Press Release

BLOCKSTONE Study of Xofluza® (Baloxavir Marboxil) for the Prevention of Influenza in Household Contacts Published in The New England Journal of Medicine

OSAKA, Japan, July, 9, 2020 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announced today that the full results from the positive Phase III BLOCKSTONE study investigating Xofluza® (baloxavir marboxil) as a post-exposure prophylaxis treatment to prevent influenza in household members, has been published in The New England Journal of Medicine on July 8, 2020.

In the BLOCKSTONE[1] study, following exposure to a person with confirmed influenza, preventive treatment with Xofluza® significantly reduced the proportion of household contacts who developed clinical influenza, compared with placebo. The prophylactic effects of Xofluza® were also observed in people at high-risk of influenza related complications,[2] as well as in children under 12 years old, irrespective of vaccine status. The risk of influenza infection,in addition to clinical influenzawas reduced in participants treated with Xofluza® compared to those treated with placebo. The incidence of adverse events in people treated with Xofluza® in the BLOCKSTONE study was similar to those who received placebo.

"The BLOCKSTONE study demonstrated that baloxavir marboxil strongly prevents influenza infection in the household setting, which plays a major role in influenza epidemics. The strong antiviral activity of baloxavir marboxil resulted in the prevention of influenza infection and the suppression of the onset of influenza symptoms. I believe that baloxavir marboxil is a promising option for the prophylaxis and prevention of influenza for persons at high-risk of influenza complications and healthcare professionals who are at the front lines and must be protected during influenza epidemic." said Hideyuki Ikematsu, President of Ricerca Clinica Co., the research director of the influenza study group of the Japan Physicians Association, and the lead author of the published paper.

The full data from BLOCKSTONE demonstrate that a single oral dose Xofluza® was highly effective in preventing influenza in the household setting over the 10 days following treatment. Xofluza® previously showed positive results in the global Phase III CAPSTONE-1[3] study in otherwise healthy patients 12 years of age and older, and in the CAPSTONE-2[4] study in patients at high-risk of influenza related complications. Additionally, the CAPSTONE-2 study was the first clinical study to demonstrate clear benefit of any antiviral medicine in patients at high-risk of influenza complications. Xofluza® is therefore expected to contribute to the management of influenza, both for patients with influenza and as a prophylactic treatment for those in contact with influenza patients.

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. Xofluza® is approved and available for the treatment of influenza in several countries including Japan and the U.S. Shionogi has submitted a supplemental New Drug Application (sNDA) in Japan and Taiwan for Xofluza® as a post-exposure prophylaxis treatment based on the positive results from the BLOCKSTONE study.[5, 6] In the U.S., the Food and Drug Administration (FDA) accepted a NDA for a new formulation of Xofluza® as single-dose granules for oral suspension, potentially offering a more convenient option for children and those who have difficulty swallowing. In addition, the 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. The FDA also accepted an sNDA for post-exposure prophylaxis of influenza in people one year of age and older for both the oral suspension and currently-available tablet formulation. The FDA is expected to make a decision by November 23, 2020.[7]

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 the BLOCKSTONE[1] Study

The BLOCKSTONE study was a phase III, multicenter, double-blind, placebo-controlled study conducted in Japan during the 2018/19 season in household contacts (participants) of index patients with confirmed influenza. The primary endpoint of the study was the proportion of participants who developed clinical influenza (defined as infected with the influenza virus) and had fever and at least one respiratory symptom after exposure to an infected household member (index patient), in the ten day observation period after administration of Xofluza®. The proportion of participants who developed clinical influenza was 1.9% (7/374) in participants treated with Xofluza® and 13.6% (51/375) in the placebo-treated group ($p<0.0001$), demonstrating an 86% reduction in risk.

Key subgroup analyses:

- In participants at high-risk for influenza-related complications, Xofluza® reduced the risk of participants developing clinical influenza versus placebo (2.2% [1/46] vs 15.4% [8/52]).
- In children under 12 years of age, Xofluza® reduced the risk of participants developing clinical influenza versus placebo (4.2% [3/71] vs 15.5% [11/71]).
- Regardless of influenza A subtype, Xofluza® reduced the risk of participants treated developing influenza versus placebo (A/H1N1pdm: 1.1% [2/176] vs 10.6% [19/180]; A/H3: 2.8% [5/181] vs 17.5% [32/183]).
- Regardless of vaccination status, Xofluza® reduced the risk of participants treated developing influenza versus placebo (vaccinated: 2.3% [3/131] vs 16.9% [21/124]; non-vaccinated: 1.6% [4/243] vs 12.0% [30/251]).

Key secondary endpoints:

- The proportion of participants who became infected with the influenza virus and showed fever or one or more respiratory symptoms was 5.3% (20/374) in participants treated with Xofluza® and 22.4% (84/375) in those treated with placebo. Xofluza® reduced the risk of participants developing influenza illness by 76% versus placebo.

Safety:

- The incidence of adverse events was 22.2% and 20.5% for Xofluza® and placebo, respectively. No serious adverse events were reported for Xofluza®.

About Xofluza® (baloxavir marboxil)

Discovered by Shionogi, Xofluza® 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 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 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).

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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Shionogi Filed for the Supplemental New Drug Application of XOFLUZA® in Japan for the Post-Exposure Prophylaxis of Influenza Virus Infection
6. 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
7. Press release on March 27, 2020
FDA Accepts a New Drug Application for a New Formulation and Two Supplemental New Drug Applications for XOFLUZA® (Baloxavir Marboxil)
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