

Shionogi Announces FDA Approval of XOFLUZA™ (Baloxavir Marboxil) - for the Treatment of Acute, Uncomplicated Influenza -

OSAKA, Japan, October 25, 2018 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announced today that, after completing a Priority Review, the United States Food and Drug Administration (FDA) has approved XOFLUZA™ (baloxavir marboxil) for the treatment of acute, uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. XOFLUZA is a first-in-class, single-dose oral medicine with 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 FDA approval is based on the clinical efficacy and safety data from a phase II study conducted in Japan and phase III study (CAPSTONE-1) conducted in Japan and the U.S. in otherwise-healthy patients. A single dose of XOFLUZA significantly reduced the duration of influenza symptoms compared to placebo, and demonstrated clinical efficacy which was not significantly different from that of oseltamivir with twice-daily doses administered for 5 days.¹ “XOFLUZA showed robust efficacy and safety in clinical studies after a single, oral dose for uncomplicated influenza, that allows for low treatment burden and high rate of adherence by patients. We believe that XOFLUZA will become a promising treatment option for influenza.” said Dr. Tsutae Den Nagata, Chief Medical Officer.

XOFLUZA was discovered and developed by Shionogi. Shionogi and the Roche Group, which includes Genentech in the U.S., have a license and collaboration agreement to further develop and commercialize XOFLUZA globally. Under the terms of this agreement, Genentech has development and commercialization rights of XOFLUZA in the U.S. XOFLUZA will be available across the U.S. in the coming weeks. For more information, please read [the Genentech press release](#).

Shionogi's research and development efforts target infectious diseases as one of its priority therapeutic 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 and well being of the many patients we serve.

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About XOFLUZA

XOFLUZA, discovered and developed by Shionogi, has a novel mechanism of action that inhibits cap-dependent 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).^{2, 3, 4} XOFLUZA was approved and is now available in Japan for the treatment of influenza Types A and B in adults and pediatric patients.⁵ Shionogi submitted a NDA for XOFLUZA in Taiwan on June 29, 2018, for the treatment of influenza in patients 12 years of age and older.⁶

Shionogi recently announced that the global Phase III study (CAPSTONE-2) assessing XOFLUZA in individuals at high risk for influenza-related complications met the study's primary objective and showed superior efficacy in the primary endpoint of time to improvement of influenza symptoms (TTIS) versus placebo. XOFLUZA also demonstrated superiority to oseltamivir in TTIS for influenza B virus infection.⁷

Roche will further study XOFLUZA in a phase III development program including pediatric populations, severely ill hospitalized people with influenza and to assess the potential to reduce transmission in otherwise healthy patients. Shionogi will conduct a post-exposure phase III prophylaxis study in Japan in the 2018/2019 flu season.

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 12 years of age and older diagnosed with influenza. In this study, XOFLUZA significantly reduced the time to alleviation of symptoms compared with placebo (median time; 53.7 hours versus 80.2 hours; $p < 0.0001$) and demonstrated clinical efficacy which was not significantly different from that of oseltamivir (median time; 53.5 hours versus 53.8 hours). XOFLUZA 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 XOFLUZA, 24.6% for placebo, 24.8% for oseltamivir).

The CAPSTONE-1 and Phase II study results were recently published in the September 6, 2018 issue of the New England Journal of Medicine.¹

About Influenza

Seasonal 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.^{8, 9, 10, 11, 12}

In the U.S., an estimated 3-11 percent of the U.S. population gets the flu each year, and it can be very serious, resulting in hospitalization or even death.¹³ In the 2017/2018 flu season, more than 900,000

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people were hospitalized and more than 80,000 people died in the U.S.¹⁴ Since 2010, the Centers for Disease Control and Prevention (CDC) estimates that the flu has resulted in 9.2 to 35.6 million illnesses, 140,000 to 900,000 hospitalizations and 12,000 to 80,000 deaths.^{14, 15}

About Shionogi

Shionogi & Co., Ltd. is a Japanese major research-driven pharmaceutical company dedicated to bringing benefits to patients based on its corporate philosophy of “supplying the best possible medicine to protect the health and wellbeing of the patients we serve.” The company currently markets products in several therapeutic areas including anti-infectives, pain, cardiovascular diseases and gastroenterology. Our pipeline is focused on infectious disease, pain, CNS and oncology. For more information on Shionogi & Co., Ltd., visit www.shionogi.co.jp/en.

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

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Baloxavir Marboxil Phase II and III Studies for the Treatment of Influenza Published in the New England Journal of Medicine
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3. K.Taniguchi et al. Inhibitory Effect of S-033188, a novel inhibitor of influenza virus cap-dependent endonuclease, against avian influenza A/H7N9 virus in vitro and in vivo. Poster presentation at ESWI, September 2017.
4. K.Taniguchi et al. Inhibitory Effect of S-033188/S-033447, a novel inhibitor of influenza virus cap-dependent endonuclease, against highly pathogenic avian influenza virus A/H5N1. Poster presentation at ECCMID, April 2017.
5. [Press release on March 14, 2018](#)
XOFLUZA (Baloxavir Marboxil) Tablets 10mg/20mg for the Treatment of Influenza Types A and B launched in Japan
6. [Press release on July 2, 2018](#)
Shionogi Filed for the New Drug Application of Baloxavir Marboxil in Taiwan for the Treatment of Influenza
7. [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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