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**Shionogi Announces New Phase 3 Data Showing Early Resolution of Many Common COVID-19 Symptoms in *JAMA Network Open***

*Publication Includes Results of the Phase 3 Trial Evaluating Once-Daily Ensitrelvir in Asia*
*Trial Met Primary and Key Secondary Endpoints*

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**OSAKA, Japan, February 13, 2024** – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announced the first peer-reviewed publication of the Phase 3 portion of its pivotal, double-blind, randomized, placebo-controlled Phase 2/3 study (SCORPIO-SR) in patients with mild to moderate COVID-19 in Japan, South Korea and Vietnam in *JAMA Network Open*. The trial met its primary and key secondary endpoints, making ensitrelvir (Generic name: ensitrelvir fumaric acid, Code No.: S-217622, hereafter "ensitrelvir") the first antiviral agent to show both clinical symptom improvement and antiviral effect in a predominantly vaccinated population with Omicron infection regardless of risk factors.*

The publication reports that treatment with once-daily ensitrelvir in the primary analysis population led to a statistically significant reduction in the time to resolution of five typical COVID-19 symptoms characteristic of Omicron (runny/stuffy nose, sore throat, cough, feeling hot or feverish, and low energy/tiredness[1]) versus placebo (p=0.04). The median time to symptom resolution was approximately one day shorter in the 125 mg ensitrelvir group versus placebo (approximately 7 days versus 8 days, respectively).[1] Patients included in the primary analysis population were randomized less than 72 hours from symptom onset.[1] More than 90% of patients had received two or more doses of the SARS-CoV-2 vaccine and patients were included regardless of risk factors for severe disease.[1]

Known as Xocova® in Japan, ensitrelvir received emergency regulatory approval from the Ministry of Health, Labour and Welfare in Japan for the treatment of SARS-CoV-2 infection in 2022. Ensitrelvir was approved in Singapore in November 2023 based on the Special Access Route application. It remains an investigational drug outside of Japan and Singapore. Ensitrelvir was granted Fast Track designation by the U.S. Food and Drug Administration.

"We're pleased to present the data from our Phase 3 study conducted in Asia in this peer-reviewed article. These results demonstrate accelerated resolution in a range of symptoms, reinforcing the potential of ensitrelvir across multiple patient profiles. Additionally, ensitrelvir reduced viral RNA levels and time to first negative viral titer, suggesting it could help reduce transmission of SARS-CoV-2," said Takeki Uehara, Ph.D., Senior Vice President, Drug Development and Regulatory Science at Shionogi. "This study was conducted in a largely vaccinated population that included patients infected with Omicron. The patients also had varying risk factors for severe disease. This is relevant as there is a lack of data and a need for additional treatment options for this population."

**Key Secondary Endpoints**

The study also met its two key secondary endpoints (primary analysis population), as previously presented at the Conference on Retroviruses and Opportunistic Infections 2023. The amount of viral RNA was significantly

lower on Day 4 in the 125 mg ensitrelvir group compared with placebo (least squares mean change from baseline -2.48 $log_{10}$ copies/mL versus -1.01 $log_{10}$ copies/mL, $p<0.001$).[1] The time to achieve first negative infectious viral titer in nasal swabs, indicating clearance of infectious virus from the upper airways, was significantly shorter in the ensitrelvir 125 mg group compared with placebo (a median time of 36.2 hours versus 65.3 hours, $p<0.001$).[1] This is the first study of an oral antiviral for COVID-19 in humans to show a statistically significant reduction in the time to negative infectious viral titer versus placebo.*

"We continue to see COVID-19 surges and we need additional treatment options for more patients, irrespective of risk factors for severe disease, as the virus continues to evolve, adapt, infect and re-infect people across the world," said Yohei Doi, M.D., Ph.D., Professor of Medicine, Fujita Health University, Japan, and one of the study authors. "Seeing the comprehensive data from the study in Asia signals that ensitrelvir has promising potential to treat patients with many common COVID-19 symptoms."

