Press Release

Shionogi Announces FDA Approval of XOFLUZA® (Baloxavir Marboxil) for the prevention of Influenza following contact with an infected person.

OSAKA, Japan, November, 24, 2020 – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") today announced that its License Partner F. Hoffmann-La Roche Ltd. (Head Office: Basel, Switzerland; CEO: Severin Schwan, L.L.D.; hereafter "Roche") holds worldwide rights to Xofluza® excluding Japan and Taiwan, has received the U.S. Food and Drug Administration (FDA) approval for a supplemental New Drug Applications (sNDA) for Xofluza® (baloxavir marboxil) as a treatment to prevent influenza in people 12 years of age and older following contact with someone with influenza (known as post-exposure prophylaxis). Xofluza® is the first single-dose influenza medicine approved for post-exposure prophylaxis. This approval was determined based on the phase III study, BLOCKSTONE.[1] The approval was in advance of the Prescription Drug User Fee Act (PDUFA) date for an FDA decision of November 23, 2020.

Post-exposure prophylaxis with single-dose Xofluza® was evaluated in the BLOCKSTONE study, which was recently published in *The New England Journal of Medicine*. In the study, Xofluza® was compared with placebo as a preventive treatment for household members (adults and children) who were living with someone with influenza. The proportion of subjects who became infected with influenza virus and showed fever and at least one respiratory symptom was 1.9% in subjects treated with Xofluza® and 13.6% in the placebo-treated group. Xofluza® was well tolerated in this study and no new safety signals were identified.

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 already FDA-approved to treat acute 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.[2, 3] In the United States, Xofluza® is the only drug approved for high-risk patients with influenza, which alongside the new approval as a preventive treatment, may also potentially mitigate the burden of the upcoming influenza season on the U.S. healthcare system amid the COVID-19 pandemic. The Centers for Disease Control and Prevention (CDC) guidelines list Xofluza® as a treatment option for outpatients with influenza without complications.[4] Additionally, Roche is determining a path forward with the FDA for an indication for Xofluza® as a treatment for acute uncomplicated influenza in otherwise healthy children (one to 12 years of age) and for the prevention of influenza in the same age group who have been exposed to influenza. Xofluza® is currently not approved for use in this population.

On November 12th , the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion recommending the granting of a marketing authorization for XOFLUZA for the treatment of uncomplicated influenza in patients aged 12 years and above. In addition, the CHMP has also adopted a positive opinion for XOFLUZA for the preventive treatment (post-exposure prophylaxis) of influenza in individuals aged 12 years and above following contact with someone with influenza.[5]

Shionogi is committed to "Protect people worldwide from the threat of infectious diseases" as our key focus. We are not limiting ourselves to the research and development of therapeutic medications, but are also focused on the total care of infectious disease through awareness building, prevention and diagnosis and suppression of exacerbation. 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 the BLOCKSTONE Study[1]
BLOCKSTONE was a Phase III, double blind, multicenter, randomized, placebo-controlled, post-exposure prophylaxis study that evaluated a single-dose of Xofluza® compared with placebo in household members (adults and children) 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.

Those diagnosed with influenza were required to have onset of symptoms within less than 48 hours, and participants were required to have lived with those diagnosed for more than 48 hours. The participants were randomised to receive a single-dose of Xofluza® (dosed according to body weight) or placebo as a preventive measure against developing influenza.

Xofluza® showed a statistically significant prophylactic effect on influenza after a single-dose in people exposed to an infected household contact. The proportion of household members 12 years of age and older who developed influenza was 1.9% in participants treated with Xofluza® and 13.6% in the placebo-treated group. Xofluza® was well tolerated in this study and no new safety signals were identified.

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 single-dose oral 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).[6, 7] Xofluza® is available in many other countries for the treatment of influenza types A and B, 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), as well as to assess the potential to reduce transmission of influenza from an infected person to healthy people (NCT03969212). Shionogi submitted a sNDA for the post-exposure prophylaxis on October 16, 2019 in Japan and also filed sNDA for Xofluza® in Taiwan for the post-exposure prophylaxis of influenza virus infection in adults and children 12 years of age and older on March 31, 2020 based on the positive results from the Phase III BLOCKSTONE study.[8, 9]

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. Hideyuki Ikematsu, MD et al. Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts. N Engl J Med 2020 Jul 8
https://www.nejm.org/doi/full/10.1056/NEJMoa1915341
2. Press release on October 25, 2018
Shionogi Announces FDA Approval of Xofluza® (Baloxavir Marboxil) - for the Treatment of Acute, Uncomplicated Influenza
3. 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
4. CDC Guideline
CDC website, What You Should Know About Flu Antiviral Drugs
5. Xofluza: Pending EC decision | European Medicines Agency
https://www.ema.europa.eu/en/medicines/human/summaries-opinion/xofluza
6. 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
7. 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)
8. 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
9. Press release on March 31, 2020
Shionogi Filed for the Supplemental New Drug Application of Xofluza® in Taiwan for the Post-Exposure Prophylaxis of Influenza Virus Infection