Press Release

CAPSTONE-2 study of Xofluza® (Baloxavir Marboxil) for the Treatment of Influenza Published in The Lancet Infectious Diseases

OSAKA, Japan, June 9, 2020 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announced today that the full results from the positive Phase III CAPSTONE-2 study investigating Xofluza® (baloxavir marboxil) for the treatment of influenza (flu) in high-risk adolescent and adult outpatients with influenza, has been published in The Lancet Infectious Diseases on June 8, 2020.

In a global CAPSTONE-2[1] study in patients 12 years of age and older with influenza and considered to be at high risk of influenza complications according to the United States Centers for Disease Control and Prevention (CDC) criteria[2] including asthma or chronic lung disease, endocrine disorders, heart disease, age ≥65 years, and metabolic disorders, Xofluza® significantly reduced the time to improvement of influenza symptoms (TTIIS) compared with placebo (the primary endpoint). In all patients in the study (those infected with influenza types A and B), the TTIIS in patients treated with Xofluza was similar to oseltamivir, but was significantly shorter versus oseltamivir in patients infected with influenza type B. Also, influenza-related complications such as bronchitis were significantly less frequent in patients treated with Xofluza® versus placebo, and were similar to oseltamivir. Regarding safety, Xofluza® was well tolerated and no new safety signals were identified.

“The CAPSTONE 2 study is an important study on two fronts. It demonstrated the efficacy of antiviral therapy in preventing complications in patients at high risk of complications. Second, it demonstrated differential response to therapy between patients infected with influenza A or B. Baloxavir resulted in more rapid clinical and virologic improvement compared to placebo and oseltamivir for influenza B.” said Michael G. Ison, M.D. M.S, Professor, Divisions of Infectious Diseases & Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA, the lead author of the published paper.

The full data from CAPSTONE-2 demonstrate that Xofluza® provides a clinically meaningful benefit for patients who are most at risk of developing influenza-related complications. The CAPSTONE-2 study is the first clinical study to demonstrate clear benefit of any antiviral medication specifically in the high-risk population. Xofluza® also previously showed positive results in the global Phase III CAPSTONE-1[3] study in otherwise healthy patients 12 years of age and older. Therefore Xofluza® is expected to contribute to the treatment of influenza, in both otherwise health and high risk patients.

Shionogi and the Roche Group (hereafter “Roche”) are in a license and collaboration agreement to further develop and commercialize Xofluza®. Under the terms of this agreement, Roche holds worldwide rights to Xofluza® excluding Japan and Taiwan, where the rights are retained exclusively by Shionogi. Xofluza® is approved and is available in Japan.[4] In the U.S., Xofluza® is available for the treatment of acute, uncomplicated influenza in people 12 years of age or older who have been symptomatic for no more than 48 hours[4] and is recommended for the treatment of acute, uncomplicated influenza in people 12 years of age or older in the guidelines of the CDC.[6] In addition, Roche’s supplemental New Drug Application (sNDA) of Xofluza® for the treatment of acute, uncomplicated influenza in people aged 12 years and older, who have been symptomatic for no more than 48 hours and who are at high-risk of influenza-related complications, was approved by the U.S. Food and Drug Administration (FDA) on October 16, 2019.[7] This was based on the efficacy and safety results of the global Phase III CAPSTONE-2 study.[1] The FDA accepted a NDA for a new formulation of Xofluza® as single-dose granules for oral suspension, potentially offering a more convenient option for children and those who have difficulty swallowing. In addition, the application seeks approval of Xofluza® for the treatment of acute uncomplicated influenza in otherwise healthy children aged one to less than 12 years of age who have been symptomatic for no more than 48 hours. The FDA also accepted an sNDA for post-exposure prophylaxis of influenza in people one year of age and older for both the oral suspension and currently-available tablet formulation. The FDA is expected to make a decision on approval by November 23, 2020.[8]

Shionogi is committed to "Protect people worldwide from the threat of infectious diseases" as our key focus. We are not limiting ourselves to the research and development of therapeutic medications, but are also focused on the total care of infectious disease through awareness building, prevention and diagnosis and suppression of exacerbation. Shionogi will continue to work diligently to collect and analyze data on the efficacy and safety of Xofluza® and provide information for appropriate use.

