PRESSRELEASE

SHIONOGI

CONFIDENTIAL DRAFT NOT FOR DISTRIBUTION

Late-Breaking at CROI 2025: SCORPIO-PEP Phase 3 Trial: Ensitrelvir is the First and Only COVID-19 Oral Antiviral to Demonstrate Prevention of COVID-19 as Post Exposure Prophylaxis

- Ensitrelvir demonstrated a statistically significant reduction (67%) in the risk of COVID-19, meeting its primary endpoint, in uninfected individuals treated after exposure, compared to placebo at day 10.[1]
- Currently, there are no approved medicines to prevent COVID-19 in people who have been exposed to a person with SARS-CoV-2 infection.[2]
- Ensitrelvir was granted Fast Track designation by the U.S. Food and Drug Administration (FDA) in 2025 for post-exposure prophylaxis of COVID-19 following contact with an individual who has COVID-19.[3]
- Shionogi plans to continue interacting with regulatory authorities worldwide.

OSAKA, Japan, March 13, 2025 – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") delivered a late-breaking scientific oral presentation at the Conference of Retroviruses and Opportunistic Infections (CROI) 2025, including new data from its global, double-blind, randomized, placebo-controlled Phase 3 study, **S**topping **CO**VID-19 p**R**ogression with early **P**rotease **I**nhibit**O**r treatment – **P**ost-**E**xposure **P**rophylaxis (SCORPIO-PEP) assessing ensitrelvir (Generic name: ensitrelvir fumaric acid, Code No.: S-217622, hereafter "ensitrelvir") as oral post-exposure prophylaxis. SCORPIO-PEP is the first and only Phase 3 study of a COVID-19 oral antiviral as a post-exposure prophylaxis to meet the primary endpoint of preventing COVID-19.*

The study met both the primary endpoint and the key secondary endpoint. The primary analysis population included 2,041 household contact participants with a negative screening SARS-CoV-2 test and excluded those found to already be positive by PCR at the central laboratory.[1] Of the study participants treated with ensitrelvir, 2.9% developed symptomatic COVID-19 compared to 9.0% of participants on placebo (risk ratio: 0.33; 95% CI: 0.22-0.49; $p<0.0001$) at Day 10, the primary endpoint, representing a 67% relative risk reduction.[1] The secondary analysis population included 2,387 household contact participants who had a negative local test for SARS-CoV-2 but did not exclude those with a central laboratory positive SARS-CoV-2 PCR at baseline.[1] The results were similar to the primary analysis population with 4.4% of participants treated with ensitrelvir developing symptomatic COVID-19 compared to 10.2% of participants on placebo (risk ratio: 0.43; 95% CI: 0.32-0.59; $p<0.0001$).[1]

"COVID-19 remains a major threat to public health, and the best way to avoid the serious and long-term complications associated with the virus is to reduce the risk of being infected in the first place," said Frederick Hayden, MD, Professor Emeritus of Clinical Virology and Professor Emeritus of Medicine, University of Virginia School of Medicine. "In addition to vaccination, post-exposure prophylaxis with timely use of an oral antiviral would be a valuable way to help prevent COVID-19 illness in people who have been exposed, especially people at high risk for severe disease."

Ensitrelvir, known as Xocova® in countries where it is approved, received emergency regulatory approval in Japan in 2022 and full approval in March 2024 for the treatment of COVID-19. It became available in Singapore via a Special Access Route application in 2023, and it is currently under regulatory review in Taiwan. Ensitrelvir was granted Fast Track designation by the U.S. Food and Drug Administration (FDA) in 2025 for post-exposure

prophylaxis of COVID-19 following contact with an individual who has COVID-19.[3] In addition, ensitrelvir was granted Fast Track designation by the U.S. FDA in 2023 for the treatment of COVID-19. Ensitrelvir is 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.

SCORPIO-PEP assessed 2,387 study participants aged 12 years and older with a negative screening test for SARS-CoV-2 infection and no symptoms at the time of enrollment, who were exposed to a person living in their household with symptomatic COVID-19.[1] Study participants were randomly assigned in a 1:1 ratio to receive ensitrelvir (125 mg) or placebo, once daily, and began treatment within three days of when the household member with COVID-19 began showing symptoms.[1] Participants then continued ensitrelvir or placebo for five days.[1]

Overall, ensitrelvir was generally well tolerated, with similar rates of adverse events in the ensitrelvir group and the placebo group (15.1% and 15.5%, respectively).[1] There were no COVID-19 related hospitalizations or deaths.[1]

"SARS-CoV-2 continues to circulate and there are still thousands of hospitalizations and hundreds of COVID-19 deaths each week," said Simon Portsmouth, MD, FRCP, Senior Vice President, Head of Clinical Development. "If we can reduce the risk of infection among individuals who are exposed to SARS-CoV-2, this fulfills an important unmet medical need. Oral antivirals have changed the way we treat and prevent other infectious diseases, including influenza and HIV, and there is an opportunity to do the same with COVID-19."

COVID-19 continues to pose a health risk for many people and remains a public health threat.[4,5] It can impact quality of life, lead to absence from work, cause long COVID, and can progress to severe disease, hospitalizations and death.[4,5] Additional protective options are needed for those who have close contact with people with COVID-19.

