SHIONOGI ANNOUNCES *IN VITRO* AND REAL-WORLD DATA PRESENTED AT ECCMID 2021 DEMONSTRATING ACTIVITY OF CEFIDEROCOL AGAINST CRITICAL PRIORITY GRAM-NEGATIVE BACTERIAL PATHOGENS

- *In vitro* activity of cefiderocol has been demonstrated against the most difficult-to-treat Gram-negative bacteria, including carbapenem-resistant isolates of *Pseudomonas aeruginosa, Acinetobacter baumannii-calcoaceticus* complex, *Stenotrophomonas maltophilia*, and Enterobacterales collected from across Europe and the US. For the resistant phenotypes, cefiderocol was the most active agent tested[1,2,3,4]

- Encouraging real-world data for cefiderocol are emerging, both from use on compassionate grounds and also from the Early Access Programme, in which over a third of patients receiving cefiderocol for a Gram-negative bacterial infection were co-infected with COVID-19[5,6]

- Data have also shown that multi-drug resistant Gram-negative bacteria are prevalent across several countries in Europe, of which a notable proportion are carbapenem-resistant Gram-negative isolates like *P. aeruginosa*, associated with high mortality and high unmet medical need[7,8,9]

OSAKA, Japan, JULY 08, 2021 – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President & CEO: Isao Teshirogi, Ph.D.) (hereafter "Shionogi") today announces key data for cefiderocol, a novel siderophore cephalosporin, presented at the virtual European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), July 9-12, 2021.

Cefiderocol has extensive *in vitro* activity against some of the most difficult to treat carbapenem-resistant Gram-negative bacteria

The susceptibility profiles of cefiderocol and comparators were evaluated against a European and US collection of Gram-negative bacteria as part of the SENTRY Antimicrobial Surveillance Program. In these studies, the *in vitro* activity of cefiderocol was evaluated against non-fermenters such as *P. aeruginosa, A. baumannii-calcoaceticus complex*, and *S. maltophilia,* as well as Enterobacterales isolates, including carbapenem-resistant strains. Cefiderocol also demonstrated broad activity against the isolates resistant to recently approved beta-lactam / beta-lactamase inhibitor combinations. For the resistant phenotypes, cefiderocol was the most active agent tested.[1,2,3,4]

"These data from the SENTRY studies are very encouraging as they show that cefiderocol is broadly active against Enterobacterales and non-fermenters like Pseudomonas, Acinetobacter and Stenotrophomonas, including multidrug resistant strains, performing better than all other comparators tested. Infections caused by multidrug resistant Pseudomonas are inherently difficult to treat as many antibiotics are not effective against this critical pathogen," commented Dr. Dee Shortridge, Senior Director for Antimicrobial Development at JMI Laboratories. *"Increasing*

resistance in Gram-negative bacteria is a real issue, especially where it compromises carbapenems."

Real-world data for early use of cefiderocol are presented, including in those co-infected with COVID-19

An overview of susceptibility and clinical outcomes for isolates from 141 patients who received cefiderocol in a global compassionate use programme reported that clinical response was positive overall in patients receiving cefiderocol to treat Gram-negative infections caused by pathogens resistant to all alternative antibiotics, or where unacceptable toxicity of alternative antibiotics had been documented. The most frequent pathogens were *P. aeruginosa* (50%) and *A. baumannii* complex (24%).[5]

Initial data from the cefiderocol Early Access Programme for patients with no appropriate therapeutic alternative for resistant Gram-negative infections have also been presented. Of the 237 patients treated with cefiderocol, 37.1% (n=88) were also co-infected with COVID-19. Carbapenem-resistant *A. baumannii* (n=96; 40.5%) and carbapenem-resistant *P. aeruginosa* (n=78; 32.9%) were the most common pathogens. The most common infections were pneumonia (n=106; 44.7%) and BSI/sepsis (n=93; 39.2%). The high level of requests for cefiderocol between 1 April and 31 December 2020 demonstrate the continued high unmet need for new antimicrobials, especially for pathogens associated with high rates of resistance such as carbapenem-resistant *A. baumannii* and carbapenem-resistant *P. aeruginosa.*

