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Shionogi Presents Pivotal Ensitrelvir Fumaric Acid Phase 3 Data and Exploratory Long COVID Data at CROI

OSAKA, Japan, February 21, 2023 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") today, at the 30th Conference on Retroviruses and Opportunistic Infections (CROI), presented further results from the Phase 3 part of the pivotal SCORPIO-SR trial (Phase 2/3 study) conducted in Japan, South Korea, and Vietnam (hereafter, the "Study") of the novel COVID-19 oral antiviral ensitrelvir (Generic name: ensitrelvir fumaric acid, Code No.: S-217622, hereafter "ensitrelvir"). Shionogi also presented exploratory data from the Study evaluating the potential effect of ensitrelvir on the symptoms of long COVID.

Ensitrelvir, known as Xocova® 125 mg tablet in Japan, recently received emergency regulatory approval from the Ministry of Health, Labour and Welfare (MHLW) for the treatment of SARS-CoV-2 infection. It remains an investigational drug outside Japan.

Ensitrelvir Meets Primary and Key Secondary Endpoints in Pivotal Phase 3 Study

In the Study, ensitrelvir met the primary endpoint, demonstrating a statistically significant reduction compared to placebo in the time to resolution of five typical COVID-19-related symptoms in the current Omicron-dominant phase of the pandemic – runny/stuffy nose, sore throat, cough, feeling hot or feverish, and low energy/tiredness. The Study was also the first to show a statistically significant reduction ($p<0.0001$) in the time to negative infectious viral titer versus placebo, a key secondary endpoint. Regarding safety, ensitrelvir was well tolerated, and there were no serious treatment-related adverse events or deaths in the Study. Among the most common treatment-related adverse events were temporary decreases in high-density lipoprotein and increased blood triglycerides, as observed in previous studies.

The Study results presented today included:

- **Primary endpoint:** the time to resolution of five symptoms of COVID-19 was 167.9 hours in patients treated with 125 mg ensitrelvir, compared to 192.2 hours in the placebo group, a difference of a median time of 24.3 hours ($p=0.0407$).
- **Secondary endpoint:** the time to achieve a negative infectious viral titer was significantly shorter in the ensitrelvir 125 mg group compared with placebo (a median time of 36.2 hours versus 65.3 hours, $p<0.0001$).
- **Safety:** ensitrelvir was well-tolerated, with no serious adverse drug reactions, and no deaths.

The Study was conducted in patients with mild/moderate COVID-19 enrolled across Japan, South Korea, and Vietnam, irrespective of risk factors for COVID-19 progression. The population was predominantly (more than 90%) COVID-19 vaccinated. A total of 1,203 patients with viral RNA positive at baseline received 125 mg ensitrelvir, with an initial 375 mg loading dose (n = 603), or placebo (n = 600), administered orally once-daily over five days, within five days of symptom onset. The population for the primary and key secondary endpoint

analyses was the 690 patients (347 ensitrelvir 125 mg; 343 placebo) randomized within 72 hours from the onset of symptoms. In addition to the above presented results, 125 mg ensitrelvir was shown to reduce the amount of viral RNA compared with placebo on Day 4 (least squares mean change from baseline -2.48 $\log_{10}$ copies/mL versus -1.01 $\log_{10}$ copies/mL, $p<0.0001$), another key secondary endpoint of the Study.

"The critical evaluation and discussion of these Phase 3 study results by the leaders of the scientific community at CROI will help to advance our ensitrelvir clinical program as we seek to continue to pursue our objective of making this COVID-19 treatment available for more people worldwide," said Isao Teshirogi, Ph.D. "These results are encouraging, and we will continue to investigate the efficacy and safety of ensitrelvir across a range of COVID-19 patient populations."

Exploratory Data Shows Relative Risk Reduction of Long COVID Symptoms

At CROI, Shionogi also presented exploratory data (not included as primary or secondary endpoints) from the Phase 3 part of the Study evaluating the potential of ensitrelvir to have an effect on the symptoms of long COVID. Symptoms of long COVID were examined at three and/or six months (Day 85 and/or Day 169) after initiating treatment within five days of symptom onset.

In a subpopulation of patients who self-reported a high score for 14 COVID-19 symptoms at baseline, the overall risk of the presence of long COVID (at least two consecutive reports of the same symptom from among these 14 symptoms as of the time of the last available patient diary (e.g., Day 21 to Day 169), in the 125 mg ensitrelvir group significantly decreased compared with placebo (14.5% and 26.3% reported consecutive symptoms in the 125 mg ensitrelvir and placebo groups, respectively, 45% relative risk reduction, $p<0.05$). Additionally, the overall risk of reporting four neurological symptoms of long COVID at Day 85 or Day 169 in the 125 mg ensitrelvir group significantly decreased compared with placebo (29.4% and 44.0% reported symptoms at either Day 85 or Day 169 in the 125 mg ensitrelvir and placebo groups, respectively, 33% relative risk reduction, $p<0.05$). In an overall population of patients, 125 mg ensitrelvir group showed the same declining trend, 25% ($p=0.1774$) and 26% ($p<0.05$) relative risk reduction versus placebo for the 14 COVID-19 symptoms and the four neurological symptoms, respectively.

This is the first prospective placebo-controlled study which included an evaluation of whether a SARS-CoV-2 antiviral has the potential to reduce the frequency of patients developing long COVID symptoms based on patient-reported symptom results. These results are interim, and follow-up will continue until about one year (Day 337) from the first day of treatment. Additional studies are ongoing to provide confirmation of these results.

"A treatment addressing the symptoms of long COVID remains one of the largest unmet needs of the pandemic. An antiviral for this condition would be a welcome addition to the tools we have to care for patients with COVID-19," said Amesh Adalja, MD, FIDSA, an infectious disease physician and Senior Scholar at the Johns Hopkins Center for Health Security. "As these data are from an exploratory analysis, this promising signal will hopefully be followed up with further evaluation of ensitrelvir for long COVID."

About ensitrelvir

Ensitrelvir (known in Japan as Xocova®), an oral antiviral drug for COVID-19 currently approved under the emergency regulatory approval system in Japan, is a 3CL protease inhibitor created through joint research between Hokkaido University and Shionogi. SARS-CoV-2 has an enzyme called 3CL protease, which is essential for the replication of the virus. Ensitrelvir suppresses the replication of SARS-CoV-2 by selectively inhibiting 3CL protease. Ensitrelvir is the first antiviral agent to show both clinical symptomatic efficacy for five typical Omicron-related symptoms (primary endpoint) and antiviral efficacy (key secondary endpoint) in a predominantly vaccinated population of patients with mild to moderate SARS-CoV-2 infection, regardless of

risk factors in the Phase 3 part of the Phase 2/3 study conducted during the Omicron-dominant phase of the epidemic. With regard to safety, ensitrelvir was well tolerated, and there were no serious treatment-related adverse events or deaths in the study. Among the most common treatment-related adverse events were temporary decreases in high-density lipoprotein and increased blood triglycerides, as observed in previous studies. Currently, the Phase 2b/3 part of the Phase 2/3 study targeting SARS-CoV-2 infected persons who were asymptomatic or only had mild symptoms is being conducted in Asia, mainly in Japan.

Note that ensitrelvir is an investigational drug outside of Japan and has not been approved outside of Japan. In addition, the brand name Xocova® has not been approved for use outside of Japan and pertains only to the approved drug in Japan.

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.

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