Press Release

FDA Accepts Baloxavir Marboxil New Drug Application and Grants Priority Review for the Treatment of Influenza

OSAKA, Japan, June 26, 2018 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") today announced that the U.S. Food and Drug Administration (FDA) has accepted the New Drug Application (NDA) for baloxavir marboxil for the treatment of uncomplicated influenza in patients 12 years of age and older. In addition, the FDA granted the application of Priority Review, which is granted to drugs that the FDA has determined to have the potential to provide significant improvements in the treatment, prevention or diagnosis of a disease. The Prescription Drug User Fee Act (PDUFA) date for an FDA decision is December 24, 2018.

Baloxavir marboxil has a novel mechanism of action that inhibits cap-dependent endonuclease, an essential enzyme for viral replication. Baloxavir marboxil was approved in Japan on February 23, 2018 and is available under the brand name XOFLUZA™ for the treatment of influenza Types A and B in adults and pediatric patients.[1] Clinical efficacy and safety data from a phase II study in Japan and a global phase III study (CAPSTONE-1) in otherwise healthy patients supported this NDA.

Shionogi and F. Hoffmann-La Roche Ltd. (hereafter “Roche”) are in a license and collaboration agreement to further develop and commercialize baloxavir marboxil. Under the terms of this agreement, Roche holds worldwide rights to baloxavir marboxil excluding Japan and Taiwan where the rights are retained exclusively by Shionogi. Shionogi is currently conducting a global Phase III study (CAPSTONE-2) in individuals at high risk for influenza-related complications.

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 Baloxavir Marboxil

Baloxavir marboxil, discovered by Shionogi, has a novel mechanism of action that inhibits cap-dependent endonuclease, an essential enzyme for viral replication. The proposed regimen for baloxavir marboxil is a single-oral dose to treat influenza, which is different from currently available antiviral treatments. In non-clinical studies, baloxavir marboxil demonstrated an antiviral effect against a wide range of influenza viruses including oseltamivir-resistant strains and avian strains (H7N9, H5N1).[2, 3, 4]

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.[5, 6]

About Influenza

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.[7, 8, 9, 10, 11] 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.[12]

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.

Press Release

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. T. Noshi et al. S-033447/S-033188, a Novel Small Molecule Inhibitor of Cap-dependent Endonuclease of Influenza A and B Virus: In Vitro Antiviral Activity against Laboratory Strains of Influenza A and B Virus in Madin-Darby Canine Kidney Cells. Poster presentation at OPTIONS IX, August 2016.
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 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
6. Press release on October 5, 2017
   SHIONOGI TO PRESENT S-033188 PHASE 3 CAPSTONE-1 STUDY RESULTS FOR

TREATMENT OF INFLUENZA AT IDWEEK 2017

7. http://www.who.int/mediacentre/news/releases/2017/seasonal-flu/en/ World Health Organization website, Up to 650 000 people die of respiratory diseases linked to seasonal flu each year, Accessed December 14, 2017.
8. http://www.who.int/mediacentre/factsheets/fs211/en World Health Organization website, Influenza (Seasonal), Accessed January 31, 2018.
9. Baxter D. Evaluating the case for trivalent or quadrivalent influenza vaccines. Hum Vaccin Immunother. 2016; 12(10):2712-2717.
10. https://www.cdc.gov/flu/about/disease/2015-16.htm CDC website, Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United State. Accessed April 19, 2017.
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12. https://www.cdc.gov/flu/about/disease/high_risk.htm CDC website, People at High Risk of Developing Flu–Related Complications, Accessed January 23, 2018.