Table 1: Results from the regression models by PK parameter

(A): the linear model

$$y = E_0 - \beta x$$

PK Parameter	Model parameter	Estimate	SE	95% confidential interval	P value	COD [adjusted COD]
$AUC_{0\text{-}24}$ (ng·hr/mL)	E_0	5.705	0.326	(5.056, 6.354)	<0.0001	0.399 [0.392]
	β	0.400	0.052	(0.296, 0.504)	<0.0001	
C_{max} (ng/mL)	E_0	4.542	0.248	(4.050, 5.034)	<0.0001	0.249 [0.241]
	β	0.335	0.062	(0.212, 0.458)	<0.0001	
C_{24} (ng/mL)	E_0	3.624	0.066	(3.493, 3.756)	<0.0001	0.527 [0.522]
	β	0.303	0.031	(0.242, 0.364)	<0.0001	
C_τ (ng/mL)	E_0	3.603	0.064	(3.475, 3.731)	<0.0001	**0.532 [0.527]**
	β	0.318	0.032	(0.255, 0.381)	<0.0001	
$T_{>2}$ (hr)	E_0	5.141	0.297	(4.550, 5.732)	<0.0001	0.324 [0.317]
	β	0.090	0.014	(0.062, 0.117)	<0.0001	
$T_{>10}$ (hr)	E_0	4.095	0.103	(3.890, 4.301)	<0.0001	0.513 [0.508]
	β	0.060	0.006	(0.048, 0.072)	<0.0001	
$T_{>50}$ (hr)	E_0	3.569	0.083	(3.403, 3.734)	<0.0001	0.303 [0.295]
	β	0.055	0.009	(0.037, 0.072)	<0.0001	

(B): the sigmoid Emax model

$$y = E_0 - \frac{E_{max} \times x^\gamma}{EC_{50}^\gamma + x^\gamma}$$

PK Parameter	Model parameter	Estimate	SE	95% confidential interval	P value	COD [adjusted COD]
$AUC_{0\text{-}24}$ (ng·hr/mL)	E_0	3.821	0.116	(3.590, 4.052)	<0.0001	0.415 [0.395]
	E_{max}	1.091	0.170	(0.752, 1.429)	<0.0001	
	EC_{50}	431.596	81.757	(269.068, 594.124)	<0.0001	
	γ	4.170	2.291	(-0.385, 8.725)	0.0722	
C_{max} (ng/mL)	E_0	3.806	0.208	(3.391, 4.220)	<0.0001	0.261 [0.236]
	E_{max}	1.022	0.333	(0.360, 1.683)	0.0029	
	EC_{50}	42.528	14.034	(14.629, 70.427)	0.0032	
	γ	2.421	1.972	(-1.500, 6.342)	0.2230	
C_{24} (ng/mL)	E_0	3.928	0.116	(3.697, 4.159)	<0.0001	**0.595 [0.581]**
	E_{max}	1.499	0.206	(1.090, 1.908)	<0.0001	
	EC_{50}	4.767	1.047	(2.687, 6.848)	<0.0001	
	γ	1.843	0.649	(0.554, 3.133)	0.0056	
C_τ (ng/mL)	E_0	3.958	0.126	(3.707, 4.210)	<0.0001	**0.595 [0.581]**
	E_{max}	1.554	0.233	(1.091, 2.016)	<0.0001	
	EC_{50}	4.108	0.961	(2.199, 6.018)	<0.0001	
	γ	1.697	0.604	(0.498, 2.897)	0.0061	
$T_{>50}$ (hr)	E_0	3.588	0.094	(3.403, 3.774)	<0.0001	0.309 [0.285]
	E_{max}	1.913	2.859	(-3.770, 7.596)	0.5051	
	EC_{50}	16.534	38.174	(-59.353, 92.421)	0.6660	
	γ	1.324	1.438	(-1.534, 4.183)	0.3597	

Abbreviation: SE, standard error; COD, coefficient of determination; adjusted COD, coefficient of determination adjusted for degrees of freedom

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

Time (hr)	Plasma concentration (ng/mL)				
	0.5 mg/kg	1.5 mg/kg	5 mg/kg	15 mg/kg	50 mg/kg
0.5	4.84±1.75	12.9±1.7	45.7±24.5	175±37	216±57
1	5.05±2.13	14.3±5.8	44.6±10.3	139±45	249±40
2	3.75±0.80	8.38±3.17	42.7±8.1	104±14	284±26
4	2.08±0.66	5.72±0.60	25.7±1.7	70.4±12.3	217±92
6	1.60±0.60	4.91±0.85	15.7±2.4	41.0±9.3	102±20
8	1.12±0.77	3.35±0.64	11.9±2.4	24.0±9.4	54.7±11.7
10	0.299±0.517	1.95±1.10	5.89±3.15	11.1±4.8	43.6±18.4
12	BLQ	0.967±0.139	3.00±0.84	**6.85±0.77**	25.2±14.5
24 [a]	0.438±0.380	2.31±0.58	5.02±0.13	9.03±6.48	14.3±7.9

BLQ, below quantification limit (< 0.005 ng/mL), [a] BID administration

Table 3: Virus titers in the lungs of A/WSN/33 or B/Hong Kong/5/72 infected mice 24 hours after oral administration of S-033188

Article	Dose (mg/kg)	A/WSN/33	B/Hong Kong/5/72
		Log_{10} $TCID_{50}$/mL ± S.D.	
Vehicle	–	5.10 ± 0.41	3.92 ± 0.35
S-033188	0.5	4.36 ± 0.22	3.74 ± 0.50
	1.5	**3.57 ± 0.36**	3.42 ± 0.37
	5	2.95 ± 0.58	2.87 ± 0.47
	15	1.93 ± 0.41	**2.59 ± 0.41**
	50	1.71 ± 0.31	2.30 ± 0.30
Oseltamivir phosphate	5	**4.56 ± 0.38**	**3.56 ± 0.30**

Results

- In the linear model, the adjusted coefficient of determination (COD) of C_τ was larger than that of the other PK parameters. In the sigmoid E_{max} model, the adjusted COD of C_τ and C_{24hr} 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/3315 or B/Hong Kong/5/72 infected mice.

Conclusion

- C_τ was the best PK parameter predicting viral titer at 24 hours after the first subcutaneous administration of S-033447 in mice model.
- In order to achieve rapid reduction to more than one-tenth viral titer compared to oseltamivir against influenza A and B virus, 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.