Press Release

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.

OSAKA, Japan, August 29, 2019 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") today announced that Xofluza® has been approved in Taiwan for the treatment of acute influenza Types A and B in patients 12 years of age and older on August 28, 2019.

Xofluza® has a novel mechanism of action that inhibits cap-dependent endonuclease, an essential enzyme for viral replication. Support for this approval includes clinical efficacy and safety data from a phase II study in Japan, a global phase III study (CAPSTONE-1) in otherwise healthy patients, and a global phase III study (CAPSTONE-2) in individuals at high risk for influenza-related complications. Taiwan Shionogi & Co., Ltd., (hereafter “Taiwan Shionogi”), the Taiwan subsidiary of Shionogi, will launch Xofluza® in Taiwan. Taiwan Shionogi will provide scientific information on the drug’s novel mechanism of action, its unique single oral dosing regimen, as well as its effects on the virus, including PA/I38X-substituted viruses with reduced susceptibility to Xofluza®. In addition, Taiwan shionogi will offer this medicine as a new option through the collection and investigation of safety information and providing an accurate information to medical institutions.

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 and 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 positioned “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.

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® was reviewed by each country's regulatory authorities and was approved in several countries including Japan and the U.S. In addition, 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 12 years and older. The Prescription Drug User Fee Act (PDUFA) date for an FDA decision on this additional indication is November 4, 2019.[5] For more information, please refer to the XOFLUZA website.

Roche is now conducting a phase III development program including pediatric populations, hospitalized patients with severe influenza and will further assess the potential to reduce transmission in otherwise healthy patients.

About CAPSTONE-1 Study

The CAPSTONE-1 study was a randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled study that enrolled 1,436 otherwise healthy patients diagnosed with influenza. In this study, baloxavir marboxil significantly reduced the time to alleviation of symptoms compared with placebo (median time; 53.7 hours versus 80.2 hours; $p<0.0001$). Baloxavir marboxil 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 baloxavir marboxil, 96.0 hours for placebo, 72.0 hours for oseltamivir; $p<0.0001$). Additionally, baloxavir marboxil was generally well tolerated with a numerically lower overall incidence of adverse events reported compared with both placebo and oseltamivir (incidence of adverse events; 20.7% for baloxavir marboxil, 24.6% for placebo, 24.8% for oseltamivir). The study design and key findings from the CAPSTONE-1 study are summarized in the press releases issued on September 13 and October 5, 2017.[6, 7]

About CAPSTONE-2 Study

The CAPSTONE-2 study is a phase III, multicentre, randomised, double-blind study that evaluated a single oral dose of 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 2184 participants enrolled in the study were randomly assigned to receive a single dose of 40 mg or 80 mg of baloxavir marboxil (according to body weight), placebo or 75 mg of oseltamivir twice a day for 5 days. Among them, 1163 (53%) patients were confirmed to have influenza virus infection with RT-PCR (influenza virus subtype: 47.9% for A/H3N2, 6.9% for

A/H1N1, 41.6% for B). 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 the time to improvement of influenza symptoms. Important secondary endpoints were time to resolution of fever, time to cessation of viral shedding and virus levels in the body by time point, and incidences of influenza-related complications.The study design and key findings from the CAPSTONE-2 study are summarized in the press releases issued on October 4, 2018. [8]

About Taiwan Shionogi & Co., Ltd

Taiwan Shionogi & Co., Ltd was incorporated locally in Taiwan in 1964. It is a wholly owned subsidiary, and also the oldest subsidiary of Shionogi & Co., Ltd, headquartered in Osaka, Japan. Taiwan Shionogi has long history of developing drugs especially in the field of antibiotics and anti-infective agents to save the lives and wellbeing of patients. Under the corporate mission, Taiwan Shionogi continuously strives to save the lives of patients and improving their quality of life by providing better medicines. In addition to the sales expansion of its main existing antibiotic Flumarin® and Finibax®, and anti flu drug Rapiacta®, Taiwan Shionogi is making its best efforts to introduce new drugs and aiming at contributing to the medium-and-long term growth of the Shionogi Group.

About Influenza

Seasonal, epidemic and pandemic influenza remain a major public health concern, and novel influenza drugs that will offer significant improvement over current therapy are urgently needed. Globally, annual epidemics result in 3 to 5 million cases of severe disease, millions of hospitalizations and up to 650,000 deaths worldwide.[9, 10, 11, 12, 13] In general, those at highest risk of influenza-related complications include children under 2 years of age, adults over 65 years of age, pregnant women, and people of any age with certain medical conditions, including chronic heart, lung, metabolic diseases (such as diabetes) and weakened immune systems.[14] In Taiwan, approximately 14% of the population need treatments for influenza or related pneumonia every year.[15] The influenza epidemic period occurs in the winter, from late November through March. The overall health impact (e.g., infections, hospitalizations, and deaths) of a flu season varies from year to year. Taiwan CDC monitors circulating flu viruses and their related disease activity and provides influenza reports (Influenza Express) each week from October through May. In Taiwan, among outpatient cases of influenza, about 0.5% require hospitalization, of which 7% of the patients with serious complications need intensive care, and of which the mortality rate is about 20%.[16]

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 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 XOFLUZATM (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 (2019)
5. Press release on March 6, 2019
   Shionogi Announces FDA Approval of XOFLUZA™ (Baloxavir Marboxil)- for the Treatment of Acute, Uncomplicated Influenza -
6. Press release on September 13, 2017
   S-033188 Phase 3 CAPSTONE-1 Study Results for Treatment of Influenza Presented at the European Scientific Working Group on Influenza Conference
7. Press release on October 5, 2017
   SHIONOGI TO PRESENT S-033188 PHASE 3 CAPSTONE-1 STUDY RESULTS FOR TREATMENT OF INFLUENZA AT IDWEEK 2017
8. Press release on October 4, 2018
   Shionogi Presents Positive Results for Baloxavir Marboxil Phase III Study (CAPSTONE-2) in

Individuals at High Risk for Influenza-Related Complications at IDWeek 2018

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