With regard to safety, most adverse events were mild in severity and no deaths were seen 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. Serious adverse events were observed in two patients, one in the 125 mg ensitrelvir group and one in the placebo group, both of which were determined to not be treatment related.[1]

Of the total study population (n=1,821), 1,030 patients were randomized in less than 72 hours of disease onset. Patients were randomized to receive once-daily ensitrelvir 125 mg (375 mg on Day 1 followed by 125 mg on Days 2-5), or 250 mg (750 mg on Day 1 followed by 250 mg on Days 2-5) or placebo for five days.

In the earlier Phase 2 part of the Phase 2/3 study, the 125 mg dose of ensitrelvir demonstrated statistically significant antiviral effect in patients with mild-to-moderate COVID-19 and was well-tolerated.[2] Shionogi secured emergency regulatory approval in Japan with the 125 mg dose and has proceeded with the 125 mg dose for the ensitrelvir clinical development program.[1]

COVID-19 is a serious disease that can lead to a range of acute and lasting health problems, and still carries a risk of severe disease, hospitalization and death in some people.[3,4] COVID-19 has yet to settle into a predictable or stable pattern and continues to significantly impact populations, healthcare systems and economies around the world.[5,6,7,8,9] New variants continue to emerge, and future surges are likely.[5,6] Although vaccines and some therapeutics are available, the World Health Organization has emphasized that more treatment options are still needed for COVID-19.[10]

**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 the 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 results of the Phase 3 part of the Phase 2/3 study conducted during the Omicron-dominant phase of the epidemic. With regard to safety, most adverse events were mild in severity and no deaths were seen 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. Initial exploratory analyses from the Phase 2/3 study also indicated a potential for reduced risk of development of long COVID and further evaluations in this regard are still ongoing.

The U.S. Food and Drug Administration (FDA) granted Fast Track designation to ensitrelvir for COVID-19. FDA Fast Track designation is designed to facilitate the development and expedite the review of potential new therapies that treat serious conditions and fulfill an unmet medical need. Ensitrelvir was approved in Singapore in November 2023 based on the Special Access Route application. Ensitrelvir remains an investigational drug outside of Japan and Singapore. In addition, the brand name Xocova® has not been approved for use outside of Japan and Singapore and pertains only to the approved drug in Japan and Singapore.

**About the ensitrelvir Clinical Development Program**

As SARS-CoV-2 continuously evolves, Shionogi is studying its investigational oral antiviral, ensitrelvir, across a range of patient populations and disease severity to evaluate how ensitrelvir may address the current needs. Shionogi has a comprehensive, global clinical development program underway for ensitrelvir that includes four Phase 3 trials, including SCORPIO-HR, a trial for non-hospitalized, symptomatic COVID-19 patients who have tested positive for COVID-19. SCORPIO-HR is also evaluating the potential effect of ensitrelvir on the symptoms of long COVID. An investigator-initiated research study is also ongoing in hospitalized patients for the management of COVID-19 as part of the new Strategies and Treatments for Respiratory Infections & Viral Emergencies (STRIVE) platform protocol. SCORPIO-PEP is evaluating the safety and efficacy in the prevention of symptomatic SARS-CoV-2 infection when exposed to household contacts who are symptomatic and tested positive for SARS-CoV-2. Lastly, Shionogi is studying the safety and efficacy of ensitrelvir in Japan for children between the ages of 6 to 11 years old.

**About Shionogi in Infectious Disease**

Shionogi is committed to "Protect people worldwide from the threat of infectious diseases" with research and development of therapeutics, whilst also working towards total care through awareness building, epidemiologic monitoring, prevention, diagnosis, and addressing exacerbations, as well as treating infections directly. As SARS-CoV-2 continues to have a major impact on people's lives and to represent a global threat, Shionogi will seek to contribute to re-establishing the safety and security of society by developing new products and services to address this pandemic. Shionogi is committed to equitable access worldwide, including by working with the Medicines Patent Pool to provide access to low- and middle-income countries (LMICs), and by strengthening its manufacturing and global supply chain.

**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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*Literature search conducted January 2024