PRESSRELEASE

SHIONOGI

Shionogi Presented New Clinical Data on the COVID-19 Treatment Ensitrelvir

- New Results Suggest Ensitrelvir May Be Effective for Patients with Risk Factors for Disease Progression in COVID-19, As A Result of Reduction of Severe Outcomes Effects

OSAKA, Japan, June 28, 2024 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") announced that the newly obtained clinical data for the novel COVID-19 oral antiviral Xocova® (generic name: ensitrelvir fumaric acid, Code No.: S-217622, hereafter "ensitrelvir") was presented at the joint conference of the 98th Annual Meeting of the Japanese Association for Infectious Diseases and the 72nd Annual Meeting of the Japanese Society of Chemotherapy, held in Japan from June 27 to 29, 2024.

The summary of two new data presented at the conference is as follows.

Real-world effectiveness of ensitrelvir in reducing severe outcomes in outpatients at high-risk for COVID-19 progression

This was a retrospective study using the JMDC Claims Database (JMDC Inc., Tokyo, Japan), a large Japanese health insurance claims database. The study included 167,310 outpatients aged ≥18 years, who were at high-risk for severe desease and received their first COVID-19 diagnosis between November 2022 and July 2023. The primary endpoint was all-cause hospitalization during the 4-week period from the date of outpatient diagnosis and medication, comparing the ensitrelvir group and the no antiviral treatment group. As a result, the incidence of hospitalization from all causes was statistically lower by approximately 37% in the ensitrelvir group than those receiving no antiviral treatment (: 0.494% vs. 0.785%; Risk Ratio: 0.629, 95% CI: 0.420 to 0.943; The risk difference: −0.291, 95% CI: −0.494 to −0.088). These results suggest that ensitrelvir may be an effective treatment option for patients at high-risk of severe COVID-19 not only in Phase2/3 clinical trials in Japan but also in the real world, where vaccination has become widespread and the Omicron strain is prevalent.

"Currently, the predominant strain of COVID-19 is the Omicron variant, and although the severity rate has decreased, there are still many patients, especially among the elderly, who become seriously ill and are hospitalized.", said Dr. Hiroshi Mukae, Department of Respiratory Medicine, Nagasaki University Hospital, Nagasaki, Japan. "This study provides strong evidence suggesting the efficacy of ensitrelvir in reducing severe outcomes among high-risk COVID-19 patients based on real-world clinical data during the Omicron variant outbreak. However, further prospective studies are needed to confirm these findings. Early administration of ensitrelvir, which has potent antiviral effects, is expected to mitigate severe COVID-19 in high-risk patients."

This manuscript has already been accepted for publication by the international peer-reviewed journal 'Infectious Diseases and Therapy'.

Safety and Effectiveness of Ensitrelvir for the Treatment of COVID-19 in Japanese Clinical Practice: Final Analysis Report from a Post-Marketing Surveillance

This report was new data evaluating the effectiveness and tolerability of ensitrelvir in clinical practice in Japan. Following emergency regulatory approval from the MHLW in Japan, an ongoing post-marketing surveillance

study enrolled a total of 4,125 patients. Of these patients, 3,760 were evaluated for safety and 3,638 for effectiveness. The summary of the tally is as follows.

- **Safety:**
  - Treatment-related adverse events were observed in 271 patients (7.2%), with the common treatment-related adverse events being diarrhea in 91 patients (2.4%), nausea in 43 patients (1.1%), and headache in 42 patients (1.1%).
  - Serious adverse events occurred in 3 patients (5 events) (headache, nausea, vomiting, cold sweats, generalized edema), all of which resolved within 5 days.
  - No occurrence of the specific identified risk anaphylaxis was confirmed.

- **Effectiveness:**
  - After administration of ensitrelvir, the median time to fever resolution was about 1.5 days (36.0 hours), and the median time to complete symptom disappearance was about 6.5days (156.0 hours).
  - Within 28 days of starting ensitrelvir treatment, 14 patients (0.4%) required hospitalization, of which 10 were due to worsening of COVID-19.
  - There were 2 deaths (0.1%), both believed to be related to incidental events or underlying conditions/complications.

These results provide important additional evidence to the clinical trial programme by demonstrating the effectiveness of ensitrelvir in the real-world among a diverse and large group of patients. Further, these findings provide important evidence supporting the safety profile observed in the clinical trial programme.

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. 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. Shionogi evaluated the safety and efficacy of ensitrelvir through SCORPIO-SR, 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.

For Further Information, Contact:

SHIONOGI Website Inquiry Form: https://www.shionogi.com/global/en/contact.html