

One Day Oral Dosing of S-033188, a Novel Inhibitor of Influenza Virus Cap-dependent Endonuclease, Exhibited Significant Reduction of Viral Titer and Prolonged Survival in Mice Infected with Influenza B Virus.

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Introduction

S-033447, an active form of orally available prodrug S-033188, is a novel small molecule inhibitor of cap-dependent endonuclease (CEN) of influenza A and B virus. CEN is an enzyme that is unique to influenza virus and essential for transcription and replication and, therefore, S-033188 represents a novel anti-influenza drug against a promising target [1, 2, 3]. We previously demonstrated effectiveness of S-033188 against influenza A virus in nonclinical pharmacology models [1]. In this study, we evaluated the efficacy of 1 day oral dosing of S-033188 in mice infected with influenza B virus.

Study Objective

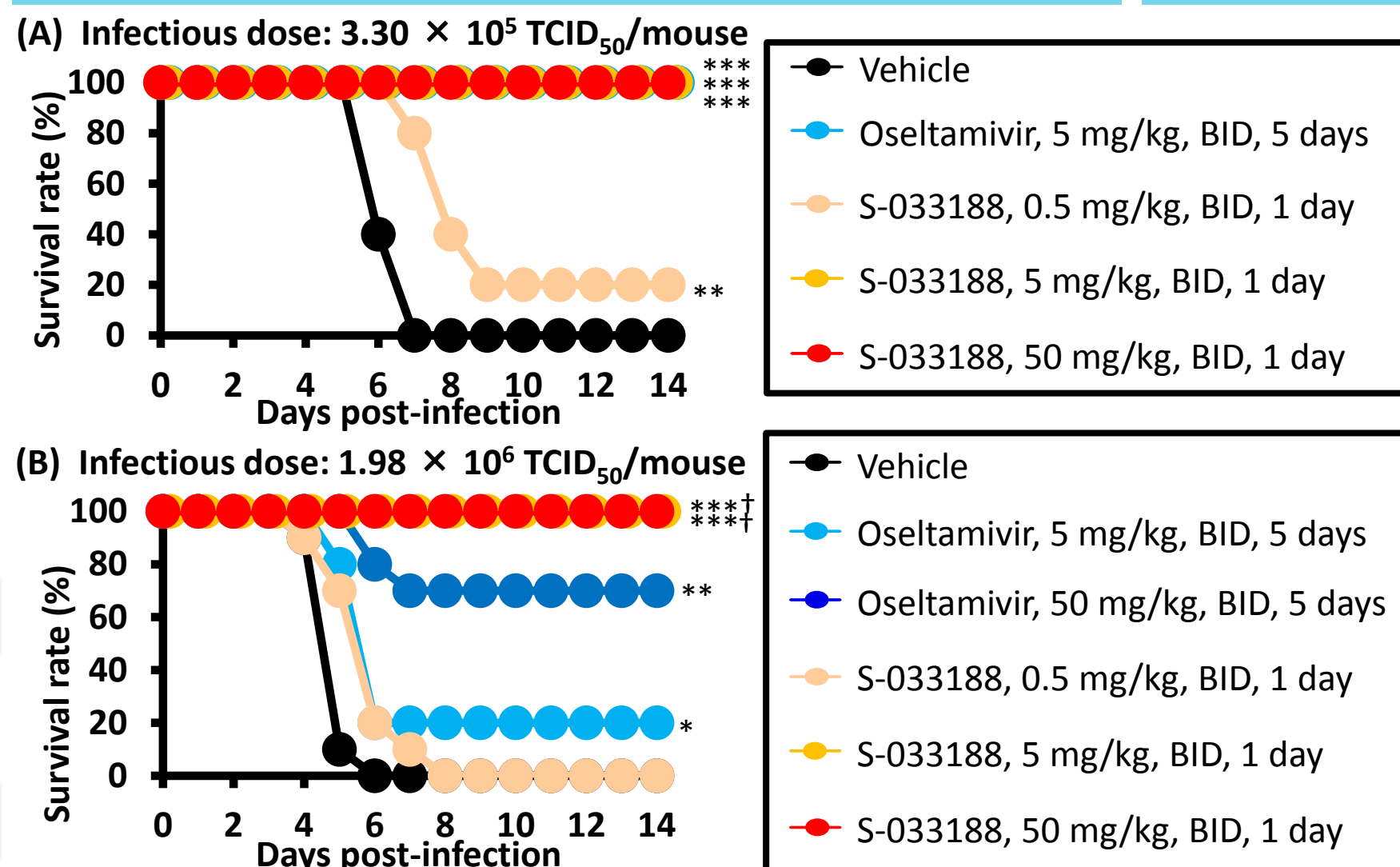
To evaluate the protective effect of S-033188 against lethal infection with influenza B virus (B/Hong Kong/5/72 strain) in mice.