Post-exposure prophylaxis (PEP) is needed to reduce the risk of developing the disease after exposure, particularly those at high risk of developing severe illness, such as those with weakened immune systems, chronic health conditions, the elderly or those who could transmit COVID-19 to high-risk populations.[6] In settings like hospitals, nursing homes, or long-term facilities, PEP could help protect against COVID-19 and contain the potential clinical and economic impact.[7,8] PEP may help reduce the risk of developing acute COVID-19, thereby reducing the risk of developing long COVID.[8,9]

PEP is also an important preventive option as new variants emerge, which may escape vaccine-induced or infection-acquired immunity.[10] Additionally, low vaccination rates and waning immunity after vaccination call for additional preventative measures.[11]

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.[12] Ensitrelvir suppresses the replication of SARS-CoV-2 by selectively inhibiting the 3CL protease.[12]

Shionogi evaluated the safety and efficacy of ensitrelvir through SCORPIO-SR, a Phase 3 study conducted in Asia, during the Omicron-dominant phase of the epidemic.[13] In this study, ensitrelvir showed both clinical symptomatic efficacy (symptom resolution sustained for at least 24 hours) 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.[13] Regarding

safety, most adverse events were mild in severity and no deaths were seen in the study.[13] Among the most common treatment-related adverse events were temporary decreases in high-density lipoprotein and increased blood triglycerides, as observed in previous studies.[13] The data from this study were published in JAMA Network Open.

Additionally, the Phase 3 SCORPIO-HR study assessed ensitrelvir in a broad range of symptomatic, non-hospitalized participants with COVID-19, regardless of past SARS-CoV-2 infection. The study did not meet its primary endpoint of a statistically significant reduction in time to sustained resolution (symptom resolution sustained for at least 48 hours) of 15 common COVID-19 related symptoms for once-daily ensitrelvir compared to placebo.[14] No new safety concerns were identified in the study, and treatment with ensitrelvir was well tolerated, with a similar adverse event profile as placebo.[14]

An investigator-initiated research study with ensitrelvir is ongoing in hospitalized patients for the management of COVID-19 as part of the 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.

Shionogi also recently released preliminary results from a multicenter, randomized, double-blind, placebo-controlled trial of ensitrelvir in mild to moderate COVID-19 patients aged 6 to under 12 years in Japan. The study confirmed safety and tolerability and found the pharmacokinetics of ensitrelvir in this age group similar to adults.[15]

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
SEU Press Office: pressoffice@shionogi.eu

* Literature search conducted December 2024.

Reference List:

1. Hayden F. Ensitrelvir to Prevent COVID-19 in Households: SCORPIO-PEP Phase III Placebo-Controlled Trial Results. Abstract 200. Presented at CROI 2025, San Francisco, CA: March 9-12, 2025.

2. U.S. Food and Drug Administration. Available at: https://www.fda.gov/search?s=COVID%20post%20exposure%20prophylaxis&sort_bef_combine=rel_DESC&f%5B0%5D=section%3A23692.
3. U.S. Food and Drug Administration. Fast Track Designation of S-217622 (ensitrelvir).
4. The changing threat of COVID-19. Centers for Disease Control and Prevention. Accessed February 24, 2025. Available at: https://www.cdc.gov/ncird/whats-new/changing-threat-covid-19.html.
5. Long COVID Basics. Centers for Disease Control and Prevention. Accessed February 24, 2025. Available at: https://www.cdc.gov/covid/long-term_effects/?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html.
6. Bartoszko JJ, et al. Prophylaxis against covid-19: living systematic review and network meta-analysis. *BMJ*. 26 Apr 2021;373:n949. doi:10.1136/bmj.n949.
7. Lee SH, Son H, Peck KR. Can post-exposure prophylaxis for COVID-19 be considered as an outbreak response strategy in long-term care hospitals? *Science Direct*. 17 Apr 2020;55:6. doi:10.1016/j.ijantimicag.2020.105988.
8. Gentile I, Maraolo AE, Piscitelli P, Colao A. COVID-19: Time for Post-Exposure Prophylaxis? *Int J Environ Res Public Health*. 2020 Jun 4;17(11):3997. doi:10.3390/ijerph17113997.
9. Al-Aly Z, Topol E. Solving the puzzle of Long Covid. *Science*. 22 Feb 2024; 383:6685,830-832. doiI:10.1126/science.adl0867.
10. Carabelli AM, Peacock TP, Thorne LG, et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. *Nature Reviews Microbiology*. 18 Jan 2023;21:162–177. doi:10.1038/s41579-022-00841-7.
11. Kriss JL, Black CL, Razzaghi H, et al. Influenza, COVID-19, and Respiratory Syncytial Virus Vaccination Coverage Among Adults — United States, Fall 2024. *MMWR Morb Mortal Wkly Rep*. 21 Nov 2024;73:1044–1051. doi:10.15585/mmwr.mm7346a1.
12. Unoh Y, et al. Discovery of S-217622, a noncovalent oral SARS-CoV-2 3CL protease inhibitor clinical candidate for treating COVID-19. *Journal of Medicinal Chemistry*. 30 Mar 2022;65:9,6499-6512. doi:10.1021/acs.jmedchem.2c00117.
13. Yotsuyanagi H, et al. Efficacy and safety of 5-day oral Ensitrelvir for patients with mild to moderate COVID-19. JAMA Netw Open. 9 Feb 2024;7(2):e2354991. doi:10.1001/jamanetworkopen.2023.54991.
14. Luetkemeyer A, et al. Ensitrelvir for the Treatment of Nonhospitalized Adults with COVID-19: Results from the SCORPIO-HR, Phase 3, Randomized, Double-blind, Placebo-Controlled Trial, *Clinical Infectious Diseases*, 2025;, ciaf029, https://doi.org/10.1093/cid/ciaf029.
15. 3rd Quarter of Fiscal 2024 Financial Results. January 31, 2025. Page 20. Accessed March 5, 2025. Available at: https://www.shionogi.com/content/dam/shionogi/jp/investors/ir-library/presentation-materials/fy2024/%EF%BC%93q/E_FY2024_3Q%20financial%20results_.pdf.