Positive phase III results for baloxavir marboxil in people at high risk of complications from influenza to be presented at IDWeek 2018

- Baloxavir marboxil - a first-in-class, single-dose, investigational oral medicine - is the first potential influenza treatment in clinical trials to demonstrate a clinically meaningful benefit for people highly vulnerable to serious influenza complications
- CAPSTONE-2 showed that baloxavir marboxil significantly reduced time to improvement of influenza symptoms versus placebo
- Influenza, or ‘flu’, results in millions of debilitating illnesses each year and for those who are considered high-risk, influenza can increase the risk of serious complications, lead to hospitalisation or even death. [1]

Basel, 4 October 2018 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the phase III CAPSTONE-2 study showed treatment with baloxavir marboxil significantly reduced the time to improvement of influenza symptoms versus placebo (median time of 73.2 hours versus 102.3 hours; p<0.0001) in people at high risk of serious complications from the flu,[1] which includes adults 65 years of age or older, or those who have conditions such as asthma, chronic lung disease, morbid obesity, or heart disease. Baloxavir marboxil was well-tolerated and no new safety signals were identified. Results of the study will be presented as a late-breaking oral presentation during IDWeek 2018 in San Francisco, CA on Saturday 6 October 2018 (Abstract #LB16). Baloxavir marboxil was discovered and developed by Shionogi & Co., Ltd., and is sold in Japan under the trade name Xofluza”.

“This is the first phase III trial to demonstrate a significant, clinically meaningful benefit in people at high-risk for complications from the flu for which there are no currently approved medicines.” said Sandra Horning, MD, Roche’s Chief Medical Officer and Head of Global Product Development. “This study adds to the growing body of evidence supporting baloxavir marboxil as a potential first-in-class antiviral flu treatment, and we plan to discuss these data with health authorities around the world.”

The CAPSTONE-2 study also showed that baloxavir marboxil demonstrated efficacy (reduced time to improvement of influenza symptoms) in influenza type A/H3N2 (median time of 75.4 hours and 100.4 hours; p<0.05) and type B (median time of 74.6 hours and 100.6 hours; p<0.05) versus placebo. [2]

In addition, results for the overall patient population of the study showed numerically shorter time to improvement of influenza symptoms of baloxavir marboxil versus oseltamivir with a median time to improvement of symptoms of 73.2 hours for baloxavir marboxil compared with 81.0 hours for oseltamivir (p=0.8347). [2] In the subpopulation of patients with influenza type B, a subgroup where some antiviral treatments have shown only limited efficacy or inconclusive data, baloxavir marboxil was significantly more efficacious than oseltamivir in reducing the time to improvement of symptoms (median time of 74.6 hours versus 101.6 hours; p<0.05). [2]
Baloxavir marboxil demonstrated efficacy compared to placebo and oseltamivir for key secondary endpoints, including reducing the time that the virus continued to be released from the body (viral shedding; median time of 48.0 hours for baloxavir marboxil versus 96.0 hours for both placebo and oseltamivir; p<0.0001). [2] Baloxavir marboxil also reduced the use of antibiotics and incidence of influenza-related complications (3.4% and 2.8% respectively) compared to placebo (7.5% and 10.4%; p=0.01 and p<0.05). [2] Baloxavir marboxil had a numerically lower overall incidence of reported adverse events (25.1%) compared with placebo (29.7%) or oseltamivir (28.0%). [2]

Baloxavir marboxil is a single-dose, investigational oral medicine that represents the first of a new class of antivirals with a novel proposed mechanism of action that differs from other currently available treatments. [4,5] Baloxavir marboxil has already demonstrated a clinically significant benefit over placebo in otherwise healthy influenza patients in the phase III CAPSTONE-1 study. [6] The Food and Drug Administration (FDA) accepted a New Drug Application (NDA) and granted Priority Review to baloxavir marboxil as a single-dose, oral treatment for acute, uncomplicated influenza in people 12 years and older based on the results from CAPSTONE-1 and an earlier phase II study. [7] The FDA is expected to make a decision on approval by 24 December 2018. If approved, baloxavir marboxil will be the first single-dose oral antiviral, and the first medicine with a novel proposed mechanism of action to treat the flu in nearly 20 years. [8]

Genentech, a member of the Roche Group, also announced that they have entered into a private-public partnership with the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services (HSS), to advance the development of medicines for infectious diseases for which there is a significant unmet need. As part of the agreement, BARDA will provide funding that will support the development of baloxavir marboxil for severely ill hospitalised influenza patients, with the potential for funding of other studies.

About CAPSTONE-2 [2]
CAPSTONE-2 is a phase III, multicentre, randomised, double-blind study that evaluated the efficacy and safety of a single dose of baloxavir marboxil compared with placebo and oseltamivir in people 12 years or older who are at a high risk of complications from the flu. The Centers for Disease Control and Prevention (CDC) defines people at high risk for serious flu complications to include adults 65 years of age or older, or those who have conditions such as asthma, chronic lung disease, morbid obesity, or heart disease. [1] The study was conducted globally by Shionogi & Co., Ltd.

A total of 2184 participants enrolled in the study and were randomly assigned to receive a single, oral dose of 40 mg or 80 mg of baloxavir marboxil (according to body weight), placebo or 75 mg of oseltamivir twice daily for five days. Among them, 1163 (53%) patients were confirmed to have influenza virus infection with RT-PCR (influenza virus subtype: 47.9% for A/H3N2, 6.9% for A/H1N1, 41.6% for B). The most common risk factors were asthma or chronic lung disease (39.2%), age ≥65 years (27.4%), endocrine disorders (32.8%), metabolic disorders (13.5%), heart disease (12.7%), and morbid obesity (10.6%). The primary objective of the study evaluated the efficacy of a single dose of baloxavir marboxil compared with placebo by measuring the time to improvement of influenza symptoms.
Key secondary endpoints compared outcomes in baloxavir marboxil versus placebo or oseltamivir – these included time to resolution of fever, time to cessation of viral shedding, infectious virus detection in swabs of the nose and throat, prescription of antibiotics, and influenza-related complications.

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 (e.g. H7N9, H5N1)\(^{9-11}\). 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 influenza virus, preventing the virus from replicating in the body early in its lifecycle.\(^{4,5}\)

In the phase III CAPSTONE-1 study in otherwise healthy people with flu, conducted globally by Shionogi & Co., Ltd., baloxavir marboxil demonstrated a clinically significant benefit over placebo.\(^{6}\) Baloxavir marboxil will also be further studied in a phase III development programme including paediatric patients and severely ill hospitalised patients with influenza.

Baloxavir marboxil was discovered by Shionogi & Co., Ltd. and is being further developed and commercialised globally in collaboration with the Roche Group (which includes Genentech in the US). 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, representing a significant 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.\(^{12-16}\) For people who are considered at high-risk of serious complications, like pneumonia and bronchitis, the flu can worsen existing health problems, lead to hospitalisation or even death.\(^{11}\) 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 antiviral drugs have limitations with respect to efficacy, convenience of dosing, and resistance. 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. Moreover, for the tenth consecutive year, Roche has been recognised as the most sustainable company in the Pharmaceuticals Industry 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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References
[8] Portsmouth S et al. Cap-Dependent Endonuclease Inhibitor S-033188 for the Treatment of Influenza: Results from a Phase 3, Randomized, Double-Blind, Placebo- and Active-Controlled Study in Otherwise Healthy Adolescents and Adults with Seasonal Influenza. ID Week 2017.

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