Press Release

Pivotal Trial Results for Shionogi's Cefiderocol Published in *The Lancet Infectious Diseases*

Osaka, Japan and Florham Park, N.J., October 25, 2018 – Shionogi & Co., Ltd. (hereafter "Shionogi") announced today that *The Lancet Infectious Diseases* journal has published clinical results from the pivotal randomized controlled trial evaluating cefiderocol for the treatment of complicated urinary tract infection (cUTI) in patients at risk of multidrug-resistant Gram-negative infections.

The paper is titled "Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative pathogens: a phase 2, randomised, double-blind, non-inferiority trial."

Results from the study demonstrated treatment with cefiderocol met non-inferiority versus imipenem/cilastatin (IPM/CS) in patients with cUTI at test of cure (TOC). In the study, 73 percent (183/252) of patients in the cefiderocol group met the primary endpoint (combination of clinical response and microbiological response at TOC) versus 55 percent (65/119) in the IPM/CS group, with an adjusted treatment difference of 18.58 percent. These results in a post-hoc analysis showed that cefiderocol was superior to IPM/CS. The study enrolled 452 patients with cUTI and patients were randomly assigned 2:1 to cefiderocol and IPM/CS with a median duration of treatment of nine days for both groups.

The microbiologic response rate at TOC for the cefiderocol group was 73 percent (184/252) versus 56 percent (67/119) in the IPM/CS group, with the difference between groups at TOC at 17.25 percent. Although the study was designed to determine non-inferiority, the findings showed that cefiderocol resulted in a clinically meaningful microbiological eradication rates and outperformed IPM/CS. Additionally, cefiderocol exhibited a safety profile consistent with that of other cephalosporins.

"The data presented in *The Lancet Infectious Diseases* shows the potential of cefiderocol, particularly in a complicated patient population with comorbidities and at greater risk of multidrug-resistant infection with difficult to treat Gram-negative bacteria," said Dr. Tsutae "Den" Nagata, Chief Medical Officer, Shionogi & Co. Ltd. "Once approved, cefiderocol will be an important, new antibiotic option for providers caring for these very sick patients who may have very limited treatment options."

The article can be accessed online here.

About Cefiderocol—An Investigational Antibiotic Agent

Cefiderocol is a siderophore cephalosporin with a novel mechanism for penetrating the outer cell membrane of Gram-negative pathogens including MDR strains. Cefiderocol binds to ferric iron and is

actively transported into bacterial cells through the outer membrane via the bacterial iron transporters, which function to incorporate this essential nutrient for bacteria.[1] This mechanism allows cefiderocol to achieve higher concentrations in the periplasmic space where it can then bind to receptors and inhibit cell wall synthesis in the bacterial cells.[2] In addition, cefiderocol can also enter cells by passive diffusion through porin channels and is stable against all known classes of beta-lactamases, including both the metallo- and serine-β-lactamases.[3] Data from global surveillance studies for cefiderocol demonstrated potent *in vitro* activity against a wide spectrum of Gram-negative pathogens including carbapenem-resistant *Acinetobacter baumannii*, *P. aeruginosa*, Enterobacteriaceae, and *S. maltophilia*.[4] Cefiderocol has poor *in vitro* activity against Gram-positive or anaerobic bacteria.

Cefiderocol is currently in clinical development. Two Phase III studies are ongoing and enrolling patients with carbapenem-resistant pathogens at various infection sites (CREDIBLE-CR) and a HAP/VAP/HCAP clinical trial (APEKS-NP). The company plans to submit a New Drug Application to the United States Food and Drug Administration late in the year followed by a marketing authorization application to the European Medicines Agency and other countries. Information is available at www.clinicaltrials.gov under the identifiers NCT02714595 and NCT03032380, respectively.

About Shionogi

Shionogi & Co., Ltd. is a Japanese major research-driven pharmaceutical company 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.” Shionogi Inc., the U.S. based subsidiary of Shionogi & Co., Ltd., continues this focus on the development and commercialization of high-quality medicines that protect the health and well-being of the patients we serve. The company currently markets products in several therapeutic areas including anti-infectives, pain, cardiovascular diseases and gastroenterology. Our pipeline is focused on infectious disease, pain, CNS and oncology. For more information on Shionogi & Co., Ltd., please visit www.shionogi.co.jp/en. For more information on Shionogi Inc., please visit www.shionogi.com.

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,

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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