2-LBS-30 Late-Breaking Session

Pharmacology of Baloxavir (Xofluza®); a First-in-Class Cap-dependent Endonuclease Inhibitor for Treatment of Influenza

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Baloxavir marboxil is an oral prodrug that is rapidly converted to its active form baloxavir acid, a potent inhibitor of influenza cap-dependent endonuclease function of influenza A and B viruses. Baloxavir was approved for treatment of uncomplicated influenza A and B virus infections in 2018 in Japan (for those weighing >10 kg) and the United States (for those aged 12 years and older)

Key nonclinical characteristics of baloxavir include broad spectrum activity against various types and subtypes of influenza virus strains *in vitro* as well as rapid and profound reduction in viral load *in vivo*. The phase III study (CAPSTONE-1) was a multicenter, randomised, double-blind, placebo- and oseltamivir-controlled study of otherwise-healthy patients in Japan and US (n=1436). The primary endpoint was time to alleviation of influenza symptoms (TTAS). TTAS was shorter with baloxavir than placebo (median 53.7 hr vs 80.2 hr, $p<0.0001$). Median time to cessation of viral shedding was 24 hr in baloxavir-treated patients, compared with 72 hr for oseltamivir ($p<0.0001$) and 96 hr for placebo ($p<0.0001$). Baloxavir was well tolerated and appeared to have no significant safety issues identified. Testing of laboratory isolates passage or clinical isolates identified isoleucine-to-threonine substitution at amino acid position 38 in N-terminal domain (PA/I38T). PA/I38 substitutions conferred reduced susceptibility to baloxavir and reduced fitness in variants. In the poster session, we report the key nonclinical and clinical profiles of baloxavir.