PRESSRELEASE

SHIONOGI

Shionogi Announces Achievement of the Primary Endpoint for Ensitrelvir Fumaric Acid (S-217622) in the Phase 3 part of the Phase 2/3 Clinical Trial in Asia

- Ensitrelvir achieved the primary endpoint in the Phase 3 part of the Asian Phase 2/3 clinical trial, demonstrating a significant reduction vs placebo in the time to first resolution of five typical Omicron-related symptoms. This study was conducted in a predominantly vaccinated patient population with mild/moderate COVID-19, irrespective of risk factors for severe complications.
- Ensitrelvir also showed a significant reduction in viral RNA on day 4 (following the third dose) relative to placebo (a greater than 1.4 $\log_{10}$ copies/mL vs. placebo for change from baseline on day 4).
- With the results of this study, conducted during the Omicron phase of the pandemic, ensitrelvir has become the first investigational oral antiviral to demonstrate a statistically significant effect compared to placebo in the time to resolution of symptoms.

OSAKA, Japan, September 28, 2022 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announced that ensitrelvir fumaric acid (S-217622: hereafter "ensitrelvir"), an investigational, 3CL protease inhibitor, administered once daily for five days, being evaluated as an antiviral treatment for COVID-19, achieved the primary endpoint in the Phase 3 part of a Phase 2/3 study conducted in Asia.

This study was conducted in patients with mild/moderate symptoms of COVID-19 and assessed clinical symptom resolution with ensitrelvir (2 dose groups; high dose and low dose), orally administered once daily for five days, compared to placebo. A total of 1,821 patients were enrolled, in Japan, South Korea, and Vietnam, irrespective of risk factors for COVID-19 progression. The majority of patients were previously vaccinated. The primary endpoint in the study was the time to first resolution of five key COVID-19 symptoms (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness) which are characteristic of infection with the SARS-CoV-2 Omicron variant, in patients randomized within 72 hours from the onset of symptoms. The five assessed symptoms were selected in consultation with medical experts and regulatory authorities including the Ministry of Health, Labor and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and the U.S. Food and Drug Administration (FDA), based on their scientific and medical validity.

In this population, the median time to first resolution of the five COVID-19 symptoms was significantly reduced in those treated with the low dose of ensitrelvir (the dose level submitted for approval in Japan) compared to placebo: 167.9 hours versus 192.2 hours, a statistically significant difference of 24 hours (p=0.04). In addition, with respect to the key secondary endpoint of reduction in viral RNA on day 4 (following the third dose), ensitrelvir showed a significant difference versus placebo ($p<0.0001$) in the Least Squares mean change from baseline in viral RNA; a reduction of more than 1.4 $\log_{10}$ copies/mL versus placebo, similar to the results observed in previous studies[1-3]. With regard to safety, both doses of ensitrelvir were well tolerated, and there were no serious adverse events or deaths in this study. In the low-dose group, the most common treatment-related adverse events were decreased high-density lipoprotein and increased blood triglycerides, as observed in previous studies.

The emergency approval of ensitrelvir was deliberated in the Pharmaceutical Affairs and Food Sanitation Council meeting held on July 20, 2022, in Japan, and review will continue based on the results of the Phase 3 part of the study. The top-line results of the Phase 3 part have been reported to MHLW and PMDA. We will continue to consult closely with both organizations for review and deliberation on approval of ensitrelvir while we continue analyses of data and the preparation of additional filing documents.

Shionogi is committed to "Protect people worldwide from the threat of infectious diseases" as our key focus. As SARS-CoV-2 continues to have a major impact on people's lives and to represent a global threat, we will seek to contribute to re-establishing the safety and security of society by developing new products and services to address this pandemic, and will keep all of our stakeholders informed regarding the progress of our efforts.

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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, lack of availability 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:
SHIONOGI Website Inquiry Form : https://www.shionogi.com/global/en/contact.html

About ensitrelvir fumaric acid (S-217622)

Ensitrelvir fumaric acid, an investigational drug for COVID-19, is a 3CL protease inhibitor created through joint research between Hokkaido University and Shionogi. Clinical trials in Asia through the Phase 2b part of the Phase 2/3 clinical trial in patients with mild/moderate symptoms have been completed, and the Phase 3 part of the Phase 2/3 clinical trial in patients with mild/moderate symptoms is the subject of this press release. The Phase 2b/3 part of a trial in Asian patients (mainly in Japan) with asymptomatic/mild symptoms is still in progress. Globally, the global Phase 3 trial (SCORPIO-HR) for SARS-CoV-2 infected patients is also underway.

References

1. Press release on February 7,2022
   Shionogi Presents Phase 2/3 Clinical Trial Results (Phase 2a Part) for the COVID-19 Therapeutic Drug S-217622
2. Press release on February 25,2022
   Notice Regarding the Signing of a Basic Agreement with the Ministry of Health, Labor and Welfare for Domestic Supply of S-217622, a Therapeutic Drug for COVID-19
3. Press release on April 24,2022
   New Data for Shionogi's COVID-19 Once-Daily Oral Antiviral S-217622 Show Rapid Virus Clearance