

FDA grants Priority Review to Roche's baloxavir marboxil for the treatment of influenza

- **Influenza, or “flu,” represents a serious threat to public health – globally, annual epidemics result in 3 to 5 million cases of severe disease, millions of hospitalisations and up to 650,000 deaths worldwide^{1,2,3,4,5}**
- **If approved, baloxavir marboxil would be the first oral, single-dose antiviral and the first medicine with a novel proposed mechanism of action to treat the flu in nearly 20 years⁶**

Roche (SIX: RO, ROG; OTCQX: RHHBY), today announced that the U.S. Food and Drug Administration (FDA) has accepted a New Drug Application (NDA) and granted Priority Review for baloxavir marboxil as a single-dose, oral treatment for acute, uncomplicated influenza in patients 12 years and older. The FDA is expected to make a decision on approval by 24 December 2018. A Priority Review designation is granted to medicines that the FDA has determined to have the potential to provide significant improvements in the treatment, prevention or diagnosis of a disease.

“The severity of the recent flu season underscores the need for new options beyond currently available treatments, and if approved, baloxavir marboxil would be the first flu medicine with a novel proposed mechanism of action in nearly 20 years,” said Sandra Horning, M.D., chief medical officer and head of Global Product Development. “Baloxavir marboxil has been shown in clinical trials to decrease the duration of symptoms with one dose, and demonstrated a significant reduction in viral shedding in just one day. We look forward to working with the FDA during the review process.”

Baloxavir marboxil is a first-in-class, single-dose investigational oral medicine with a novel proposed mechanism of action designed to target the flu virus, including oseltamivir-resistant strains and avian strains (H7N9, H5N1).^{7,8,9} Unlike other currently available antiviral treatments, baloxavir marboxil is designed to inhibit the cap-dependent endonuclease protein within the flu virus, which is essential for viral replication.^{10,11}

The NDA is based on results from the phase III CAPSTONE-1 study of a single dose of baloxavir marboxil compared with placebo or oseltamivir 75 mg, twice daily for five days, in otherwise healthy people with flu. Additionally, results from a placebo-controlled phase II study in otherwise healthy people with the flu is included as supporting data in the NDA.

About CAPSTONE-1

CAPSTONE-1 is a phase III multicentre, randomised, double-blind, placebo-controlled study that evaluated the efficacy and safety of baloxavir marboxil in 1,436 people in the United States and Japan. The primary endpoint of the study was time to alleviation of symptoms (TTAS), and important secondary endpoints were time to resolution of fever, time to cessation of viral shedding and the proportion of participants positive for influenza virus titre, or virus levels in the body, by time point. The study found the following results:

- Baloxavir marboxil met its primary and secondary endpoints compared to placebo:
 - Significantly reduced the duration of flu symptoms by more than one day (median time 53.7 hours versus 80.2 hours; $p < 0.0001$);
 - Significantly reduced the duration of fever by nearly a day (median time 24.5 hours versus 42.0 hours; $p < 0.0001$);
 - Significantly reduced the length of time viruses continued to be released from the body (median time of viral shedding; 24.0 hours versus 96.0 hours; $p < 0.0001$);
 - Significantly reduced the levels of virus in the nose and throat from 24 hours through 120 hours.
- Similar efficacy results were seen between baloxavir marboxil and oseltamivir in relation to duration of symptoms and fever reduction, but significant differences were observed in time to cessation of viral shedding favouring baloxavir marboxil:
 - No significant reduction in duration of symptoms (median time 53.5 hours versus 53.8 hours; $p = 0.7560$);
 - No significant reduction in time to resolution of fever (median time 24.4 hours versus 24.0 hours; $p = 0.9225$);
 - Significantly reduced the length of time the virus continued to be released from the body (viral shedding; 24.0 hours versus 72.0 hours; $p < 0.0001$);
 - Significantly reduced the levels of virus in the nose and throat at 24 hours and 72 hours.

Baloxavir marboxil was well-tolerated and had a numerically lower overall incidence of adverse events (20.7%) reported compared with placebo (24.6%) or oseltamivir (24.8%). The most common adverse events reported were diarrhoea (3.0%), bronchitis (2.6%), nausea (1.3%) and sinusitis (1.1%), and all of these adverse events occurred at a lower frequency than placebo.

