**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**

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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.

**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).

**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 in all dose compared to the placebo.

**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, and -3.8 and -7.2 in the 40 mg group. Statistically significant differences were found in the change of virus titer compared to the placebo.

**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.