# Press Release

## FDA Accepts a New Drug Application for a New Formulation and Two Supplemental New Drug Applications for XOFLUZA® (Baloxavir Marboxil)

**OSAKA, Japan, March, 27, 2020 –** Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") today announced that the U.S. Food and Drug Administration (FDA) has accepted a New Drug Application (NDA) for a new formulation of Xofluza® (baloxavir marboxil) as one-dose granules for oral suspension. In addition, the FDA has accepted two supplemental New Drug Applications (sNDA). The first 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. A second application seeks approval for post-exposure prophylaxis of influenza in people one year of age and older. The Prescription Drug User Fee Act (PDUFA) date for an FDA decision is November 23, 2020.

The filings are based on positive results from two phase III studies, the miniSTONE-2 study[1] and the BLOCKSTONE study[2]. miniSTONE-2 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. If approved, the NDA for a new formulation of Xofluza as granules for oral suspension would be administered as a one-time dose, potentially offering a more convenient option for children and those who have difficulty swallowing. BLOCKSTONE evaluated Xofluza compared with placebo as a preventive treatment for household members (adults and children) who were living with someone with influenza.

Shionogi and the 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. In the U.S., Xofluza is available for the treatment of acute, uncomplicated influenza in people 12 years of age or older who have been symptomatic for no more than 48 hours and is recommended for the treatment of acute, uncomplicated influenza in people 12 years of age or older in the guidelines of the CDC.[3,4] In addition, Roche’s sNDA of Xofluza for the treatment of acute, uncomplicated influenza in people aged 12 years and older, who have been symptomatic for no more than 48 hours and who are at high-risk of influenza-related complications, was approved by the U.S. FDA on October 16, 2019.[5]

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 appropriate use.

**About miniSTONE-2 study[1] (NCT03629184)**

miniSTONE-2 is a Phase III, multicentre, randomized, 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 for 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 138.1 hours (95% CI: 116.6, 163.2) and 150.0 hours (95% CI: 115.0, 165.7) for those who received Xofluza or oseltamivir, respectively. Xofluza was well tolerated with no new safety signals identified.[6]

**About BLOCKSTONE Study[2]**

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 flu 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 flu 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: 1.9% versus 13.6%; $p<0.0001$). Xofluza was well tolerated and no new adverse drug reactions were identified.[7]

**About Xofluza® (baloxavir marboxil)**

Xofluza discovered by Shionogi, has a novel mechanism of action that inhibits the 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. Xofluza is a one-doseoral treatment for influenza, which is different from all other 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).[8,9] Xofluza has been reviewed and is currently approved in several countries including Japan and the U.S. For more information about the use in the U.S., please refer to the Xofluza® website. Roche is now conducting a phase III development program investigating Xofluza in several populations, including children under the age of one year (NCT03653364), and severely ill, hospitalized patients (NCT03684044), as well as to assess the potential to reduce transmission of influenza from an infected person to healthy people (NCT03969212). Shionogi assessed the potential of Xofluza as a post-exposure prophylaxis treatment to prevent the spread of influenza in adults and children, and submitted a sNDA based on the positive results from the Phase III BLOCKSTONE study on October 16, 2019 in Japan.[10]

**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.*

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**References**

1. Press release on September 2, 2019
   Positive Results for XOFLUZA™ Global Phase III Study (miniSTONE-2) in Children with Influenza
2. Press release on September 2, 2019
   Shionogi Announces Positive Post-Exposure Prophylaxis Results for XOFLUZA® in Phase III Study (BLOCKSTONE) of Influenza Virus Infection in Household Members
3. Press release on October 25, 2018
   Shionogi Announces FDA Approval of Xofluza® (Baloxavir Marboxil) - for the Treatment of Acute, Uncomplicated Influenza
4. CDC Guideline
   CDC website, Influenza Antiviral Medications: Summary for Clinicians
5. Press release on October 18, 2019
   FDA Approves Xofluza® (Baloxavir Marboxil) for the Treatment of Acute Uncomplicated Influenza for People at High Risk of Developing Influenza-Related Complications
6. J Baker et al. Single-dose baloxavir marboxil for the treatment of influenza in otherwise-healthy children aged 1 to <12 years (miniSTONE-2). Presented at: OPTIONS X; 2019 August 28-September 1; Singapore. Abstract #11756
7. H. Ikematsu et al. Single-dose baloxavir for the prevention of influenza among household contacts: a randomized, double-blinded, placebo controlled post-exposure prophylaxis study (BLOCKSTONE). OPTIONS X 2019; 2019 Aug 28-Sept 1; Singapore. Abstract #11718
8. 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
9. 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 (2019)
10. Press release on October 16, 2019
    Shionogi Filed for the Supplemental New Drug Application of XOFLUZA® in Japan for the Post-Exposure Prophylaxis of Influenza Virus Infection