Press Release

Baloxavir Marboxil Phase II and III Studies for the Treatment of Influenza Published in the New England Journal of Medicine

Osaka, Japan and Florham park, N.J., September 6, 2018 - Shionogi & Co., Ltd. (Head Office: Osaka; President & CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") today announced that the positive results from Phase II and III studies of baloxavir marboxil for the treatment of influenza in otherwise-healthy patients have been published in the New England Journal of Medicine (NEJM) on September 6, 2018.[1] Baloxavir marboxil was disovered by Shionogi and has a novel mechanism of action that inhibits viral cap-dependent endonuclease.

In the Phase II study conducted in adults in Japan, baloxavir marboxil demonstrated a reduction in time to allevation of symptoms and in influenza virus titers compared with placebo.[2, 3, 4] In the global Phase III study (CAPSTONE-1) in patients 12 years of age and older, baloxavir marboxil reduced time to allevations of symptoms (TTAS) compared with placebo. On the other hand, there was no statistical difference in TTAS between baloxavir marboxil and oseltamivir. Of note, baloxavir marboxil demonstrated more rapid declines in infectious virus titers compared with both placebo and oseltamivir. Regarding safety, baloxavir marboxil was well tolerated with a numerically lower overall incidence of adverse events compared with both placebo and oseltamivir.[5, 6, 7]

"In addition to its favorable safety and pharmacokinetic profile enabling single dose oral therapy in uncomplicated influenza, baloxavir marboxil's antiviral potency offers promise of potentially reducing complications and transmission of the virus to others and in treating more serious forms of influenza illness. It also addresses an important unmet medical need in inhibiting influenza viruses that are resistant to currently available agents." said Frederick G. Hayden, M.D., Stuart S. Richardson Professor Emeritus of Clinical Virology and Professor Emeritus of Medicine, University of Virginia School of Medicine, the lead author of the published paper.

A timeline of important events in 2018 are as follows:

- February 23: Baloxavir marboxil was approved in Japan. Baloxavir marboxil is now available in Japan under the brand name XOFLUZA® for the treatment of influenza Types A and B in adults and pediatric patients.[8]
- April 24: Shionogi submitted a New Drug Application (NDA) to the United State's Food and Drug Administration (FDA) for the treatment of acute uncomplicated influenza in patients 12 years of age and older in collaboration with F. Hoffmann-La Roche Ltd. (hereafter "Roche"). On June 26, the FDA accepted the NDA and granted Priority Review. The Prescription Drug User Fee Act (PDUFA) date for an FDA decision is December 24, 2018.[9]
- June 29: Shionogi submitted a NDA for baloxavir marboxil in Taiwan for the treatment of influenza in patients 12 years of age and older.[10]
- July 17: Shionogi announced positive top-line results of CAPSTONE-2, a Phase III study in patients at high risk for influenza-related complications. The results from the CAPSTONE-2 study will be presented

at upcoming medical meetings.[11]

- September 6: The NEJM published the results of Phase II and Phase III studies of baloxavir marboxil for the treatment of influenza in otherwise-healthy patients.[1]

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 many patients we serve.

About Baloxavir Marboxil

Baloxavir marboxil, discovered and developed by Shionogi, has a novel mechanism of action that inhibits cap-dependent endonuclease, an essential enzyme for viral replication. The regimen for baloxavir marboxil is a single-oral dose to treat uncomplicated influenza, which is different from most 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).[12, 13, 14]

Shionogi and the Roche Group which includes Genentech in the U.S. are in a license and collaboration agreement to further develop and commercialize baloxavir marboxil globally. Under the terms of this agreement, the Roche Group holds worldwide rights to baloxavir marboxil excluding Japan and Taiwan where the rights are retained exclusively by Shionogi. Roche will further investigate baloxavir marboxil in a global Phase III development program including pediatric and severely ill hospitalized populations with influenza. Shionogi will conduct a post-exposure Phase III prophylaxis study in Japan in the 2018/2019 flu season.

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.[15, 16, 17, 18, 19]

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.” Shionogi Inc., the U.S. based subsidiary of Shionogi & Co., Ltd., continues this focus on the development and commercialization of high quality medicines that protect the health and well-being 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., please visit www.shionogi.co.jp/en. For more information on Shionogi Inc., please visit www.shionogi.com.

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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Reference:

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. https://www.nejm.org/doi/full/10.1056/NEJMoa1716197?query=featured_home
2. Press release on August 29, 2016
   Shionogi Presents Results from a Phase 2 Proof-of-Concept Clinical Trial and Non-Clinical Studies of S-033188, a Novel Cap-Dependent Endonuclease Inhibitor for Treatment of Influenza - Oral Presentation and Posters Presented at Options IX –
3. Press release on December 1, 2016
   Secondary Endpoint Data for S-033188, a Novel Cap-Dependent Endonuclease Inhibitor for Treatment of Influenza, Support Favorable Primary Endpoint Data Previously Released - Oral Presentation Presented at APCCMI -
4. Press release on April 25, 2017
   Shionogi Presents Results of the First Clinical Efficacy Trial and In Vitro Data on Cefiderocol (S-649266), a Siderophore Cephalosporin
5. Press release on July 24, 2017
   Shionogi Announces Positive Top-Line Results for S-033188 Phase 3 Study (CAPSTONE-1) in Otherwise Healthy Influenza Patients
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 March 14, 2018
   XOFLUZA (Baloxavir Marboxil) Tablets 10mg/20mg for the Treatment of Influenza Types A and B

launched in Japan

9. Press release on June 26, 2018
   FDA Accepts Baloxavir Marboxil New Drug Application and Grants Priority Review for the Treatment of Influenza
10. Press release on July 2, 2018
    Shionogi Filed for the New Drug Application of Baloxavir Marboxil in Taiwan for the Treatment of Influenza
11. Press release on July 17, 2018
    Shionogi Announces Positive Top-Line Results for Baloxavir Marboxil Phase III Study (CAPSTONE-2) in Individuals at High Risk for Influenza-Related Complications
12. 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.
13. 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.
14. 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.
15. 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.
16. http://www.who.int/mediacentre/factsheets/fs211/en World Health Organization website, Influenza (Seasonal), Accessed January 31, 2018.
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18. 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.
19. Nair H, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011 Dec 3;378(9807):1917-30.