PRESSRELEASE

SHIONOGI

Shionogi Provides Updates from SCORPIO-HR, a Global Phase 3 Study of Ensitrelvir for Non-Hospitalized Participants with COVID-19

- *The primary endpoint of the SCORPIO-HR study was the time to sustained symptom resolution (the first day of two consecutive days with complete resolution of 15 common COVID-19-related symptoms).*
- *Although ensitrelvir demonstrated a numerical reduction in the time to symptom resolution compared to placebo among participants treated within 3 days of symptom onset, the difference was not statistically significant.*
- *A pre-defined supportive analysis of resolution of six symptoms for one day using a statistical method similar to that used in the SCORPIO-SR Study (Phase 3 part of the Phase 2/3 study of ensitrelvir conducted in Asia) yielded a significant difference ($p<0.05$) in the time to resolution of symptoms.*
- *Ensitrelvir demonstrated a potent antiviral effect for both viral RNA and culture, compared to placebo.*
- *Symptomatic viral rebound was not observed in this study, supporting previous findings from SCORPIO-SR.*
- *Ensitrelvir did not demonstrate a statistically significant reduction in the proportion of participants with post COVID-19 symptoms (Long COVID) at three months, but there was a tendency for a higher proportion of participants to report "having returned to pre-COVID health" and "felt no fatigue" compared to placebo. Further detailed analysis is planned, including additional follow-up at six months.*
- *No dysgeusia (drug-related abnormal taste) was reported.*
- *No deaths were observed in either group up to Day 29 of follow up, and very few cases of COVID-19 related hospitalization were observed in either arm.*
- *Shionogi will continue discussions with regulatory bodies and is committed to providing people worldwide with a potent COVID-19 antiviral treatment that is well-tolerated.*

OSAKA, Japan, May 13, 2024 – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") today announced that its pivotal, double-blind, randomized, placebo-controlled global Phase 3 study (SCORPIO-HR) did not meet its primary endpoint of a statistically significant reduction in time to sustained resolution (symptoms completely absent for at least two days) of 15 common COVID-19 related symptoms for once-daily ensitrelvir (Generic name: ensitrelvir fumaric acid, Code No.: S-217622, hereafter "ensitrelvir"), when treatment was initiated within three days of symptom onset, compared to placebo.

A pre-defined supportive analysis of resolution (symptoms completely absent for at least one day) of six symptoms using a statistical method similar to that used in the SCORPIO-SR Study (Phase 3 part of the Phase 2/3 study of ensitrelvir conducted in Asia) yielded a significant difference ($p<0.05$) in the time to resolution of

symptoms. Ensitrelvir demonstrated a potent antiviral effect, leading to a substantial reduction from baseline in viral RNA levels and viral culture positivity compared to placebo. Symptomatic viral rebound did not occur in this study, which is consistent with previous findings from SCORPIO-SR.

The SCORPIO-HR study was carried out across a broad range of symptomatic, non-hospitalized participants with COVID-19, regardless of past SARS-CoV-2 infection. This study enrolled participants in North America, South America, Europe, Africa and Asia and was conducted when Omicron variant infection was predominant. Most participants were vaccinated, and approximately 30% had risk factors for severe disease, including obesity (BMI≥30 kg/m^2), hypertension and diabetes mellitus.

The SCORPIO-HR trial is a part of the National Institutes of Health's (NIH) Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership, and it is being conducted as a collaboration between Shionogi, the National Institute of Allergy and Infectious Diseases (NIAID), a part of the NIH, and ACTG, a global clinical trials network focused on HIV and other infectious diseases and funded by NIAID.

Ensitrelvir was granted Fast Track designation by the U.S. Food and Drug Administration in 2023. The Fast Track program facilitates the expedited development and review of new drugs that are intended to treat serious or life-threatening conditions and to demonstrate the potential to address unmet medical needs. In Japan, ensitrelvir, known as Xocova®, received emergency regulatory approval in 2022 and full approval in March 2024. Since its emergency approval, more than one million people have been treated with ensitrelvir in Japan. Ensitrelvir was also approved in Singapore based on the Special Access Route application in 2023. It remains an investigational drug outside of Japan and Singapore.

"These topline results, while mixed, confirm an antiviral effect and add to the existing clinical data and real-world evidence that we have seen for ensitrelvir in Asia. No new safety concerns were identified. Ensitrelvir had similar tolerability to placebo and there were no reports of taste disturbance. We will continue working with regulatory bodies to explore routes to making ensitrelvir available," said Simon Portsmouth, MD, FRCP, Senior Vice President, Head of Clinical Development at Shionogi Inc.

Detailed results from SCORPIO-HR will be submitted for a presentation at a future scientific conference.

About ensitrelvir
Ensitrelvir 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.

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. Known as Xocova® in Japan, ensitrelvir received emergency regulatory approval in 2022 and full approval in March 2024. 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 program
Shionogi has a robust clinical development program for ensitrelvir and is committed to making it available to populations worldwide. In addition to SCORPIO-HR, Shionogi evaluated the safety and efficacy of ensitrelvir

through SCORPIO-SR, a Phase 2/3 study conducted in Asia, during the Omicron-dominant phase of the epidemic. The data from this study were recently published in *JAMA Network Open*.

Additionally, an investigator-initiated research study is 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. STRIVE was developed under the auspices of NIH's Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership. A further study, 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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