27O-ISMS37 **S-033188: A Novel, First-in-Class, Orally Bioavailable Cap-dependent Endonuclease Inhibitor of Influenza**

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Influenza is an acute respiratory infectious disease caused by influenza virus. Neuraminidase inhibitors suppress budding and release of influenza viruses from host cells. However, there are still unmet needs for new anti-influenza drugs that have better efficacy and safety profile, and activity against resistant strains and highly pathogenic strains.

Cap-dependent endonuclease (CEN) is an enzyme residing in the PA subunit of influenza virus polymerase. CEN mediates the “cap-snatching” process during viral mRNA biosynthesis and is essential for viral replication. Therefore, CEN is an attractive target for anti-influenza drugs.

S-033447, an active form of orally available prodrug S-033188, is a novel small molecule inhibitor of CEN, and exhibited broad and potent antiviral activity against clinically isolated influenza virus A and B strains that were collected from hospitals in Japan between 2006 and 2014 (EC_{50} in plaque reduction assay ranged from 0.20 to 0.99 nM for type A and from 4.01 to 11.26 nM for type B, data from poster# 645 of ID week in 2017). In clinical studies, S-033188 has demonstrated a favorable PK profile and evidence of anti-viral activity.

In this presentation, we will describe how we successfully discovered a novel and orally active CEN inhibitor, S-033188 and the early clinical profile.