Press Release

The Results of Analyses of PA/I38X-substituted Viruses in XOFLUZA® Clinical Studies

OSAKA, Japan, September 2, 2019 - Shionogi & Co., Ltd. (hereafter "Shionogi") has announced the results of additional analyses of PA/I38X-substituted viruses in the completed clinical studies of XOFLUZA®(baloxavir marboxil), that were presented at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), held in Amsterdam on April 13 – 16, 2019, and Options X for the Control of Influenza (OPTIONS X), held in Singapore on August 28 – September 1, 2019.

Summary of presentations about PA/I38X-substituted viruses are as follows:

1. Incidence of PA/I38X-substituted viruses
   - The incidence (rate of detecting PA/I38X-substituted viruses) was high in younger pediatric patients. With respect to type/subtype of influenza virus, the rate was higer in A/H3N2 infection.
   - The higher resistance rate in younger pediatric patients may be due to immaturity of their immune system; association was observed between low antibody titers and the rate of detection.

It is known that type/subtype of influenza virus varies by season and the rates of resistance to anti-influenza drugs are also different for each influenza season. Shionogi considers it important to continue to obtain data about the resistance rate. Shionogi will continue to monitor and characterize the incidence of PA/I38X-substituted viruses and disclose the information appropriately.

2. Association between the incidence of PA/I38X-substituted viruses and clinical symptoms
   - Adult and adolescent patients
     - ✧ CAPSTONE-1 study: The median time to alleviation of symptoms tended to be longer in patients with PA/I38X-substituted viruses after treatment with XOFLUZA than in patients without PA/I38X-substituted viruses. However, the median time to alleviation of symptoms in patients with PA/I38X-substituted viruses after treatment with XOFLUZA was shorter than that in those treated with placebo.
     - ✧ CAPSTONE-2 study: The median time to improvement of influenza symptoms tended to be shorter in patients with PA/I38X-substituted viruses after treatment with XOFLUZA than in those without PA/I38X-substituted viruses .
     - ✧ No clear association between the incidence of PA/I38X-substituted viruses and exacerbation of clinical symptoms was observed in either CAPSTONE-1 or CAPSTONE-2 studies.

   - Pediatric patients
     - ✧ Pediatric studies (tablet and granule) in Japan: The median time to alleviation of illness tended to be longer in patients with PA/I38X-substituted viruses after treatment with

XOFLUZA than in those without PA/I38X-substituted viruses. This tendency was more apparent in younger pediatric populations with A/H3N2 viruses; recurrence of fever was see in some of them. This study was not a comparator-controlled study and, no clear evaluation was possible of the impact of the substituted viruses on clinical outcome.

- ✧ Phase III global pediatric study (MINISTONE-2): The median time to alleviation of signs and symptoms tended to be longer in patients with PA/I38X-substituted viruses after treatment with XOFLUZA than in those without PA/I38X-substituted viruses. However, the median time to alleviation of signs and symptoms in patients with PA/I38X-substituted viruses after treatment with XOFLUZA was comparable to that in those treated with oseltamivir. The result of the study indicated, therefore, a clinical benefit of XOFLUZA in pediatric patients.

The above data showed that there was no clear association between the rate of detecting PA/I38X-substituted viruses and the median time to alleviation or improvement of symptoms in adult and adolescent patients. These data suggest clinical benefit of XOFLUZA in these populations irrespective of the substitution. In pediatric patients, the median time to alleviation of illness tended to be longer in patients with PA/I38X-substituted viruses after treatment with XOFLUZA in younger pediatric populations for A/H3N2 virus infection, and some of them showed recurrence of fever in pediatric studies which were conducted in Japan without a control group. On the other hand, the global pediatric controlled study showed that the median time to alleviation of symptoms was comparable between patients with PA/I38X-substituted viruses after treatment with XOFLUZA and those treated with oseltamivir, which has been confirmed to have clinical benefit in pediatric patients. Therefore, it was considered that clinical benefit of XOFLUZA was confirmed in pediatric patients in this study.
Shionogi considers that it is important to continue to obtain additional data about PA/I38X-substituted viruses because the available analysis data are limited as of this moment especially in pediatric patients.

3. Rate of detecting PA/I38X-substituted viruses in the post-exposure prophylaxis study (BLOCKSTONE)

In the exploratory, post-exposure prophylaxis study, transmission of PA/I38X-substituted viruses was evaluated. In this study, 53% of index patients had been treated with XOFLUZA; no household members of these index patients (subjects) treated with placebo were found to have been infected with PA/I38X-substituted viruses when diagnosing influenza infection. Therefore, none of the subjects treated with placebo in this study were suspected to have been transmitted with PA/I38X-substituted viruses from index patients.

Shionogi and 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 was approved in Japan on February 23, 2018 and is available for the treatment of influenza Types A and B in adults and pediatric patients[1], and was approved in the U.S. on October 25, 2018 where it is available for the treatment of acute, uncomplicated influenza in people 12 years of age or older.[2]

Shionogi's research and development efforts target infectious diseases as one of its priority areas, and Shionogi has defined "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. Shionogi will continue to work diligently to collect and analyze data on the efficacy and safety of XOFLUZA and provide information for proper use.

