# Press Release

## Positive Results for XOFLUZA™ Global Phase III Study (MINISTONE-2) in Children with Influenza

**OSAKA, Japan, September 2, 2019 -** Shionogi & Co., Ltd. (hereafter "Shionogi") has announced that the results from the global phase III study (MINISTONE-2) assessing XOFLUZA™ (baloxavir marboxil) in otherwise healthy children aged one to less than 12 years old were presented by Roche Group (hereafter "Roche") at Options X for the Control of Influenza (OPTIONS X), held in Singapore on August 28 – September 1, 2019.

The primary endpoint of this study, the proportion of patients with adverse events (AEs) or severe AEs up to Day 29, showed that XOFLUZA has a similar safety profile to oseltamivir, which is an effective and safe treatment already approved to treat children with influenza.

- In participants treated with XOFLUZA, 46.1% experienced at least one treatment emergent AE compared to 53.4% in the oseltamivir arm. The safety profile of XOFLUZA in this study was consistent with that reported in the previous studies in adults and adolescents.

Key secondary endpoints also showed the efficacy of XOFLUZA as follows.

- The time to alleviation of influenza signs and symptoms of XOFLUZA arm was comparable to oseltamivir (median time of 138.1 hours vs 150.0 hours, respectively).
- XOFLUZA reduced the length of time that the influenza virus continued to be released from the body by more than two days compared with oseltamivir (viral shedding; median time of 24.2 hours vs 75.8 hours, respectively).

Full results of the study were presented from Roche as a late-breaking abstract at OPTIONS X on September 1, 2019 (Abstract #11756).

Shionogi and Roche Group (hereafter "Roche") are in a license and collaboration agreement to further develop and commercialize XOFLUZA. Under the terms of this agreement, Roche holds worldwide rights to XOFLUZA excluding Japan and Taiwan where the rights are retained exclusively by Shionogi. XOFLUZA was approved in Japan on February 23, 2018 and is available for the treatment of influenza Types A and B in adults and pediatric patients[1] and was approved in the U.S. on October 25, 2018 where it is available for the treatment of acute, uncomplicated influenza in people 12 years of age or older.[2]

Shionogi's research and development efforts target infectious diseases as one of its priority areas, and Shionogi has defined "protecting people from the threat of infectious diseases" as one of its core social missions. Shionogi strives constantly to bring forth innovative drugs for the treatment of infectious diseases, to protect the health of the many patients we serve. Shionogi will continue to work diligently to collect and analyze data on the efficacy and safety of XOFLUZA and provide information for proper use.

**About XOFLUZA**

XOFLUZA, discovered by Shionogi, has a novel mechanism of action that inhibits cap-dependent endonuclease in the polymerase acidic (PA) protein (in the United States Prescribing Information, this enzyme is stated as polymerase acidic endonuclease), an enzyme essential for viral replication. The regimen for XOFLUZA is a single-oral dose to treat uncomplicated influenza, which is different from all currently available antiviral treatments. In non-clinical studies, XOFLUZA demonstrated an antiviral effect against a wide range of influenza viruses including oseltamivir-resistant strains and avian strains (H7N9, H5N1).[3, 4] XOFLUZA has been reviewed and is currently approved in several countries including Japan and the U.S. In addition, XOFLUZA was approved in Taiwan on August 28, 2019, for the treatment of acute influenza Types A and B in patients aged 12 years of age and older.[5] The U.S. Food and Drug Administration (FDA) has accepted a supplemental New Drug Application for XOFLUZA™ for the treatment of influenza in individuals at high-risk for influenza-related complications aged 12 years and older. The Prescription Drug User Fee Act date for an FDA decision on this additional indication is November 4, 2019.[6] For more information, please refer to the XOFLUZA website.

Roche is now conducting a phase III development program including children under one year, hospitalized patients with severe influenza and will assess the potential to reduce transmission of influenza from an infected person to healthy people.

**About MINISTONE-2 Study**

MINISTONE-2 is a phase III, multicenter, randomized, double-blind study that evaluated the safety, pharmacokinetics and efficacy of one dose of XOFLUZA compared with ten doses of oseltamivir in otherwise-healthy children aged one to less than 12 years with influenza infection and displaying influenza 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 less than 12 years and patients aged one to less than five years. Patients in both cohorts were randomly assigned to receive one dose of XOFLUZA (2 mg/kg for patients under 20 kg or 40 mg for patients 20 kg 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 included pharmacokinetics, time to alleviation of influenza signs and symptoms, and duration of symptoms, including fever.

**About Influenza**

Seasonal and pandemic influenza remain a major public health concern, and novel influenza drugs that offer significant improvement over current therapy are urgently needed. Globally, seasonal epidemics result in 3 to 5 million cases of severe disease, millions of hospitalizations and up to 650,000 deaths every year.[7, 8, 9, 10, 11]

**About Shionogi**

Shionogi & Co., Ltd. is a Japanese major research-driven pharmaceutical company dedicated to bringing benefits to patients based on its corporate philosophy of "supplying the best possible medicine to protect the health and wellbeing of the patients we serve." The company currently markets products in several therapeutic areas including anti-infectives, pain, cardiovascular diseases and gastroenterology. Our pipeline is focused on infectious disease, pain, CNS and oncology. For more information on Shionogi & Co., Ltd., visit www.shionogi.co.jp/en.

**Forward-Looking Statements**

*This announcement contains forward-looking statements. These statements are based on expectations in light of the information currently available, assumptions that are subject to risks and uncertainties which could cause actual results to differ materially from these statements. Risks and uncertainties include general domestic and international economic conditions such as general industry and market conditions, and changes of interest rate and currency exchange rate. These risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. Also for existing products, there are manufacturing and marketing risks, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials and entry of competitive products. The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.*

**For Further Information, Contact:**
Corporate Communications Department
Shionogi & Co., Ltd.
Telephone: +81-6-6209-7885

**References**

1. Press release on March 14, 2018
   XOFLUZA™ (Baloxavir Marboxil) Tablets 10mg/20mg for the Treatment of Influenza Types A and B launched in Japan
2. Press release on October 25, 2018
   Shionogi Announces FDA Approval of XOFLUZA™ (Baloxavir Marboxil)- for the Treatment of Acute, Uncomplicated Influenza –
3. T. Noshi 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
4. K. Taniguchi et al. Inhibition of avian-origin influenza A(H7N9) virus by the novel cap-dependent endonuclease inhibitor baloxavir marboxil. Scientific Reports volume 9, Article number: 3466

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5. Press release on August 29, 2019
   Shionogi Announces XOFLUZA® Tablets 20mg for The Treatment of Influenza Types A and B in Patients 12 years of Age and older Approved in Taiwan
6. Press release on March 6, 2019
   FDA Accepts XOFLUZA™ (Baloxavir Marboxil) Supplemental New Drug Application for the Treatment of Influenza in Individuals at High Risk for Influenza-Related Complications -
7. http://www.who.int/mediacentre/news/releases/2017/seasonal-flu/en/ World Health Organization website, Up to 650 000 people die of respiratory diseases linked to seasonal flu each year, Accessed December 14, 2017.
8. http://www.who.int/mediacentre/factsheets/fs211/en World Health Organization website, Influenza (Seasonal), Accessed January 31, 2018.
9. Baxter D. Evaluating the case for trivalent or quadrivalent influenza vaccines. Hum Vaccin Immunother. 2016; 12(10):2712-2717.
10. https://www.cdc.gov/flu/about/disease/2015-16.htm CDC website, Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United State. Accessed April 19, 2017.
11. Nair H, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011 Dec 3;378(9807):1917-30.