Effects of S-033188, a cap-dependent endonuclease inhibitor, on influenza symptoms and viral titer: Results from a phase 2, randomized, double-blind, placebo-controlled study in otherwise healthy adults with seasonal influenza

Keiko Kawaguchi[1] , Takeki Uehara[1] , Chisako Sato[1] , Nobuo Hirotsu[2] , Tadashi Ishida[3] , Akira Watanabe[4]

1: Shionogi & Co., Ltd., Japan; 2: Hirotsu Medical Clinic; 3: Department of Respiratory Medicine, Kurashiki Central Hospital;

4: Division of Anti-Infective Agents, Institute of Development, Aging and Cancer, Tohoku University

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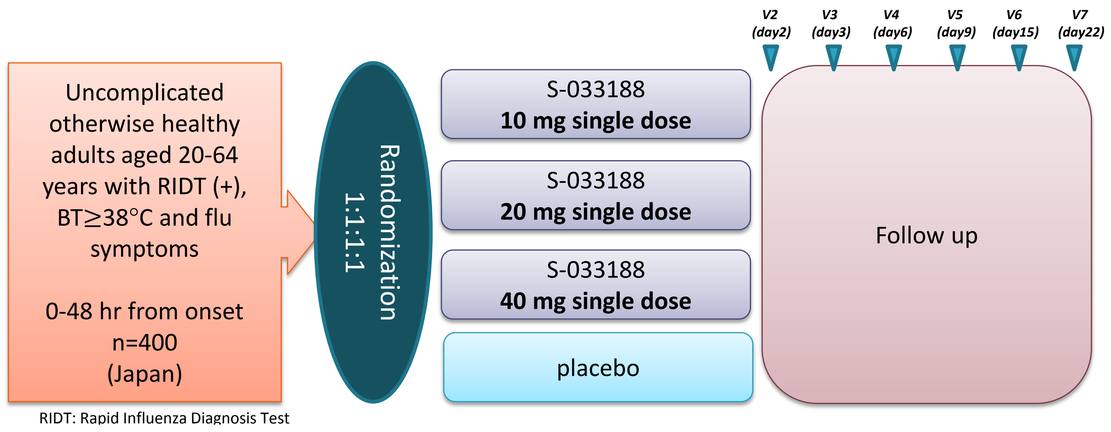
Introduction

Cap-dependent endonuclease (CEN) is located in the PA subunit of influenza virus polymerase and mediates the “cap-snatching” process during initiation of viral mRNA biosynthesis. S-033188 is a potent, selective, small molecule inhibitor of CEN. Here we report the results from a phase 2 proof-of-concept study demonstrating the effects of S-033188 on influenza symptoms and viral titer.

Methods

Key eligibility criteria included 20-65 years old, positive rapid influenza test, fever (axillary temperature ≥ 38.0°C), ≥ 1 general symptom and ≥ 1 respiratory symptom (moderate to severe), and ≤ 48 hours after symptom onset.
Patients were randomized 1:1:1:1 to receive a single oral dose of 10, 20, 40 mg of S-033188 or placebo. The primary efficacy endpoint was time to alleviation of seven influenza symptoms (TTAS). Viral titers were determined from nasal/throat swabs collected pre-dose and at various time points post-dose. Safety assessment included treatment-emergent adverse events (TEAE), vital signs, ECGs and clinical laboratory tests.

