

S-033188 Phase 3 CAPSTONE-1 Study Results for Treatment of Influenza Presented at the European Scientific Working Group on Influenza Conference

Osaka, Japan, September 13, 2017 - Results of a S-033188 Phase 3 study in influenza patients (CAPSTONE-1) were released at the 6th European Scientific Working Group on Influenza Conference (ESWI), held on September 10-13, 2017 in Riga, Latvia. Additionally, Shionogi & Co., Ltd. (hereafter "Shionogi") presented data on the nonclinical activity of this investigational drug against A/H7N9 (avian influenza).

S-033188 is a novel cap-dependent endonuclease inhibitor with potent anti-viral efficacy. Important findings for S-033188 presented at ESWI include the following:

Phase 3 CAPSTONE-1 study results (abstract # PL0501)

The CAPSTONE-1 study was a randomized, double-blind, multicenter, parallel-group, placebo and oseltamivir-controlled study that enrolled 1,436 otherwise healthy patients diagnosed with influenza. Patients aged 20 to 64 years were randomly assigned in a ratio of 2:2:1 to receive a single one-time oral dose of 40 or 80 mg of S-033188, according to body weight, 75 mg twice daily of oseltamivir or placebo for five days. Patients aged 12 to 19 years were randomly assigned in a ratio of 2:1 to receive either a single one-time oral dose of S-033188 or placebo.

Key results for S-033188 were:

- Significant improvement in time to alleviation of symptoms (TTAS) compared with placebo. The median TTAS was 53.7 hours in S-033188 group, compared to 80.2 hours in placebo group ($p < 0.0001$). TTAS was similar between S-033188 and oseltamivir groups.
- Significantly greater reduction in viral titer compared to placebo or oseltamivir. At 24 hours after start of treatment, mean viral titers decreased by approximately 4.4, 1.2 and 2.5 \log_{10} TCID₅₀/ml from baseline in the S-033188, placebo and oseltamivir groups, respectively ($p < 0.0001$, S-033188 vs placebo or oseltamivir).
- Significant reduction in time to cessation of viral shedding compared to placebo or oseltamivir. Time to cessation of viral shedding was significantly shorter in the S-033188 group (median 24.0 hours) than in either the placebo (96.0 hours, $p < 0.0001$) or oseltamivir groups (72.0 hours, $p < 0.0001$).
- Significantly faster resolution of fever compared to placebo (median 24.5 vs 42.0 hours).
- S-033188 was generally well tolerated with a numerically lower overall incidence of adverse events (20.7%) compared with placebo (24.6%) or oseltamivir (24.8%). S-033188 demonstrated a statistically significant decrease in the incidence of treatment-related adverse events compared to oseltamivir ($p = 0.0088$).

Inhibitory effect of S-033188 against avian influenza A/H7N9 virus in vitro and in vivo (abstract # SPA4P09)

S-033447, the active form of S-033188, demonstrated more potent antiviral activity against the A/Anhui/1/2013 strain than oseltamivir acid (mean EC₉₀ values: 0.80 nM vs. 15.41 nM) in the virus yield reduction assay. S-033188 completely eliminated mortality in this mouse model and exhibited significantly longer survival time compared to vehicle or oseltamivir.

In addition to Phase 3 and A/H7N9 presentations, exploratory data from the completed Phase 2 study and nonclinical activity data in an immunocompromised mice model were shown at the conference.

“We are very excited that a single one-time oral dose of S-033188 demonstrated this rapid viral load reduction and reduced duration of virus shedding, compared with oseltamivir.” said Dr. Tsutae Den Nagata, Chief Medical Officer, “Also, we believe this drug will be able to address potential public health concerns, for example, pandemic influenza caused by avian influenza viruses such as A/H7N9.”

Based on the results from CAPSTONE-1, Shionogi plans to submit a New Drug Application (NDA) to the PMDA in Japan later this year. Shionogi is currently conducting another global Phase 3 study (CAPSTONE-2) in individuals at high risk for influenza-related complications; patient enrollment in the study is ongoing. A US NDA is planned.

About S-033188

S-033188 is a cap-dependent endonuclease inhibitor with a novel mechanism of action being studied for the treatment of influenza using a one-time dosing regimen. Development and commercialization of S-033188 are in collaboration with F. Hoffmann-La Roche Ltd.

About Influenza

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. Worldwide, annual influenza epidemics are estimated to result in 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths.¹ In general, those at highest risk of influenza-related complications include children under 2 years of age, adults over 65 years of age, pregnant women, and people of any age with certain medical conditions, including chronic heart, lung, metabolic diseases (such as diabetes) and weakened immune systems.

About Shionogi

Shionogi & Co., Ltd. is a 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’s research and development currently target two therapeutic

areas: infectious diseases, and pain/CNS disorders. For over 50 years, Shionogi has developed and commercialized innovative oral and parenteral anti-infectives. In addition, Shionogi is engaged in new research areas, such as obesity/geriatric metabolic disease and oncology/immunology. Contributing to the health and quality of life of patients around the world through development in these therapeutic areas is Shionogi's primary goal. For more details, please visit www.shionogi.co.jp/en/. For more information on Shionogi Inc., the U.S. –based subsidiary of Shionogi & Co., Ltd., headquartered in Florham Park, NJ, USA, please visit www.shionogi.com. For more information on Shionogi Ltd., the UK-based subsidiary of Shionogi & Co. Ltd., headquartered in London, England, please visit www.shionogi.eu.

Forward Looking Statement

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.

Contacts:

Corporate Communications, Shionogi & Co., Ltd.
Telephone: +81-6-6209-7885
Fax: +81-6-6229-9596

References

1. <http://www.who.int/mediacentre/factsheets/fs211/en/> WHO website, Influenza (Seasonal), Fact sheet N°211, March 2014.