

Shionogi Presents Positive Results for Baloxavir Marboxil Phase III Study (CAPSTONE-2) in Individuals at High Risk for Influenza-Related Complications at IDWeek 2018

OSAKA, Japan, October 4, 2018 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") has announced that the results from the global phase III study (CAPSTONE-2) assessing baloxavir marboxil in individuals at high risk for influenza-related complications are being presented at IDWeek 2018, held in San Francisco on October 3-7, 2018.

Key results from CAPSTONE-2 are as follows:

Baloxavir marboxil 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, baloxavir marboxil 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.

Baloxavir marboxil 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%; $p < 0.05$)

Baloxavir marboxil 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%)

Baloxavir marboxil was well tolerated and no new safety signals were identified. Baloxavir marboxil 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 baloxavir marboxil were bronchitis (2.9%), diarrhoea (2.7%), nausea (2.7%) and sinusitis (1.9%), all observed at a lower frequency than placebo.

Press Release



The data from CAPSTONE-2 demonstrate that baloxavir marboxil provides a clinically meaningful benefit for patients who are most susceptible to influenza-related complications. There are no other medicines which have demonstrated clear benefit specifically in high-risk populations in clinical studies. It is remarkable that baloxavir marboxil demonstrated superiority to oseltamivir in shortening the duration of virus shedding and in resolving the symptoms of influenza B virus infection. Based on these results, Shionogi believes that baloxavir malboxil will become a promising treatment option for influenza A and B, not only for otherwise healthy patients but also for those with risk factors for influenza 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 many patients we serve.

Press Release



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 all 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).^{1, 2, 3} Baloxavir marboxil was approved and is now available in Japan under the brand name XOFLUZA[®] for the treatment of influenza Types A and B in adults and pediatric patients. Shionogi submitted the New Drug Application (NDA) for baloxavir marboxil in U.S. on April 24, 2018 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”). The U.S. Food and Drug Administration (FDA) accepted the NDA and granted Priority Review based on a phase II study in Japan and a global phase III study (CAPSTONE-1) in otherwise healthy patients.⁴ The Prescription Drug User Fee Act (PDUFA) date for an FDA decision is December 24, 2018.⁵ Shionogi submitted a NDA for baloxavir marboxil in Taiwan on June 29, 2018, for the treatment of influenza in patients 12 years of age and older.⁶

Shionogi and the Roche, 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 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 \geq 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.

Press Release



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.^{7, 8, 9, 10, 11} 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.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.

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.

For Further Information, Contact:

Corporate Communications Department
Shionogi & Co., Ltd.
Telephone: +81-6-6209-7885

Press Release



Reference:

1. 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.
2. 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.
3. 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.
4. 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
5. [Press release on June 26, 2018](#)
FDA Accepts Baloxavir Marboxil New Drug Application and Grants Priority Review for the Treatment of Influenza
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. <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.
11. 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.
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.