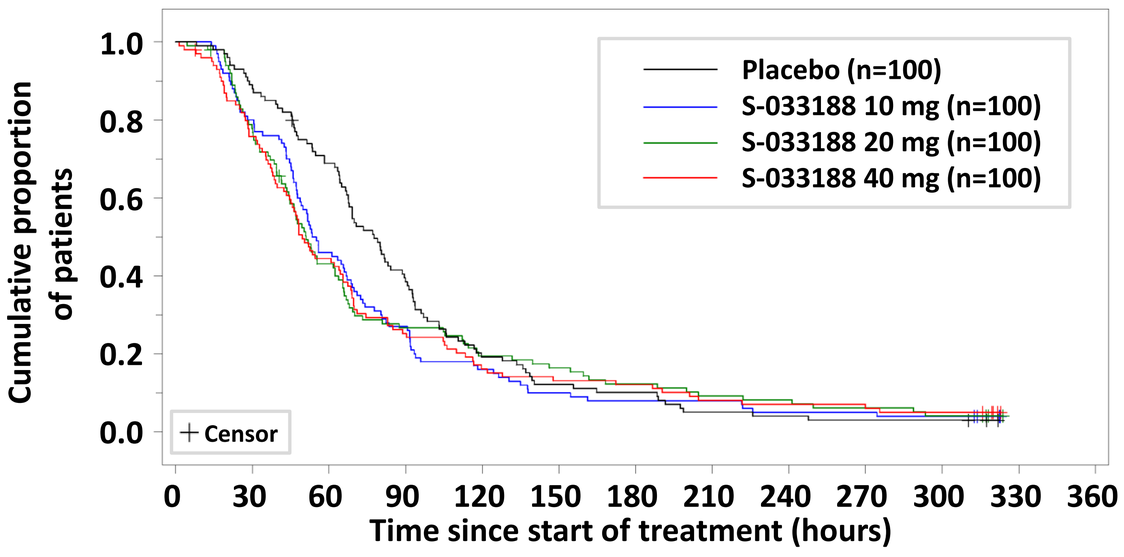


RIDT: Rapid Influenza Diagnosis Test

Results

Primary analysis: Time to alleviation of symptoms (TTAS)

The median TTAS was 77.7 hours (95% CI 67.6, 88.7) in the placebo group, 54.2 hours (95% CI 47.7, 66.8) in the 10 mg group, 51.0 hours (95% CI 44.5, 62.4) in the 20 mg group and 49.5 hours (95% CI 44.5, 64.4) in the 40 mg group (two sided p = 0.0085, 0.0182 and 0.0046 for 10, 20 and 40 mg vs placebo, respectively, stratified generalized Wilcoxon test).



The alleviation of influenza symptoms was defined as the time when all of 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feeling feverishness or having chills, aches or pains of the muscle or joints, and fatigue) were assessed by the patient as none or mild, which lasted for at least 21.5 hours.

Exploratory analysis : Percentage of patients alleviated clinically or virologically at 24 or 48 hours

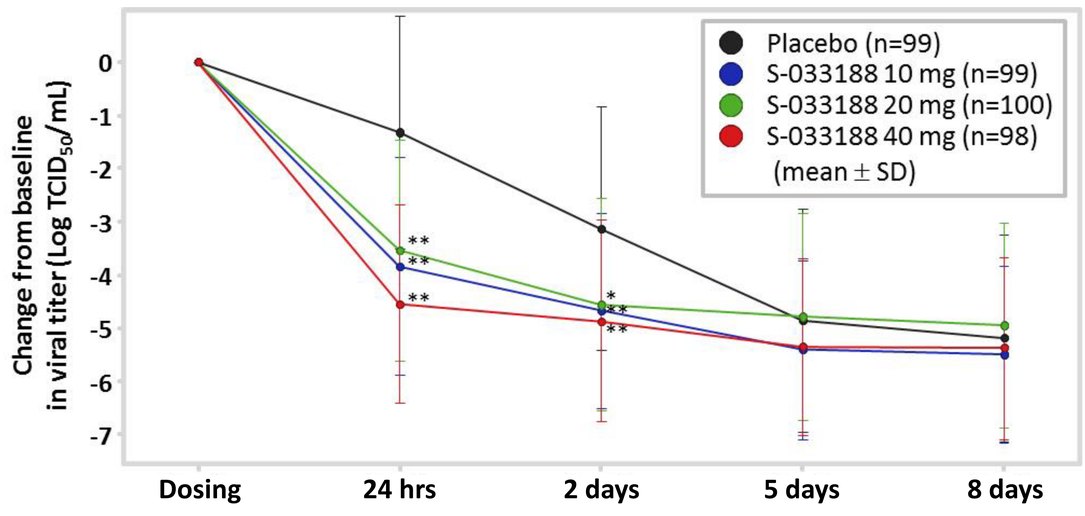
At 24 and 48 hours after treatment, the percentage of patients who had alleviation of all influenza symptoms was 7.0% and 26.0% in the placebo group, 15.0% and 40.0% in the 10 mg group, 15.0% and 48.0% in the 20 mg group, and 17.0% and 46.0% in the 40 mg group, respectively. At 24 and 48 hours after treatment, the percentage of patients who had positive influenza virus titer was 93.9% and 81.5% in the placebo group, 86.9% and 41.8% in the 10 mg group, 72.0% and 37.1% in the 20 mg group, and 51.0% and 29.0% in the 40 mg group, respectively.