Study Design

Study 1: Female BALB/c mice were infected intranasally with B/Hong Kong/5/72 strain (mouse-adapted) at 3.30×10^5 or 1.98×10^6 tissue culture infectious dose 50 (TCID₅₀)/mouse. Immediately after infection, the mice were orally administered twice a day with S-033188 (0.5, 5, or 50 mg/kg) or vehicle (0.5 w/v% MC) for 1 day, or oseltamivir (5 or 50 mg/kg) for 5 days. Mice were examined daily for death and body weights through 14 days. Mice were euthanized and regarded as dead if their body weights were lower than 70% of the initial body weights according to humane endpoints.

Study 2: To examine inhibitory effect of S-033188 on replication of virus in this lethal model, B/Hong Kong/5/72 strain (mouse-adapted)-infected mice were orally administered twice a day with S-033188, oseltamivir or vehicle for 1 day and then virus titers in lungs were measured 1 day after the administration.

Figure 1. Effect of S-033188 on mortality in mice infected with B/Hong Kong/5/72 strain (mouse-adapted) (Study 1)



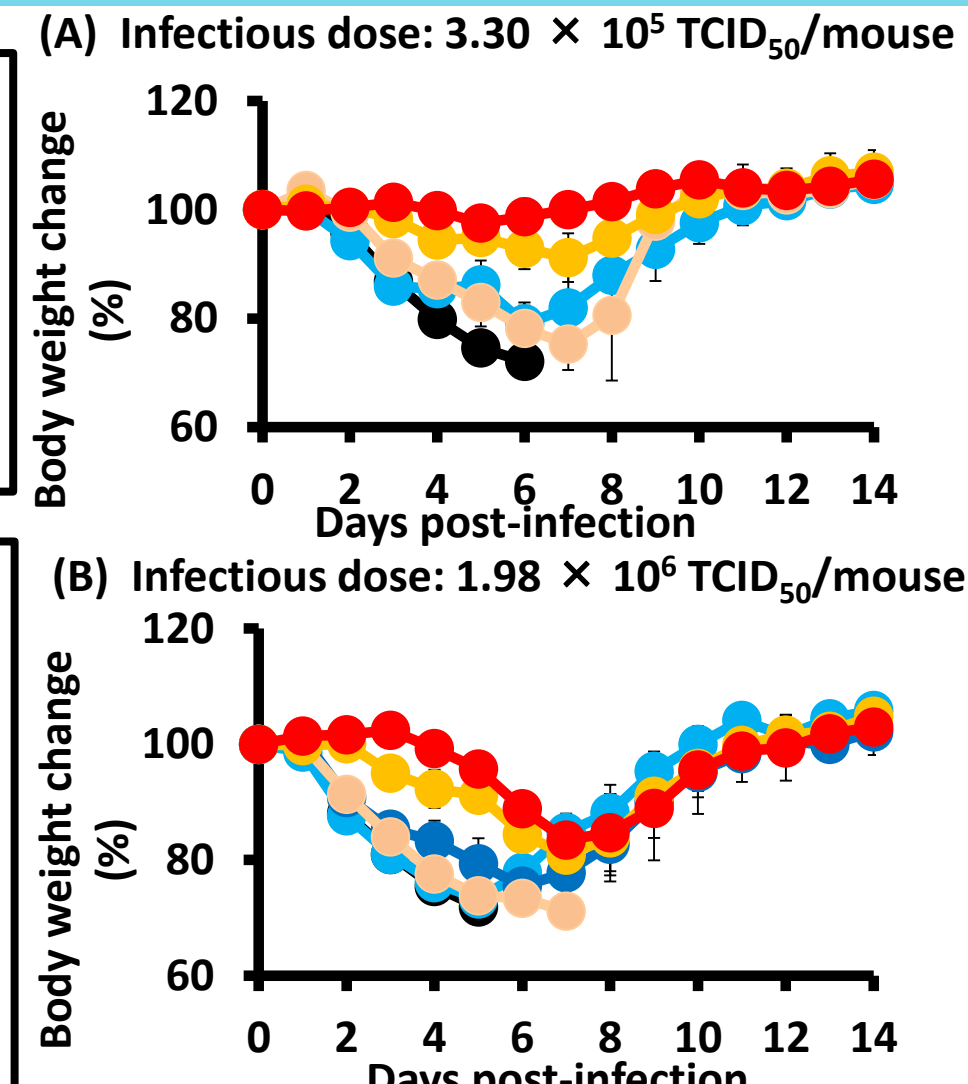
* N=10; P<0.05 vs vehicle, ** P<0.001 vs vehicle, *** P<0.0001 vs vehicle, † P<0.0005 vs Oseltamivir 5 mg/kg (Log-rank test)