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] XOFLUZA has been reviewed and is currently approved in several countries, including Japan and the U.S. In addition, XOFLUZA was approved in Taiwan on August 28, 2019, for the treatment of acute influenza Types A and B in patients 12 years of age and older.[5] The U.S. Food and Drug Administration (FDA) has accepted a supplemental New Drug Application for XOFLUZA™ for the treatment of influenza in individuals at high-risk for influenza-related complications aged 12 years and older. The Prescription Drug User Fee Act date for an FDA decision on this additional indication is November 4, 2019.[6] For more information, please refer to the XOFLUZA website.

Roche is now conducting a phase III development program including pediatric populations under one year, hospitalized patients with severe influenza and will assess the potential to reduce transmission of influenza from an infected person to healthy people.

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, XOFLUZA significantly reduced the time to alleviation of symptoms compared with placebo (median time; 53.7 hours versus 80.2 hours; $p<0.0001$). XOFLUZA 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 XOFLUZA, 96.0 hours for placebo, 72.0 hours for oseltamivir; $p<0.0001$). Additionally, 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 study design and key findings from the CAPSTONE-1 study are summarized in the press releases issued on September 13 and October 5, 2017.[7, 8]

About CAPSTONE-2 Study

The CAPSTONE-2 study is a phase III, multicentre, randomised, double-blind study that evaluated a single oral dose of XOFLUZA 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 XOFLUZA (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 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. The study design and key findings from the CAPSTONE-2 study are summarized in the press releases issued on October 4, 2018.[9]

About Japan pediatric studies (tablet)

Japan pediatric study (tablet) is a phase III open-label study for otherwise healthy patients of 6 months or older but under 12 years of age. 104 subjects received a single oral dose of XOFLUZA 5-40mg on day 1 according to body weight at the time of screening, and a 14-day efficacy assessment and a 22-day safety assessment were conducted over a 22-day study period.

About Japan pediatric studies (granule)

Japan pediatric study (granule) is a phase III open-label study for otherwise healthy patients of under 20kg. 33 subjects received a single oral dose of XOFLUZA 1 mg / kg (less than 10 kg) or 10 mg (10 kg or more) administered orally once on day 1 according to body weight at the time of screening, and a 14-day efficacy assessment and a 22-day safety assessment were conducted over a 22-day study period.

About MINISTONE-2 study

MINISTONE-2 is a phase III, multicenter, randomized, double-blind study that evaluated the safety, pharmacokinetics and efficacy of one dose of XOFLUZA compared with oseltamivir in otherwise healthy children aged one to less than 12 years with influenza infection and displaying influenza symptoms (temperature of 38°C or over, and one or more respiratory symptoms).

Participants enrolled in the study were recruited in parallel into two cohorts: patients aged five to less than 12 years and patients aged one to less than five years. Patients in both cohorts were randomly

assigned to receive one dose of XOFLUZA (2 mg/kg for patients under 20 kg or 40 mg for patients 20 kg or over) or oseltamivir twice a day over five days (dosing according to body weight). The primary endpoint of the study was the proportion of patients with adverse events or severe adverse events up to study Day 29. Secondary endpoints included pharmacokinetics, time to alleviation of influenza signs and symptoms, and duration of symptoms, including fever.

About BLOCKSTONE Study

The BLOCKSTONE study was a phase III, multicenter, randomized, double-blind study that evaluated a single oral dose of XOFLUZA compared with placebo for the post- exposure prophylaxis of influenza virus infection in subjects who are household members of influenza-infected patients. The study was conducted by Shionogi in Japan. Participants enrolled in the study were randomly assigned to receive either a single dose of XOFLUZA (the dose was set according to age and body weight*) or placebo. The primary endpoint of the study was the proportion of subjects who were infected with influenza virus and presented with fever and at least one respiratory symptom during the 10 days after taking XOFLUZA or placebo.

*Dosage of XOFLUZA in BLOCKSTONE study

1.12 years of age or older

Body weight	Dosage
80 kg or more	80 mg
Less than 80 kg	40 mg

2.Under 12 years of age

Body weight	Dosage
40 kg or more	40 mg
Less than 40 kg and 20 kg or more	20 mg
Less than 20 kg and 10 kg or more	10 mg (granule)
10 kg or less	1 mg/kg (granule)

About Influenza

Seasonal and pandemic influenza remain a major public health concern. Globally, seasonal epidemics result in 3 to 5 million cases of severe disease, millions of hospitalizations and up to 650,000 deaths every year.[10, 11, 12, 13, 14]

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

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. 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. 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)
5. Press release on August 29, 2019
   Shionogi Announces XOFLUZA® Tablets 20mg for The Treatment of Influenza Types A and B in Patients 12 years of Age and older Approved in Taiwan.
6. Press release on March 6, 2019
   FDA Accepts XOFLUZATM (Baloxavir Marboxil) Supplemental New Drug Application for the

Treatment of Influenza in Individuals at High Risk for Influenza-Related Complications.

7. 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
8. Press release on October 5, 2017
   SHIONOGI TO PRESENT S-033188 PHASE 3 CAPSTONE-1 STUDY RESULTS FOR TREATMENT OF INFLUENZA AT IDWEEK 2017
9. Press release on October 4, 2018
   Shionogi Presents Positive Results for Baloxavir Marboxil Phase III Study (CAPSTONE-2) in Individuals at High Risk for Influenza-Related Complications at IDWeek 2018
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