Roche announces positive results for first global phase III study investigating one-dose Xofluza (baloxavir marboxil) in children with flu

- **The MINISTONE-2 study showed Xofluza, given as a new oral suspension, is a well-tolerated and effective potential treatment for flu in otherwise healthy children aged one to less than 12 years**
- **Approximately one in three children develop flu every year and they are often contagious longer than adults – treating children may therefore help reduce symptoms and prevent the spread of flu to the wider community[1,2]**

Basel, 3 July 2019 – Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the phase III MINISTONE-2 study met its primary endpoint, demonstrating that Xofluza™ (baloxavir marboxil) was well tolerated in children with flu. The study also showed that Xofluza is comparable to oseltamivir – a proven effective treatment for children with flu – at reducing the duration of flu symptoms, including fever. The study assessed Xofluza versus an active comparator (oseltamivir) in children aged between one and less than 12 years old with flu. Full results from MINISTONE-2 will be presented at an upcoming medical meeting.

"Children need new medicines for flu because they are at higher risk of developing flu and more likely to have complications such as breathing problems and pneumonia. These flu complications, which in some cases can be fatal, lead to approximately one million children under five being admitted to hospital globally every year," said Sandra Horning, MD, Roche's Chief Medical Officer and Head of Global Product Development. "As a one-dose oral suspension medicine, Xofluza could potentially provide a convenient treatment option for children with flu, and we look forward to sharing these data with health authorities around the world."

The safety and efficacy of Xofluza in children with flu under the age of one is also being studied in the global phase III MINISTONE-1 study (NCT03653364).[3] Xofluza is the first and only one-dose oral medicine approved to treat flu and the first new flu medicine with a novel proposed mechanism of action approved by the FDA in nearly 20 years. Xofluza is also the only flu treatment shown to be efficacious in both otherwise healthy people with flu (CAPSTONE-1) and people at high risk of complications from flu (CAPSTONE-2), as well as a preventive measure against developing flu following exposure to an infected household member (BLOCKSTONE).[4-6]

Xofluza is currently approved in several countries, including Japan, for the treatment of influenza types A and B in children, adolescents and adults, and in the United States (US) for the treatment of acute, uncomplicated influenza in people 12 years of age and older. In addition, the FDA recently accepted a supplemental New Drug Application (sNDA) for Xofluza as a one-dose oral treatment for people at high risk of complications from flu. The FDA is expected to decide on whether to approve this additional indication by 4 November 2019.

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

About MINISTONE-2 (NCT03629184)
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 <12 years with an influenza infection confirmed by a rapid influenza diagnostic test and displaying influenza-like symptoms (temperature of 38°C or over, and one or more respiratory symptoms).

Participants enrolled in the study were recruited in parallel into two cohorts: patients aged five to <12 years and patients aged one to <5 years. Patients in both cohorts were randomly assigned to receive one dose of Xofluza (2mg/kg for patients under 20kg or 40mg for patients 20kg or over) or oseltamivir twice a day over five days (dosing according to body weight). The primary endpoint of the study was the proportion of patients with adverse events or severe adverse events up to study day 29. Secondary endpoints include pharmacokinetics, time to alleviation of influenza signs and symptoms, and duration of symptoms, including fever.

About Xofluza™ (baloxavir marboxil)
Xofluza is a first-in-class, one-dose oral medicine with a novel 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.[7,8] Unlike other currently available antiviral treatments, Xofluza is the first in a new class of antivirals designed to inhibit the CAP-dependent endonuclease protein, which is essential for viral replication.[7]

Xofluza is being further studied in a phase III development programme, including children under the age of one (NCT03653364), and severely ill, hospitalised people with flu (NCT03684044), as well as to assess the potential to reduce transmission of flu from an infected person to healthy people (NCT03969212).

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, where rights will be retained exclusively by Shionogi & Co., Ltd.

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 290,000 to 650,000 deaths worldwide.[9-13] Children are at a particularly high risk of developing flu, with an estimated global rate of 20–30% compared with 5–10% in adults, and are more vulnerable to complications such as breathing problems, pneumonia and, in some cases, even death.[1,3] Due to these complications, approximately one million children under five years old are hospitalised globally every year.[13]

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 flu, 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.[14] 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. 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 2018 employed about 94,000 people worldwide. In 2018, Roche invested CHF 11 billion in R&D and posted sales of CHF 56.8 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.

References
[1] WHO 2019. Influenza. [Internet; cited 2019 June]. Available from: https://www.who.int/biologicals/vaccines/influenza/en/
[2] Centers for Disease Control and Prevention. How Flu Spreads. [Internet; cited 2019 June]. Available from: https://www.cdc.gov/flu/about/disease/spread.htm
[3] Study to Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Healthy Pediatric Participants From Birth to < 1 Year With Influenza-Like Symptoms. [Internet; cited 2019 June]. Available from: https://clinicaltrials.gov/ct2/show/NCT03653364?term=baloxavir&rank=1.

[4] Hayden FG, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. NEJM. 2018; 379(10):913-923.
[5] Ison M, et al. CAPSTONE-2 trial. Infectious Disease Week; 2018 Oct 3-7; San Francisco. CA, USA. Abstract #LB16. Available from: https://idsa.confex.com/idsa/2018/webprogram/Paper74204.html.
[6] Roche Investor Update. Phase III study showed Xofluza (baloxavir marboxil) is effective at preventing influenza infection. [Internet; cited 2019 June]. Available from: https://www.roche.com/investors/updates/inv-update-2019-06-04b.htm.
[7] Noshi T, et al. In vitro Characterization of Baloxavir Acid, a First-in-Class Cap-dependent Endonuclease Inhibitor of the Influenza Virus Polymerase PA Subunit. Antiviral Research. 2018; 160:109-117.
[8] Taniguchi K, et al. Inhibition of avian-origin influenza A(H7N9) virus by the novel cap-dependent endonuclease inhibitor baloxavir marboxil. Scientific Reports. 2019; 9:3466.
[9] WHO 2017. Up to 650 000 people die of respiratory diseases linked to seasonal flu each year. [Internet; cited 2019 June]. Available from: http://www.who.int/mediacentre/news/releases/2017/seasonal-flu/en/.
[10] WHO 2017. Influenza (seasonal). [Internet; cited 2019 June].
Available from: https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)
[11] Baxter D. Evaluating the case for trivalent or quadrivalent influenza vaccines. Hum Vaccin Immunother. 2016; 12:2712.
[12] Centers for Disease Control and Prevention. Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United States. [Internet; cited 2019 June]. Available from: https://www.cdc.gov/flu/about/disease/2015-16.htm.
[13] Nair H, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011; 378(9807):1917-30.
[14] Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. [Internet; cited 2019 June]. Available from: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.

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