Results

Study 1: Administration with 5 or 50 mg/kg of S-033188 (BID for 1 day) completely eliminated mortality observed in the vehicle group due to virus infection at the both infectious doses. In the group administered with 5 mg/kg (clinically-equivalent dose [4]) of oseltamivir (BID for 5 days), all mice survived when infected with virus at the infectious dose of 3.30×10^5 TCID₅₀/mouse, but only 20% of mice survived when infected with virus at the infectious dose of 1.98×10^6 TCID₅₀/mouse. As a result, at the infectious dose of 1.98×10^6 TCID₅₀/mouse, 5 or 50 mg/kg of S-033188 treatment (BID for 1 day) significantly prolonged survival time as compared with 5 mg/kg of oseltamivir treatment (BID for 5 days). S-033188 (5 and 50 mg/kg, BID for 1 day) also suppressed body weight loss. In contrast, 5 or 50 mg/kg of oseltamivir (BID for 5 days) had little or weak effect on body weight in these conditions as compared to S-033188.

Study 2: Virus titers for S-033188-treated groups (5 or 50 mg/kg) were significantly lower than those in vehicle-treated group at the both infectious doses. In these conditions, there were significantly less virus titers for S-033188-treated groups (5 or 50 mg/kg) than 5 or 50 mg/kg of oseltamivir.

Figure 2. Effect of S-033188 on body weight loss due to infection with B/Hong Kong/5/72 strain (mouse-adapted) in mice (Study 1)



N=10; Values are mean body weight change ± SD from the living mice at each day.

