PRESSRELEASE

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Shionogi Presents New Ensitrelvir Clinical and Real-World Data Reinforcing Potential Across COVID-19 Populations at ESWI 2023

- *New exploratory analysis of Phase 3 SCORPIO-SR study data in Asia suggests that ensitrelvir may reduce the risk of persistent and new late-onset symptoms associated with long COVID over one year*
- *Small study in Japanese population suggests ensitrelvir as a potential treatment option in COVID-19 hospitalized patients with significant co-morbidities who did not respond to first-line treatment with remdesivir*

OSAKA, Japan, September 19, 2023 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") will present two late-breaking posters at the European Scientific Working Group on Influenza and other Respiratory Viruses' (ESWI), 9th Influenza Conference, highlighting data suggesting the potential of its investigational oral antiviral ensitrelvir on symptoms associated with long COVID and in high-risk COVID-19 hospitalized patients with significant co-morbidities who did not respond to first-line treatment with remdesivir.

Ensitrelvir is an investigational oral antiviral that suppresses the replication of SARS-CoV-2 by selectively inhibiting the viral 3CL protease. Known as Xocova® in Japan, ensitrelvir received emergency regulatory approval from the Ministry of Health, Labour and Welfare (MHLW) for the treatment of SARS-CoV-2 infection in November 2022. It remains an investigational drug outside Japan. In April 2023, ensitrelvir was granted Fast Track designation by the U.S. Food and Drug Administration.

Effect on Long COVID Symptoms

Shionogi will present a new exploratory analysis of the Phase 3 part of the pivotal SCORPIO-SR trial (Phase 2/3 study) conducted in Japan, South Korea and Vietnam, which shows that ensitrelvir may reduce the risk of a number of persistent and new late-onset symptoms associated with long COVID over one year. Long COVID was analyzed based on a patient-reported questionnaire at three months, six months and one year from the first date of treatment. In the study, long COVID was defined by patient reports of 'not having returned to pre-COVID health' and having at least one (mild or more severe) symptom out of 27 possible symptoms.[1]

Ensitrelvir 125 mg and 250 mg showed a numerical relative risk reduction (25% and 26% respectively) versus the placebo group for 27 symptoms at one year. A similar trend in risk reduction was observed at three and six months. In addition, subgroup analyses found that greater risk reduction was observed in patients with BMI ≥25 kg/m^2 and in patients with a median or higher symptom score at the start of treatment. The results of this exploratory analysis suggest that early treatment of COVID-19 with ensitrelvir may reduce the risk of a number of persistent and new late-onset symptoms associated with long COVID, but further confirmatory studies are needed.[1]

Shionogi has previously reported that the proportion of patients who experienced long COVID at six months with ensitrelvir was lower than in the placebo group using a different method of analysis of ongoing symptoms.[2]

Long COVID is an often-debilitating illness that affects between 10-20% of people who get COVID-19.[3] At least 65 million individuals worldwide are estimated to have long COVID, with cases increasing daily.[4] More than 200 symptoms have been identified with effects on multiple organ systems.[4] Experts believe it is plausible that antivirals could prevent or reduce the risk of long COVID,[5] but to date, no drug has been conclusively shown to reduce the risk of long COVID.

"As COVID-19 remains endemic, persisting symptoms continue to adversely affect millions of people worldwide," said Dr. Andreas Karas, Vice President, Medical Affairs, Shionogi Europe. "We're pursuing further research to substantiate the potential of ensitrelvir as a treatment option for acute COVID-19 infection and whether this can prevent the long-term effects the virus can cause. We look forward to sharing the results at ESWI and to hearing from the community as we advance our global ensitrelvir clinical development program."

Alternative Option for High-Risk COVID-19 Hospitalized Patients with Co-Morbidities

Shionogi will also present new data from a small real-world study in Japan conducted at the Rinku General Medical Centre, which suggests that for COVID-19 hospitalized patients with significant co-morbidities who did not respond to remdesivir, ensitrelvir may provide an alternative treatment option.[6]

The study included 21 high-risk hospitalized patients with COVID-19 infections who did not respond to at least three days of remdesivir treatment and then received five days of ensitrelvir treatment (Day 0 to Day 4). In this group, the average age was 78 years, the majority were vaccinated (76.2%), COVID-19 severity was mild or moderate, and many had co-morbidities (33.3% had malignant tumors, 19.0% had either kidney disease or renal failure, 23.8% used systemic corticosteroids). After receiving five days of ensitrelvir 125 mg, which followed at least three days of remdesivir administration, all 21 patients showed clinical improvement by Day 5. No deaths or drug-related adverse events were observed at Day 28, but one person later died in the hospital at Day 59.[6]

Viral clearance was achieved (antigen level <89.73 pg/mL) by Day 5 in 14 patients (66.7%), two of whom experienced viral rebound without clinical rebound by Day 13. This data, although limited, suggest the potential of ensitrelvir treatment for certain high-risk patients hospitalized with mild-or-moderate COVID-19, who did not respond to antiviral therapy with remdesivir.[6]

The World Health Organization (WHO) acknowledges that while COVID-19 has become endemic to many areas, patients with co-morbidities continue to face an ongoing risk from the virus,[7] including the risk of severe and/or prolonged COVID-19 and hospitalization.[7,8,9]

"While certain treatments are available for high-risk people with COVID-19 to reduce the risk of becoming seriously ill, additional treatment options are needed," said Masaya Yamato, Director of the Infectious Diseases Center at Rinku General Medical Center, Osaka, and investigator on the Shionogi trials. "These results indicate the potential for ensitrelvir to help address these needs."

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 reduced risk of development of long COVID and further evaluations in this regard are still ongoing.

Recently, 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 remains an investigational drug 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.

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 unmet medical 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 incidence 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. Additionally, Shionogi conducted SCORPIO-SR in patients with mild-to-moderate COVID-19 irrespective of risk factors for COVID-19 progression. Furthermore, Shionogi's study, SCORPIO-PEP, is evaluating the safety and efficacy of ensitrelvir for the prevention of symptomatic SARS-CoV-2 infection in study participants exposed to household contacts who are symptomatic and tested positive for SARS-CoV-2.

About Shionogi in Infectious Disease

Since 1953 Shionogi has been a leader in infectious disease discovery and commercialization. Our R&D story extends beyond antibiotics to include novel medications for HIV and influenza. Today, our global pipeline includes investigational agents developed to address global health challenges including antimicrobial resistance, COVID-19, influenza, rare fungal diseases and respiratory syncytial virus.

As part of our commitment to addressing unmet medical needs, Shionogi is partnering with several non-governmental organizations to increase equitable access to our medications worldwide. Shionogi has a voluntary license agreement with the Medicines Patent Pool (MPP) to facilitate additional production and distribution of ensitrelvir, pending regulatory authorization or approval, by granting sublicences to qualified generic manufacturers, with the goal of expanding access to people living in low- and middle-income countries (LMICs).

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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