Press Release

FDA Accepts XOFLUZA™ (Baloxavir Marboxil) Supplemental New Drug Application for the Treatment of Influenza in Individuals at High Risk for Influenza-Related Complications

OSAKA, Japan, March 6, 2019 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announced today that the U.S. Food and Drug Administration (FDA) has accepted a supplemental New Drug Application (sNDA) for XOFLUZA™ (baloxavir marboxil) for the treatment of influenza in individuals at high-risk for influenza-related complications 12 years of age or older. The Prescription Drug User Fee Act (PDUFA) date for an FDA decision is November 4, 2019.

The sNDA is based on the global phase III study (CAPSTONE-2) data in individuals 12 years of age or older who are at high risk for influenza-related complications, which met the study's primary objective, clinical endpoint compared with placebo, and secondary clinical and virologic endpoints.[1] "Influenza can lead to serious health consequences such as hospitalization or even death especially in individuals who tend to develop complications from influenza." said Dr. Tsutae Den Nagata, Chief Medical Officer at Shionogi. "There are no medicines which have demonstrated a clear benefit for influenza in high-risk populations in clinical studies. XOFLUZA would be the first medicine to reduce the time to improvement of influenza symptoms compared with placebo significantly in high-risk populations. Therefore, if this indication is approved, we believe that XOFLUZA will provide an important treatment option for individuals at high risk for influenza complications."

XOFLUZA was discovered by Shionogi and CAPSTONE-2 was conducted globally 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 is currently available across the U.S. for the treatment of acute, uncomplicated influenza in people 12 years of age or older.[2] For more information, please refer to the XOFLUZA website.

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 constantly strives 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, 5] XOFLUZA was approved and is now available in Japan for the treatment of influenza Types A and B in adults and pediatric patients.[6] Shionogi submitted a NDA for XOFLUZA in Taiwan on June 29, 2018, for the treatment of influenza in patients 12 years of age or older.[7]

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. Shionogi is conducting a post-exposure phase III prophylaxis study in Japan in the 2018/2019 flu season.

About CAPSTONE-2 Study[1]

The CAPSTONE-2 study is a phase III, multicenter, randomized, double-blind study that evaluated a single oral dose of XOFLUZA compared with placebo and oseltamivir in patients 12 years of age 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 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 study was conducted globally by Shionogi. Key results from CAPSTONE-2 are as follows:

XOFLUZA significantly reduced the time to improvement of influenza symptoms (TTIIS, the primary endpoint) compared with placebo (median time of 73.2 hours versus 102.3 hours; $p<0.0001$) and met the study's primary objective. In analysis for each influenza virus subtype, XOFLUZA significantly reduced TTIIS in influenza type A/H3N2 (median time of 75.4 hours versus 100.4 hours; $p<0.05$) and type B (median time of 74.6 hours versus 100.6 hours; $p<0.05$) compared with placebo.

XOFLUZA demonstrated superior efficacy compared with placebo for important secondary endpoints:

- Significantly reduced the length of time the virus continued to be released from the body (viral shedding; median time of 48.0 hours versus 96.0 hours; $p<0.0001$).
- Significantly reduced the usage of antibiotics for infections secondary to influenza infection (3.4% versus 7.5%; $p=0.01$).

- Significantly reduced the incidence of influenza-related complications (2.8% versus 10.4%; $p<0.05$)

XOFLUZA was also shown to be effective compared with oseltamivir for key endpoints:

- Numerically reduced the TTIIS (median time of 73.2 hours versus 81.0 hours; $p=0.8347$). In analysis for each influenza subtype, TTIIS was significantly reduced in influenza type B (median time of 74.6 hours versus 101.6 hours; $p<0.05$)
- Significantly reduced the length of time the virus continued to be released from the body (viral shedding; median time of 48.0 hours versus 96.0 hours; $p<0.0001$)
- Numerically reduced the incidence of influenza-related complications (2.8% versus 4.6%)

XOFLUZA was well tolerated and no new safety signals were identified. XOFLUZA had a numerically lower overall incidence of reported adverse events (25.1%) compared with placebo (29.7%) or oseltamivir (28.0%). The most common adverse events reported following treatment with XOFLUZA were bronchitis (2.9%), diarrhea (2.7%), nausea (2.7%) and sinusitis (1.9%), all observed at a lower frequency than placebo.

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] Since 2010, the Centers for Disease Control and Prevention (CDC) estimates that the flu has resulted in 9.3 to 49.0 million illnesses, 140,000 to 960,000 hospitalizations and 12,000 to 79,000 deaths.[14] The Centers for Disease Control and Prevention (CDC) describes high-risk categories including children under 2 years of age, adults of 65 years of age and older, pregnant women, and people of any age with certain medical conditions, including asthma and chronic lung disease, heart disease, blood disorders, endocrine disorders, metabolic diseases, extreme obesity and weakened immune systems.[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.

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 October 4, 2018
   Shionogi Presents Positive Results for XOFLUZA Phase III Study (CAPSTONE-2) in Individuals at High Risk for Influenza-Related Complications at IDWeek 2018
2. Press release on October 25, 2018
   Shionogi Announces FDA Approval of XOFLUZA™ (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. 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.
5. 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.
6. Press release on March 14, 2018
   XOFLUZA (XOFLUZA) Tablets 10mg/20mg for the Treatment of Influenza Types A and B launched in Japan
7. Press release on July 2, 2018
   Shionogi Filed for the New Drug Application of XOFLUZA in Taiwan for the Treatment of

Influenza
8. 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.
9. http://www.who.int/mediacentre/factsheets/fs211/en World Health Organization website, Influenza (Seasonal), Accessed January 31, 2018.
10. Baxter D. Evaluating the Case for Trivalent or Quadrivalent Influenza Vaccines. Hum Vaccin Immunother. 2016; 12(10):2712-2717.
11. 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.
12. 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.
13. Tokars JI et al. Seasonal Incidence of Symptomatic Influenza in the United States. Clin Infect Dis. 2018 May 2;66(10):1511-1518.
14. https://www.cdc.gov/flu/about/disease/burden.htm CDC website, Disease Burden of Influenza
15. 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.