Press Release

Shionogi Announces European Commission Approval of XOFLUZA® (Baloxavir Marboxil) for the Treatment and Post-Exposure Prophylaxis of Influenza Virus Infection

OSAKA, Japan, January, 15, 2021 – 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") which holds worldwide rights to Xofluza® (baloxavir marboxil) excluding Japan and Taiwan, has received European Commission (EC) approval for Xofluza, for the treatment of uncomplicated influenza in patients aged 12 years and above. In addition, the EC has approved Xofluza for post-exposure prophylaxis of influenza in individuals aged 12 years and above. Post-exposure prophylaxis aims to prevent influenza in individuals following contact with someone infected with the influenza virus.

This approval follows the positive opinion received from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) on November, 2020, and is based on the results of the phase III CAPSTONE-1, CAPSTONE-2 and BLOCKSTONE studies.[1, 2, 3] Xofluza is available in more than 30 countries for the treatment of influenza types A and B.

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 focusing on the total care of infectious disease through awareness building, prevention, 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 CAPSTONE-1 Study[1]

The CAPSTONE-1 study was a Phase III, randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled study that enrolled 1,436 otherwise healthy patients diagnosed with influenza. In this study, Xofluza® (baloxavir marboxil) significantly reduced the duration of influenza symptoms by more than a day compared with placebo (median time; 53.7 hours versus 80.2 hours; $p<0.001$). Similar efficacy results were seen between Xofluza and oseltamivir in relation to time to alleviation of symptoms (median time 53.5 hours versus 53.8 hours). Xofluza also significantly reduced time to cessation of infectious viral shedding compared with both placebo and oseltamivir (median time of viral shedding; 24.0 hours for Xofluza, 96.0 hours for placebo, 72.0 hours for oseltamivir; $p<0.0001$).

Xofluza was well tolerated in this study and no new safety signals were identified. The study was conducted in the US and Japan by Shionogi & Co., Ltd. The results of the CAPSTONE-1 study were published in The New England Journal of Medicine.[1]

About CAPSTONE-2 Study[2]

The CAPSTONE-2 study was a phase III, multicenter, randomized, double-blind study that evaluated the safety and efficacy of a single oral dose of Xofluza® (baloxavir marboxil) compared with placebo and oseltamivir in patients 12 years or older who are at a high risk for influenza-related complications. The study was conducted globally by Shionogi. A total of 2,184 participants enrolled in the study were randomly assigned to receive a single dose of 40 mg or 80 mg of Xofluza (according to body weight), placebo or 75 mg of oseltamivir twice a day for 5 days. The most common risk factors were asthma or chronic lung disease (39.2%), age ≥65 years (27.4%), endocrine disorders (32.8%), metabolic disorders (13.5%), heart disease (12.7%), and morbid obesity (10.6%). The primary endpoint of the study was time to improvement of influenza symptoms. CAPSTONE-2 was the first prospective, controlled phase III clinical trial to demonstrate a significant and clinically meaningful benefit from an antiviral medicine in people at high-risk of serious influenza complications (median time to improvement in symptoms 73.2 hours for Xofluza, 102.3

hours for placebo, p<0.0001). Similar median time to improvement in symptoms was seen between the Xofluza and oseltamivir groups (73.2 hours versus 81.0 hours, respectively).

Xofluza was well tolerated in this study and no new safety signals were identified. The results of the CAPSTONE-2 study were published in The Lancet Infectious Diseases.[2]

About the BLOCKSTONE Study[3]
BLOCKSTONE was a Phase III, double blind, multicenter, randomized, placebo-controlled, post-exposure prophylaxis study that evaluated a single dose of Xofluza® (baloxavir marboxil) 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 influenza 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 randomized 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 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. The results of the BLOCKSTONE study were published in The New England Journal of Medicine. [3]

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 referred to 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).[4, 5]

Xofluza is available in more than 30 countries for the treatment of influenza types A and B, including Japan and the U.S.

In Japan, Xofluza is available for the post-exposure prophylaxis of influenza virus infection, and in the U.S., the FDA approved a supplemental NDA for Xofluza 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) on November 23, 2020.[6, 7]

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).

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. Frederick G. Hayden et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl J Med 2018 Sep 6; 379:913-923.
2. Michael G. Ison, MD MS et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. Lancet Infect Dis 2020; 20 (10): 1204-1214
3. Hideyuki Ikematsu, MD et al. Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts. N Engl J Med Jul 23; 383:309-320
4. 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.
5. Keiichi 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).
6. Press release on November 27, 2020
   Shionogi Announces Supplemental New Drug Application for XOFLUZA® in Japan for the Post-Exposure Prophylaxis of Influenza Virus Infection was Approved.
7. Press release on November 23, 2020
   Shionogi Announces FDA Approval of XOFLUZA® (Baloxavir Marboxil) for the prevention of Influenza following contact with an infected person.