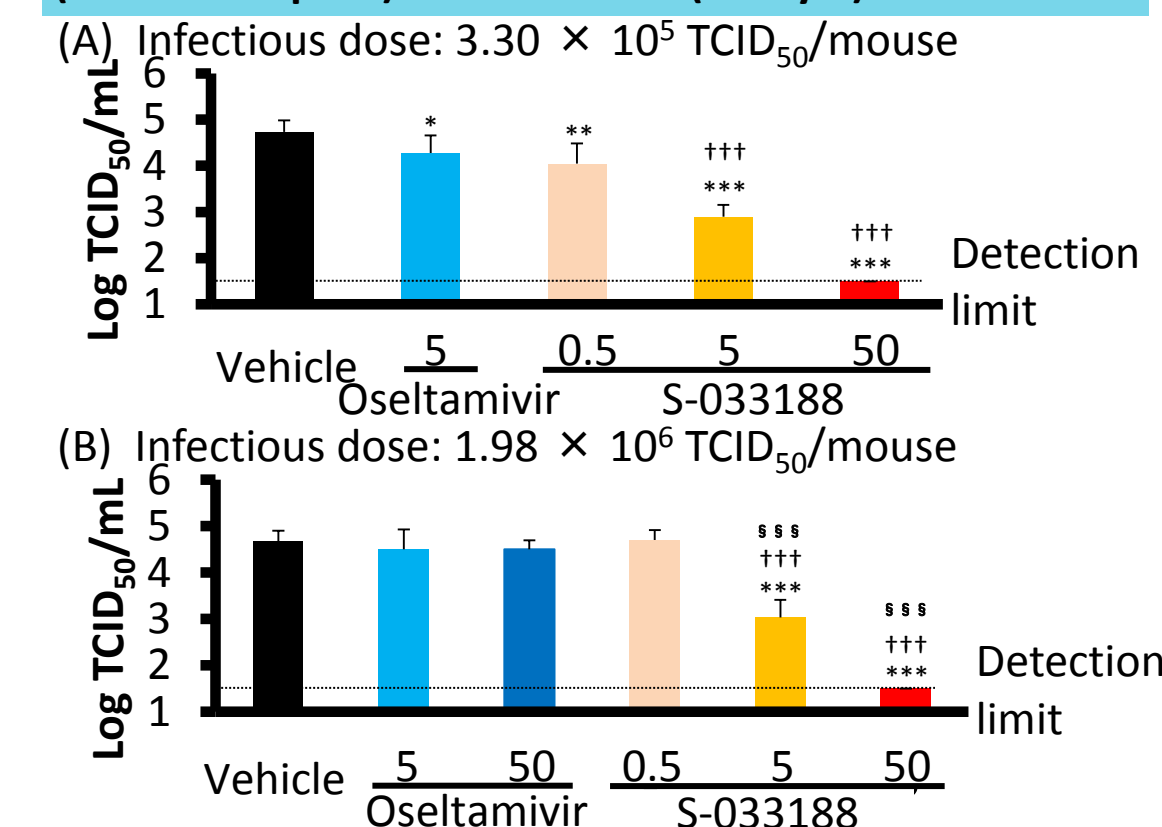
Conclusion

- One-day dosing of S-033188 (5 or 50 mg/kg, BID) completely eliminated mortality accompanied by significant prolongation of survival time and prevention from body weight loss. Furthermore, the effect was more pronounced than that of 5-day treatment with oseltamivir 5 mg/kg BID (the equivalent of oseltamivir clinical dose in human).
- One-day dosing of S-033188 (5 or 50 mg/kg, BID) strongly and rapidly reduced the virus titers of B/Hong Kong/5/72, and these effects were more pronounced as