About the CAPSTONE-2 Study[1]

The CAPSTONE-2 study was 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 & Co., Ltd. A total of 2,184 participants enrolled in the study were randomly assigned to a single dose of 40 mg or 80 mg of Xofluza® (according to body weight), placebo or 75 mg of oseltamivir twice a day for five days. Among them, 1,163 (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) versus placebo in people at high-risk of complications from influenza (median time 73.2 hours versus 102.3 hours; $p<0.001$).
- In subjects infected with type B virus, the median time to improvement of influenza symptoms was significantly shorter in the Xofluza group compared to the placebo and oseltamivir group (median time 74.6 hours for Xofluza® versus 100.6 hours for placebo and 101.6 for oseltamivir respectively).
- Patients with asthma or chronic lung disease who received Xofluza® had significantly shorter TTIIS than with placebo (median 74.6 hours versus 110.2 hours $p=0.004$).
- Xofluza® significantly reduced the median time to sustained cessation of infectious virus detection versus placebo and oseltamivir. (the median time 48.0 hours for Xofluza, 96.0 hours for placebo and 96.0 hours for oseltamivir; $P<0.001$)
- Xofluza® significantly reduced the incidence of influenza-related complications versus placebo (2.8% versus 10.4%; $p<0.05$)
- Adverse events reported in adult and adolescent subjects treated with Xofluza® included diarrhea (2.7%), bronchitis (2.9%), nausea (2.7%), sinusitis (1.9%). Xofluza® was well-tolerated and no new safety signals were identified.

About CAPSTONE-1 Study[3]

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; $p<0.001$) 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 published in the September 6, 2018 issue of the New England Journal of Medicine.[3]

About Xofluza® (baloxavir marboxil)

Discovered by Shionogi, Xofluza® 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 influenza, which is different from all other 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).[9,10] Xofluza® has been reviewed and is currently approved in several countries including Japan and the U.S. For more information about the use in the U.S., please refer to the Xofluza® website. Roche is now conducting a phase III development program including children under the age of one year (NCT03653364), and severely ill, hospitalized patients (NCT03684044), as well as to assess the potential to reduce transmission of influenza from an infected person to healthy people (NCT03969212). Shionogi assessed the potential of Xofluza® as a post-exposure prophylaxis treatment to prevent the spread of influenza in adults and children, and submitted a sNDA on October 16, 2019 in Japan[11] and also filed sNDA for Xofluza® in Taiwan for the post-exposure prophylaxis of influenza virus infection in adults and children 12 years of age and older on March 31, 2020[12] based on the positive results from the Phase III BLOCKSTONE study.

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

References

1. Michael G. Ison, MD MS et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. Lancet Infect Dis 2020; published online June 8, 2020: https://doi.org/10.1016/S1473-3099(20)30004-9
2. CDC Criteria
   CDC website, People at High Risk For Flu Complications
3. Press release on September 6, 2018
   Baloxavir Marboxil Phase II and III Studies for the Treatment of Influenza Published in the New England Journal of Medicine

4. Press release on March 14, 2018
Xofluza® (Baloxavir Marboxil) Tablets 10mg/20mg for the Treatment of Influenza Types A and B launched in Japan
5. Press release on October 25, 2018
Shionogi Announces FDA Approval of Xofluza® (Baloxavir Marboxil) - for the Treatment of Acute, Uncomplicated Influenza
6. CDC Guideline
CDC website, Influenza Antiviral Medications: Summary for Clinicians
7. Press release on October 18, 2019
FDA Approves Xofluza® (Baloxavir Marboxil) for the Treatment of Acute Uncomplicated Influenza for People at High Risk of Developing Influenza-Related Complications
8. Press release on March 27, 2020
FDA Accepts a New Drug Application for a New Formulation and Two Supplemental New Drug Applications for XOFLUZA® (Baloxavir Marboxil)
9. 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
10. K. Taniguchi et al. Inhibition of avian-origin influenza A(H7N9) virus by the novel cap-dependent endonuclease inhibitor baloxavir marboxil. Scientific Reports volume 9, Article number: 3466 (2019)
11. Press release on September 2, 2019
Shionogi Announces Positive Post-Exposure Prophylaxis Results for Xofluza®® in Phase III Study (BLOCKSTONE) of Influenza Virus Infection in Household Members
12. Press release on March 31, 2020
Shionogi Filed for the Supplemental New Drug Application of Xofluza® in Taiwan for the Post-Exposure Prophylaxis of Influenza Virus Infection