About baloxavir marboxil

Baloxavir marboxil is a first-in-class, single-dose investigational oral medicine with a novel proposed mechanism of action designed to target the influenza (“flu”) A and B viruses, including oseltamivir-resistant strains and avian strains (H7N9, H5N1).^{7,8,9} Unlike other currently available antiviral treatments, baloxavir marboxil is the first in a new class of antivirals designed to inhibit the cap-dependent endonuclease protein within the flu virus, which is essential for viral replication.

Baloxavir marboxil is being studied in an ongoing phase III development program including paediatric populations with influenza. Data from the global phase III study (CAPSTONE-2) in patients 12 years and older with a high risk of complications from influenza, as defined by the Centers for Disease Control and Prevention (CDC), will be shared at a later date.

Baloxavir marboxil was discovered by Shionogi & Co., Ltd. and is being developed globally by the Roche Group (which includes Genentech in the U.S.) and Shionogi & Co., Ltd. Under the terms of this agreement, Roche holds worldwide rights to baloxavir marboxil excluding Japan and Taiwan, which will be retained exclusively by Shionogi & Co., Ltd. Baloxavir marboxil was approved in February 2018 by the Japanese Ministry of Health, Labour and Welfare for the treatment of influenza types A and B in adult and paediatric patients and is being commercialised in Japan and marketed under the brand name Xofluza™.

About Roche in influenza

Influenza, or flu, is one of the most common, yet serious, infectious diseases. Globally, annual epidemics result in 3 to 5 million cases of severe disease, millions of hospitalisations and up to 650,000 deaths worldwide.^{1,2,3,4,5} Roche has a long heritage in developing medicines that contribute to public health. We are committed to bringing innovation in the field of infectious diseases, including influenza. Tamiflu™ (oseltamivir) has made a significant difference both to the treatment of seasonal influenza as well as in the management of recent pandemics, and we are proud to have brought this innovative medicine to patients. Although vaccines are an important first line of defence in preventing the flu, there is a need for new medical options for prophylaxis and treatment. Current treatments – including vaccines and antiviral medicines – have limitations as flu viruses are constantly changing and new antiviral medicines are necessary. Roche is committed to addressing the unmet need in this area through its agreement with Shionogi & Co., Ltd. to develop and commercialise baloxavir marboxil.

About Roche in infectious disease

Infectious diseases caused by viral or bacterial pathogens are a major cause of death and morbidity worldwide, and constitute an ever-growing medical need. As such, they form a core area of research and development at Roche with clinical development programmes focused on Hepatitis B, influenza and multi-drug resistant bacterial infections. We are committed to developing medicines that aim to be transformative, personalised, and accessible.

About Roche

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. Thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Roche has been recognised as the Group Leader in sustainability within the Pharmaceuticals, Biotechnology & Life Sciences Industry nine years in a row by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2017 employed about 94,000 people worldwide. In 2017, Roche invested CHF 10.4 billion in R&D and posted sales of CHF 53.3 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information, please visit www.roche.com.

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⁷ T. Noshi et al. S-033447/S-033188, a Novel Small Molecule Inhibitor of Cap-dependent Endonuclease of Influenza A and B Virus: In Vitro Antiviral Activity against Laboratory Strains of Influenza A and B Virus in Madin-Darby Canine Kidney Cells. Poster presentation at OPTIONS IX, August 2016

⁸ K.Taniguchi et al. Inhibitory Effect of S-033188, a novel inhibitor of influenza virus cap-dependent endonuclease, against avian influenza A/H7N9 virus in vitro and in vivo. Poster presentation at ESWI, September 2017.

⁹ K.Taniguchi et al. Inhibitory Effect of S-033188/S-033447, a novel inhibitor of influenza virus cap-dependent endonuclease, against highly pathogenic avian influenza virus A/H5N1. Poster presentation at ECCMID, April 2017.

¹⁰ Shi et al. Viral RNA polymerase: a promising antiviral target for influenza A virus. *Curr Med Chem.* 2013;20(31):3923–34.

¹¹ Kawaguchi et al. 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. Poster presented at ESWI 2017.