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ACTG and Shionogi Announce Progress on Global Phase 3 Trial of Novel COVID-19 Oral Antiviral Agent S-217622

- *FDA has cleared the IND for S-217622, a once-daily investigational oral antiviral therapy, enabling the global phase 3 trial to proceed as part of the ACTIV-2 program for COVID-19*
- *This NIH-supported study will recruit participants with COVID-19 worldwide who are at risk for progression to severe illness*

Los Angeles, Calif. and Osaka, Japan, March 16, 2022 – The AIDS Clinical Trials Group (ACTG), the largest global HIV research network that expanded its focus to include evaluating outpatient treatments for COVID-19, and Shionogi & Co., Ltd., a global pharmaceutical company headquartered in Osaka, Japan with a long-standing commitment to the research and development of innovative, high-quality infectious disease medicines, today announced progress toward the initiation of ACTIV-2d (also known as SCORPIO-HR), a global, phase 3, multicenter trial to evaluate the safety and efficacy of the COVID-19 antiviral agent S-217622. SCORPIO-HR will evaluate the investigational 3CL protease inhibitor S-217622 as a once-daily oral treatment for high-risk, non-hospitalized adults with COVID-19 within five days of symptom onset. The trial is being conducted by ACTG, sponsored by Shionogi, and funded by the National Institute of Allergy and Infectious Diseases (NIAID) part of the National Institutes of Health (NIH).

SCORPIO-HR is a phase 3, multicenter, randomized, double-blind, 48-week study that will evaluate the safety and efficacy of S-217622 among participants who have tested positive for SARS-CoV-2 in the outpatient setting, started experiencing symptoms within five days of enrolling, and have one or more risk factors that makes them more likely to progress to severe COVID-19. The U.S. Food and Drug Administration (FDA) has cleared the Investigational New Drug (IND) application for S-217622, enabling SCORPIO-HR to proceed. This trial follows supportive, positive results from phase 2a and phase 2b clinical trials (primarily conducted in Japan and used for submission to the Japanese health authority) that demonstrated proof of concept with significant antiviral activity and rapid cessation of infectious virus shedding.

“While S-217622 is in the same class of treatments as oral medications that are currently available through Emergency Use Authorizations to treat COVID-19, it is administered without a boosting agent and only once daily, which can simplify treatment,” said Annie Luetkemeyer, M.D., University of California, San Francisco and a lead investigator of S-217622. “We need more well-tolerated, highly effective options to treat COVID-19 that reduce the risk of serious complications and the duration of infectiousness. Based on preliminary clinical trial data, we are excited about the potential for S-217622 to be an important addition to our COVID-19 treatment toolkit.”

SCORPIO-HR will be conducted with trial sites in countries in Europe, South America, North America, Africa, and Asia. Approximately 1,700 participants will be randomized in a 2:1 ratio such that two thirds receive S-217622 and one third receive placebo. Participants may take locally provided COVID-19 treatment after enrollment, as long as it is compatible with S-217622.

“As more and more people begin to resume their daily lives, there remains a clear need for effective antiviral treatments for COVID-19 that can offer added protection against severe illness and reduce the burden of COVID-19 on our healthcare systems,” said Isao Teshirogi, Ph.D., President and CEO at Shionogi & Co., Ltd. “As a potent antiviral, specifically designed to inhibit SARS-CoV-2’s ability to spread through the body, S-217622 has demonstrated the largest reductions reported to date in infectious virus titer and rapid cessation of infectious virus shedding. We value the collaboration and support of the NIH and ACTG on this investigational antiviral to bring further treatment options to a broad range of COVID-19 patients, and especially to high-risk populations.”

SCORPIO-HR is led by Kara W. Chew, M.D., M.S., University of California, Los Angeles (UCLA), Dr. Luetkemeyer, and Davey Smith, M.D., University of California, San Diego (protocol co-chairs) and David Alain Wohl, M.D., University of North Carolina (UNC) and Eric S. Daar, M.D., Lundquist Institute at Harbor-UCLA Medical Center (vice-chairs), and is supported by Judith Currier, M.D., M.Sc., UCLA (ACTG Chair) and Joseph J. Eron, M.D., UNC, (ACTG Co-Chair).