Endpoint	Time after treatment	Placebo	S-033188		
			10 mg	20 mg	40 mg
% of patients who had alleviation of all influenza symptoms	24 hours	7.0% (7/100)	15.0% (15/100)	15.0% (15/100)	17.0%* (17/100)
	48 hours	26.0% (26/100)	40.0%* (40/100)	48.0%* (48/100)	46.0%* (46/100)
% of patients who had positive influenza virus titer	24 hours	93.9% (92/98)	86.9% (86/99)	72.0%** (72/100)	51.0%** (49/96)
	48 hours	81.5% (53/65)	41.8%** (28/67)	37.1%** (26/70)	29.0%** (20/69)

** Two sided p<0.0001, *p<0.05 vs placebo (Mantel-Haenszel test)
Stratified factors: smoking habit, composite symptom scores at baseline.
Subset of patients who were positive for influenza virus titer at baseline.

Secondary analysis: Change from baseline in viral titer

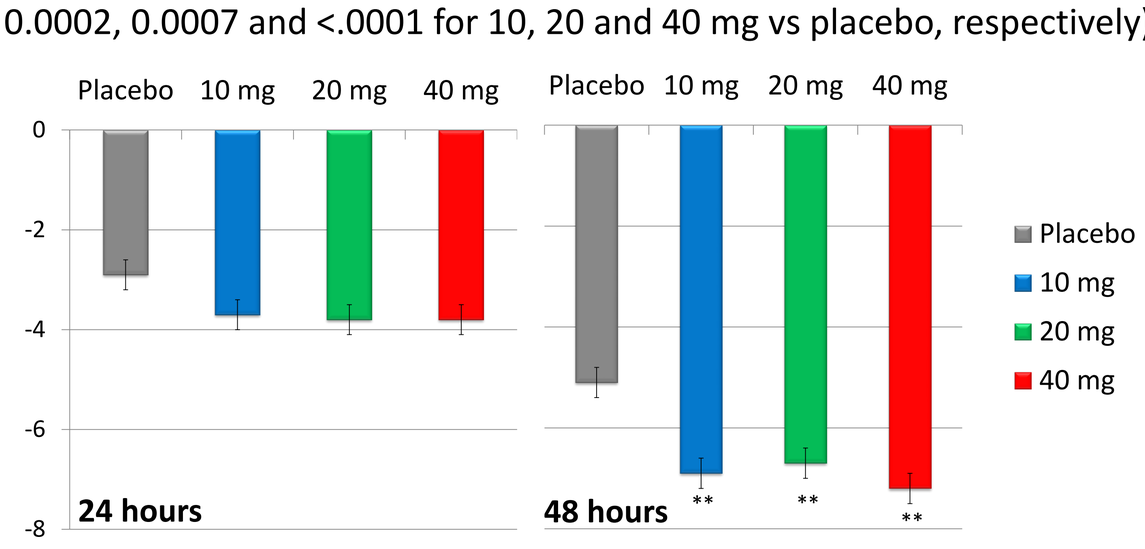
Statistically significant differences were found in the change of virus titer from baseline on 24 hours and 48 hours (2 days) after treatment and 3 in all dose compared to the placebo.



** Two sided p<0.0001, *p<0.05 vs placebo (van Elteren test, covariates: smoking habit, composite symptom scores at baseline)
Viral titer in clinical specimens was measured in MDCK-SIAT1 cells.

Exploratory analysis: Least squares mean change from baseline to 24 or 48 hours after treatment in composite symptom score

At 24 and 48 hours after treatment, the least squares mean change from baseline in composite symptom score was -2.9 and -5.1 in the placebo group, -3.7 and -6.9 in the 10 mg group, -3.8 and -6.7 in the 20 mg group, -3.8 and -7.2 in the 40 mg group. Statistically significant differences were found at 48 hours in all dose compared to the placebo (two sided p = 0.0002, 0.0007 and <.0001 for 10, 20 and 40 mg vs placebo, respectively).



** Two sided p<0.0001 vs placebo (ANCOVA, covariates: smoking habit, composite symptom scores at baseline)
Composite symptom score was defined as the change from baseline in a total of the above 7 influenza symptom scores. “None,” “mild,” “moderate,” and “severe” were scored as 0, 1, 2 and 3, respectively.

Conclusion

S-033188 was effective in alleviating influenza symptoms, and led to rapid and profound clearing of influenza virus titer in otherwise healthy patients with seasonal influenza.