References

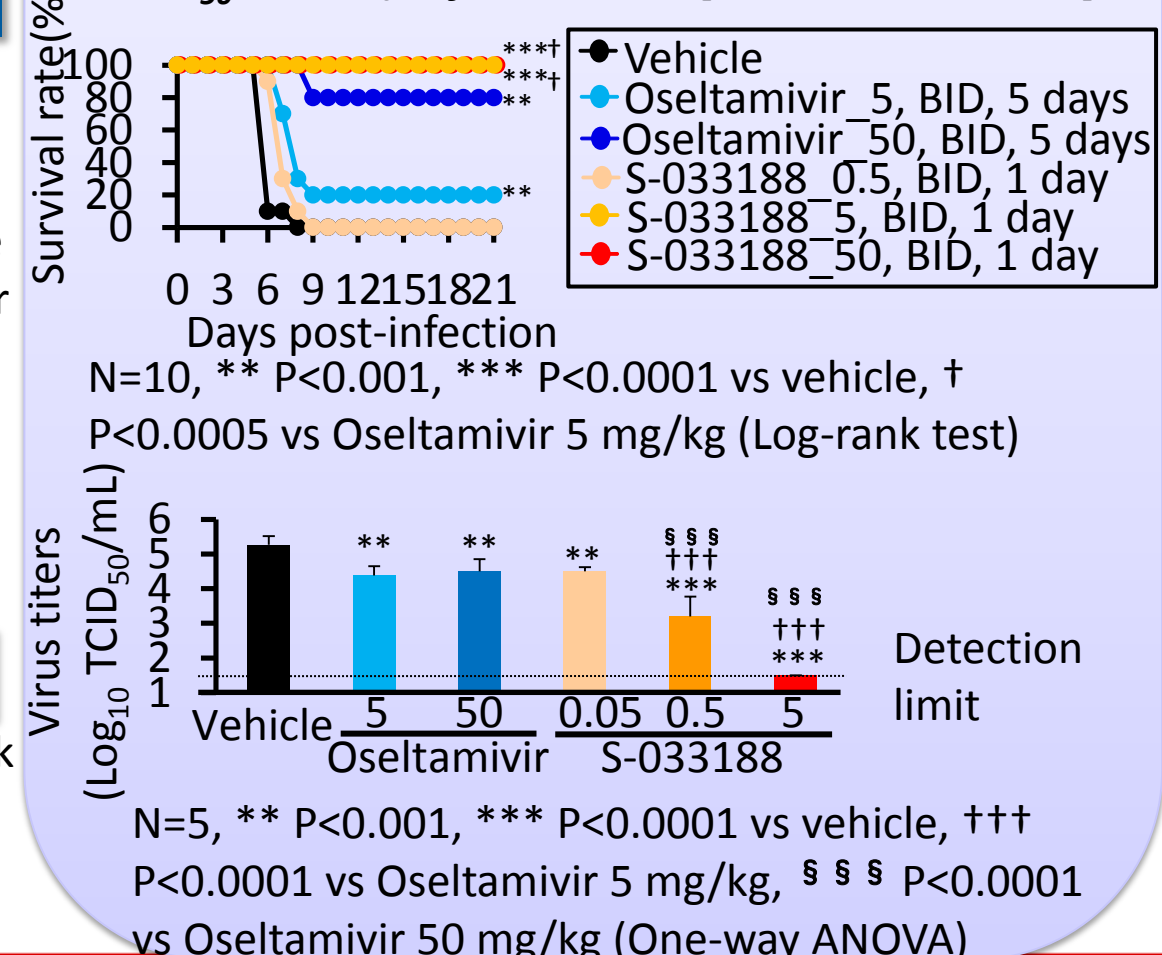
1. OPTIONS IX, Poster No. P-185, 408, 418, 610; 2. IDWeek 2016, Poster No. 645; 3. OPTIONS IX, Oral presentation No.LBO-1; 4. Ward P, Smith J, Suter P, Dutkowski R. J Antimicrob Chemother 2005; 55: Suppl 1: i5-i21.

Figure 3. Effect of S-033188 on virus titers in lungs at 1 day post-infection in B/Hong Kong/5/72 strain (mouse-adapted)-infected mice (Study 2)



N=5; * P<0.05, ** P<0.01, *** P<0.0001 vs vehicle, ††† P<0.0001 vs Oseltamivir 5 mg/kg, § § § P<0.0001 vs Oseltamivir 50 mg/kg (One-way ANOVA)

Reference: Effect of S-033188 on mortality and virus titers in A/PR/8/34 strain (4.42×10^4 TCID₅₀/mouse)-infected mice [OPTIONS IX, P-408]



N=10, ** P<0.001, *** P<0.0001 vs vehicle, ††† P<0.0001 vs Oseltamivir 5 mg/kg, § § § P<0.0001 vs Oseltamivir 50 mg/kg (One-way ANOVA)