FDA accepts Roche's New Drug Application for Xofluza (baloxavir marboxil) for the treatment of influenza in children

- **The application seeks approval of a new, additional formulation of Xofluza as granules for oral suspension for people one year of age and older with influenza**
- **The FDA also accepts a supplemental New Drug Application to expand the indication of Xofluza for post-exposure prophylaxis, potentially offering Xofluza as a preventive treatment for influenza after exposure to an infected individual**

Basel, 27 March 2020 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the US Food and Drug Administration (FDA) has accepted a New Drug Application (NDA) as well as two supplemental New Drug Applications (sNDA) for Xofluza® (baloxavir marboxil). The FDA accepted a NDA for a new formulation of Xofluza as one-dose granules for oral suspension (2 mg/mL), potentially offering a more convenient option for children and those who have difficulty swallowing. In addition, the application seeks approval of Xofluza for the treatment of acute uncomplicated influenza in otherwise healthy children aged one to less than 12 years of age who have been symptomatic for no more than 48 hours. The FDA also accepted a sNDA for post-exposure prophylaxis of influenza in people one year of age and older for both the oral suspension and currently-available tablet formulation. The FDA is expected to make a decision on approval by 23 November, 2020.

"As this has been one of the hardest-hitting influenza seasons for children in the past decade, there is a critical need for additional treatment options that attack influenza in different ways. Today's milestone brings us closer to providing one-dose Xofluza to children with influenza," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "We also look forward to working with the FDA to incorporate Xofluza as a preventive treatment following exposure to influenza."

The proposed additional formulation of Xofluza involves granules that are reconstituted with 20 mL of sterile water to form an oral suspension. If approved, this Xofluza oral suspension would be administered as a one-time dose and would be available for children aged one to less than 12 years of age and those who have difficulty swallowing. Xofluza tablets are currently approved in many countries around the world for the treatment of influenza types A and B.[1]

The filings are based on positive results from two Phase III studies, miniSTONE-2 and BLOCKSTONE, which were both recently presented as late breakers at the 2019 OPTIONS X congress in Singapore.[2,3] The miniSTONE-2 study evaluated the safety, pharmacokinetics and efficacy of one-dose, oral suspension Xofluza compared with oseltamivir in otherwise healthy children aged one to less than 12 years of age with influenza.[2] BLOCKSTONE evaluated Xofluza compared with placebo as a preventive treatment for household members (adults and children) who were living with someone with influenza.[3]

F. Hoffmann-La Roche Ltd 4070 Basel Switzerland
Investor Relations email: investor.relations@roche.com
Tel. +41 61 68-88880 Fax +41 61 69-10014 www.roche.com

Xofluza is FDA-approved to treat influenza in people 12 years of age and older who have had influenza symptoms for no more than 48 hours and who are otherwise healthy or at high risk of developing influenza-related complications.[4] Although some of the symptoms of COVID-19 and influenza can look similar, the two illnesses are caused by completely different viruses. Xofluza is specifically designed to treat influenza viruses only and has not been proven to be effective to treat human coronaviruses such as COVID-19.[1]

About miniSTONE-2 (NCT03629184)[2,5]
miniSTONE-2 is a Phase III, multicentre, randomised, double-blind study that evaluated the safety, pharmacokinetics and efficacy of one dose of Xofluza compared with oseltamivir in otherwise healthy children aged one to less than 12 years with influenza infection and displaying influenza symptoms for no more than 48 hours (temperature of 38°C or over, and one or more respiratory symptoms).

Participants enrolled in the study were recruited in parallel into two cohorts: children aged five to less than 12 years and children aged one to less than five years. Participants in both cohorts were randomly assigned to receive one dose of Xofluza or oseltamivir twice a day over five days (dosing according to body weight). Time to alleviation of influenza signs and symptoms were comparable between Xofluza and oseltamivir. The median time to alleviation of signs and symptoms in influenza-infected participants was 138 hours (95% CI: 117, 163) and 150 hours (95% CI: 115, 166) for those who received Xofluza or oseltamivir, respectively. Xofluza was well tolerated with no new safety signals identified.

