PRESSRELEASE

SHIONOGI

Shionogi Presents New Ensitrelvir COVID-19 Data Supporting Effectiveness in Real-World and Clinical Settings at IDWeek 2023

OSAKA, Japan, October 12, 2023 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") will present new real-world and clinical data at IDWeek 2023 reinforcing the potential of ensitrelvir, its investigational oral antiviral, to treat the symptoms of COVID-19.

Known as Xocova® in Japan, ensitrelvir received emergency regulatory approval from the Ministry of Health, Labour and Welfare (MHLW) in Japan for the treatment of SARS-CoV-2 infection in November 2022. It remains an investigational drug outside Japan. Ensitrelvir was granted Fast Track designation by the U.S. Food and Drug Administration (FDA), which is designed to expedite review of potential new therapies for serious conditions with an unmet medical need.

Real-World Clinical Practice

Shionogi will present 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 is enrolling 3,000 Japanese patients. As of July 20, 2023, a total of 1,682 patients were enrolled, of which, 1,589 were evaluated for safety and 1,584 for effectiveness. After ensitrelvir administration, the median time to resolution of fever was about 1.5 days and median time to resolution of all symptoms was about 6.5 days, independent of age or presence of risk factors for severe disease. There were no deaths due to COVID-19. No new concerns about tolerability or effectiveness of ensitrelvir have been identified.[1]

“The interim results further support the tolerability and effectiveness of ensitrelvir regardless of risk factors, in real-world settings in Japan,” said Takeki Uehara, Ph.D., Senior Vice President, Drug Development and Regulatory Science at Shionogi. “The data we are seeing in Japan are promising as we work to meet unmet medical needs of COVID-19 and make ensitrelvir available worldwide, pending regulatory approvals.”

Effect on Taste and Smell Symptoms

In addition, Shionogi will present new data demonstrating that administration of ensitrelvir within three days of COVID-19 symptom onset may have prevented or improved taste and smell symptoms. An analysis from the Phase 3 part of the pivotal SCORPIO-SR trial (Phase 2/3 study) conducted in Japan, South Korea and Vietnam found a significantly smaller proportion of patients had taste disorder or smell disorder on Day 7 when treated with 125 mg of ensitrelvir versus placebo ($p<0.05$).[2]

Globally, millions of people experience smell or taste dysfunction after COVID-19.[3,4,5] In addition to impacting quality of life, smell and taste disorders caused by COVID-19 may persist for many months.[4,5]

“As an investigator who has evaluated both clinical data and real-world experience with ensitrelvir, I am optimistic about its potential to become an important tool in managing the unpredictability of COVID-19,” said Yohei Doi, M.D., Ph.D., Professor of Medicine, Fujita Health University, Japan. “The new data presented at

IDWeek regarding taste and smell symptoms, offer another reason to have confidence in this investigational agent and its potential to be a meaningful treatment option for patients."

The data at IDWeek follow results recently presented at the European Scientific Working Group on Influenza and other Respiratory Viruses' (ESWI), 9th Influenza Conference. New data presented highlighted the potential of ensitrelvir to reduce the risk of persistent symptoms and new late-onset symptoms associated with long COVID over one year.[6] Additional data, including a case series in high-risk COVID-19 hospitalized patients with co-morbidities, suggested that ensitrelvir may be effective in treating persistent SARS-CoV-2 infection in those who did not respond to first-line treatment with remdesivir.[7]

COVID-19 is a serious disease that can lead to a range of acute and lasting health problems, and even death in some people.[8] 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.[9,10,11,12,13] New variants continue to emerge, and future surges are possible.[9,10] Although vaccines and some therapeutics are available, the World Health Organization has emphasized that more treatment options are still needed for COVID-19.[14] Shionogi has a robust clinical development program for ensitrelvir and is committed to making it available to populations worldwide.

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 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. 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 landmark license and technology transfer agreement with Global Antibiotic Research and Development Partnership (GARDP) and a collaboration agreement with the Clinton Health Access Initiative (CHAI) to transform the landscape of access to antibiotics in many low-income countries, most lower middle- and upper middle-income countries, and select high-income countries. We also have 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.

For Further Information, Contact:
SHIONOGI Website Inquiry Form: https://www.shionogi.com/global/en/contact.html
U.S. Media: ShionogiCommunications@shionogi.com

References
1. Ogura E., *et al*. Safety and Effectiveness of Ensitrelvir for the Treatment of COVID-19 in Japanese Clinical Practice: A Post-Marketing Surveillance (Interim Analysis). IDWeek 2023. Poster #537
2. Tsuge Y, *et al*. Ensitrelvir for the Treatment of COVID-19 Infection: Evaluation of Taste Disorder and Smell Disorder in the Phase 3 Part of the Phase 2/3 SCORPIO-SR Randomized Controlled Trial. IDWeek 2023. Poster #549
3. Butowt R, Bilińska K, von Bartheld C. Why Does the Omicron Variant Largely Spare Olfactory Function? Implications for the Pathogenesis of Anosmia in Coronavirus Disease 2019. J. Infect. Dis. 2022:226 https://academic.oup.com/jid/article/226/8/1304/6573859.

4. Coelho, D. H., *et al*. (2021). Quality of life and safety impact of COVID-19 associated smell and taste disturbances. American journal of otolaryngology, 42(4), 103001. https://doi.org/10.1016/j.amjoto.2021.103001
5. Tan B K J, *et al.* Prognosis and persistence of smell and taste dysfunction in patients with covid-19: meta-analysis with parametric cure modelling of recovery curves BMJ 2022; 378 :e069503 doi:10.1136/bmj-2021-069503
6. Fukushi A, et al. Effect of Ensitrelvir on Long COVID in Patients with Mild-to-Moderate COVID-19: A Post-Hoc Analysis of Phase 3 (SCORPIO-SR). Poster presented at 9th ESWI Conference 2023.
7. Yamato M, et al. Ensitrelvir as a Treatment Option for Persistent SARS-CoV-2 Infection After Remdesivir in Hospitalized Patients with Co-morbidities: A single-Center Case Series from Japan. Poster presented at 9th ESWI Conference 2023.
8. About COVID-19. Centers for Disease Control and Prevention. Accessed September 27, 2023. Available at: https://www.cdc.gov/coronavirus/2019-ncov/your-health/about-covid-19.html
9. Variants of the Virus. Centers for Disease Control and Prevention. Accessed September 27, 2023. Available at: https://www.cdc.gov/coronavirus/2019-ncov/variants/index.html.
10. Tracking SARS-CoV-2 variants. World Health Organization. Accessed September 27, 2023. Available at: https://www.who.int/activities/tracking-SARS-CoV-2-variants.
11. WHO Coronavirus (COVID-19) Dashboard. The World Health Organization. Accessed September 27, 2023. Available at: https://covid19.who.int/.
12. Post-pandemic world economu still feeling COVID-19's sting. United Nations. Accessed October 3, 2023. Available at: https://news.un.org/en/story/2023/05/1136727#:~:text=Prospects%20for%20a%20robust%20global,Prospects%20report%2C%20released%20on%20Tuesday.
13. COVID-19 Surveillance After Expiration of the Public Health Emergency Declaration — United States, May 11, 2023. Centers for Disease Control and Prevention. Accessed October 3, 2023. Available at: https://www.cdc.gov/mmwr/volumes/72/wr/mm7219e1.htm?s_mm7219e1_w.
14. Therapeutics and COVID-19. Page 8. The World Health Organization. Accessed September 26, 2023. Available at: https://apps.who.int/iris/bitstream/handle/10665/365584/WHO-2019-nCoV-therapeutics-2023.1-eng.pdf.