About S-217622
S-217622, a therapeutic drug for COVID-19, is an 3CL protease inhibitor created through joint research between Hokkaido University and Shionogi. SARS-CoV-2 utilizes an enzyme called 3CL protease that is essential for the replication of the virus. S-217622 suppresses the replication of SARS-CoV-2 by selectively inhibiting 3CL protease. In the phase 2 part of a phase 2/3 clinical trial conducted in Japan and Korea, patients treated with S-217622 showed a significant and rapid decrease in viral titer and/or viral RNA on day 4 (after the 3rd dose), in comparison to the placebo. In the phase 2 part of the phase 2/3 clinical trial, no serious safety concerns were reported. Additionally, in the preliminary *in vitro* study, S-217622 exhibited similar antiviral activity against the Omicron subvariant BA.2 and other existing variants. Recognizing the urgent global need for more therapies to address COVID-19, Shionogi has already begun to work with worldwide health authorities including those located in Japan and the United States. SCORPIO-HR is a global phase 3 trial of the ACTIV-2 NIH-funded outpatient treatment study for **S**topping **CO**VID-19 p**R**ogression with early **P**rotease **I**nhibit**O**r treatment.

About ACTIV-2
ACTIV-2 is sponsored by the NIAID, part of the NIH, which also funds the ACTG. ACTIV-2 is part of NIH’s Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) initiative, a public-private partnership program set up to create a coordinated research strategy that prioritizes and speeds development of the most promising treatments and vaccines. It also receives support from Federal COVID Response-Therapeutics, the U.S.

government's multi-agency effort to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics.

About the ACTG
Founded in 1987, the AIDS Clinical Trials Group (ACTG) was the world's first HIV research network. The ACTG conducts groundbreaking studies to improve the treatment of HIV and its complications, including tuberculosis and viral hepatitis; reduce new infections and HIV-related illness; and advance new approaches to prevent, treat, and ultimately cure HIV in adults and children. More recently, the ACTG has expanded its focus to include the evaluation of outpatient treatments for COVID-19. ACTG investigators and research units in 15 countries serve as major resources for HIV/AIDS research, treatment, care, and training/education in their communities. ACTG studies have helped establish current paradigms for managing HIV disease, and have informed HIV treatment guidelines, resulting in dramatic decreases in HIV-related mortality worldwide.

About Shionogi
Shionogi & Co., Ltd. is a leading global research-driven pharmaceutical company based in Japan, dedicated to bringing benefits to patients based on its corporate philosophy of "supplying the best possible medicine to protect the health and wellbeing of the patients we serve." The company has discovered and developed novel medicines for HIV, influenza and antimicrobial resistance, and currently markets products in several therapeutic areas including anti-infectives with the first siderophore cephalosporin, FETROJA® (cefiderocol; known as FETCROJA® in Europe). Other therapeutic areas and the focus of the company's pipeline include CNS/psychoneurological diseases, oncology and pain. For more information on Shionogi & Co., Ltd., visit https://www.shionogi.com/global/en/. Shionogi Inc. is the U.S. subsidiary of Shionogi & Co., Ltd. based in N.J. For more information on Shionogi Inc., please visit https://www.shionogi.com. Shionogi B.V. is the European headquarters of Shionogi & Co., Ltd. For more information on Shionogi B.V., please visit www.shionogi.eu.

Shionogi's Commitment to Fight COVID-19
With continued social disruption caused by the worldwide spread of the novel coronavirus (SARS-CoV-2), Shionogi continues intensive efforts to deliver pharmaceutical products to patients in need in a reliable and stable manner. As a pharmaceutical company with a major focus on infectious diseases, Shionogi is also working with public institutions, academia, and partner companies to address COVID-19, by pursuing the discovery of novel therapeutics and the development of vaccine and diagnostic products. We will continue to strive to fulfill our social responsibility and to contribute to re-establishing the safety and security of society by bringing forward new tools and technologies for the diagnosis and treatment of COVID-19 to support ending this pandemic. Shionogi will work closely with government, industry, and academia to accelerate our efforts and will keep all stakeholders informed regarding the progress of our efforts.

Forward Looking Statement
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, unavailability 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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