About BLOCKSTONE[1,3]
BLOCKSTONE is a Phase III, double blind, multicenter, randomised, placebo-controlled, post-exposure prophylaxis study that evaluated one dose of Xofluza compared with placebo in household members (adults and children) in Japan who were living with someone with an influenza infection confirmed by a rapid influenza diagnostic test (the 'index patient'). The study was conducted by Shionogi & Co., Ltd. during the 2018-2019 influenza season in Japan.

Participants enrolled in the study were household members of someone who had been diagnosed with influenza. The participants were randomised to receive one dose of Xofluza (dose according to body weight) or placebo as a preventive measure against developing influenza.

Xofluza showed a significant prophylactic effect on influenza infection after one oral dose in people exposed to an infected family member. The proportion of household members who became symptomatically ill following infection with influenza was significantly lower in those treated preventively with Xofluza compared to those treated with placebo (proportion of subjects with influenza virus infection, fever and other influenza symptoms in the 10-day observation period: 2% versus 14%). Xofluza was well tolerated and no new adverse drug reactions were identified.

About Xofluza (baloxavir marboxil)
Xofluza is a first-in-class, one-dose oral medicine with an innovative proposed mechanism of action that has demonstrated efficacy in a wide range of influenza viruses, including in vitro activity against oseltamivir-resistant strains and avian strains (H7N9, H5N1) in non-clinical studies.[6] Xofluza is the first in a class of antivirals designed to inhibit the cap-dependent endonuclease protein, which is essential for viral

replication.[6,7]

Xofluza is approved in the United States and in several other countries for the treatment of acute, uncomplicated influenza in people 12 years of age and older, who are otherwise healthy or at high risk of developing serious complications from influenza, and who have been symptomatic for no more than 48 hours.[1,4] Xofluza was the first new antiviral to be approved by the FDA in 20 years.

Robust clinical evidence has demonstrated the benefit of Xofluza in several populations (otherwise-healthy, high-risk, children) and treatment settings (symptomatic influenza, post-exposure prophylaxis). Xofluza is being further studied in a phase III development programme, including children under the age of one (NCT03653364), and severely ill, hospitalised patients (NCT03684044), as well as to assess the potential to reduce transmission of influenza from an infected person to healthy people (NCT03969212).[8,9,10]

Xofluza 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) and Shionogi & Co., Ltd. Under the terms of this agreement, Roche holds worldwide rights to Xofluza excluding Japan and Taiwan, which will be retained exclusively by Shionogi & Co., Ltd.

About Roche in influenza
Influenza is one of the most common, yet serious, infectious diseases, representing a significant threat to public health.[11]Globally, seasonal epidemics result in 3 to 5 million cases of severe disease, millions of hospitalisations and up to 650,000 deaths every year.[11,12,13,14] 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 influenza, there is a need for new medical options for prophylaxis and treatment. Other 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 Xofluza.

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. More than 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 eleventh consecutive year, Roche has been recognised as one of the most sustainable companies 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 2019 employed about 98,000 people worldwide. In 2019, Roche invested CHF 11.7 billion in R&D and posted sales of CHF 61.5 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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Roche Investor Relations

Dr. Karl Mahler
Phone: +41 61 68-78503
e-mail: karl.mahler@roche.com

Jon Kaspar Bayard
Phone: +41 61 68-83894
e-mail: jon_kaspar.bayard@roche.com

Dr. Sabine Borngräber
Phone: +41 61 68-88027
e-mail: sabine.borngraeber@roche.com

Dr. Bruno Eschli
Phone: +41 61 68-75284
e-mail: bruno.eschli@roche.com

Dr. Birgit Masjost
Phone: +41 61 68-84814
e-mail: birgit.masjost@roche.com

Dr. Gerard Tobin
Phone: +41 61 68-72942
e-mail: gerard.tobin@roche.com

Investor Relations North America

Loren Kalm
Phone: +1 650 225 3217
e-mail: kalm.loren@gene.com

Dr. Lisa Tuomi
Phone: +1 650 467 8737
e-mail: tuomi.lisa@gene.com