"Shionogi is excited to share these real-world data at ECCMID, providing initial evidence that cefiderocol is addressing the high unmet need for new antimicrobials effective against important resistant pathogens, such as carbapenem-resistant *Acinetobacter* or *Pseudomonas*," commented Dr. Mark Hill, Global Head of Market Access, Shionogi. *"Antimicrobial resistance is a major health burden responsible for approximately 700,000 deaths globally every year, and it is of critical importance that we continue to develop effective new treatments to tackle this growing threat."*

Epidemiology studies highlight the prevalence of carbapenem-resistant Gram-negative isolates which are associated with high mortality and unmet need

A retrospective chart review carried out at sites across the UK, France and Spain – the CARBAR study - identified that over 8% of Gram-negative isolates were carbapenem-resistant. Pneumonia was the most prevalent infection caused by carbapenem-resistant Gram-negative isolates (40.7%). The most frequent pathogen identified in these patients was carbapenem-resistant *P. aeruginosa* (37%) followed by Enterobacterales (36%). 59% of patients required mechanical ventilation and the mortality rate was 44% across all pathogens, indicating a high unmet need, significant healthcare utilisation and limited treatment options in this patient population.[7,8,9]

Antimicrobial resistance (AMR)

Antimicrobial resistance (AMR) is a major health burden which urgently needs to be addressed. Globally, approximately 700,000 people die as a result of infections caused by resistant pathogens every year.[10] Infections caused by carbapenem-resistant Gram-negative bacteria are often

associated with a high mortality rate.[11] If no action is taken, antimicrobial resistance is predicted to kill 10 million people every year by 2050, at a cumulative cost to global economic output of 100 trillion USD.[10]

About FETCROJA® (cefiderocol)

Cefiderocol is a siderophore cephalosporin antibiotic with a novel mechanism for penetrating the outer cell membrane of Gram-negative pathogens by acting as a siderophore. In addition to entering cells by passive diffusion through porin channels, 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.[12] These mechanisms allow cefiderocol to achieve higher concentrations in the periplasmic space where it can bind to penicillin-binding proteins and inhibit cell wall synthesis in the bacterial cells.[13] Cefiderocol has also demonstrated *in vitro* activity against certain bacteria that contain very problematic resistant enzymes such as ESBLs, AmpC, serine- and metallo-carbapenemases.[14,15] Data from multinational surveillance studies for cefiderocol demonstrated potent *in vitro* activity against a wide spectrum of Gram-negative pathogens including carbapenem-resistant *A. baumannii, P. aeruginosa*, Enterobacterales, and *S. maltophilia*.[16] The clinical significance of the *in vitro* data is unknown. Cefiderocol has no clinically relevant activity against Gram-positive or anaerobic bacteria.

Cefiderocol is commercially available in the U.S after approval by the FDA in 2019 under the brand name FETROJA® for patients 18 years of age or older who have limited or no alternative treatment options, for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following susceptible Gram-negative microorganisms: *Escherichia coli, Klebsiella pneumoniae, Proteusmirabilis, P.aeruginosa,* and *Enterobacter cloacae* complex.[17]

FETROJA is also indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *A. baumannii complex, E. coli, E. cloacae complex, K. pneumoniae, P. aeruginosa*, and *Serratia marcescens.*

Shionogi's commitment to fighting antimicrobial resistance

Shionogi has a strong heritage in the field of anti-infectives and has been developing antimicrobial therapies for more than 60 years. Shionogi is proud to be one of the few large pharmaceutical companies that continues to focus on research and development in anti-infectives. The company invests the highest proportion of its pharmaceutical revenues in relevant anti-infectives R&D compared to other large pharmaceutical companies.[18]

For more information please refer to:
https://www.shionogi.com/global/en/sustainability/amr.html

About Shionogi
Shionogi & Co., Ltd. is a 143-year-old global, research driven pharmaceutical company

headquartered in Osaka, Japan, that is 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 currently markets products in several therapeutic areas including anti-infectives, pain, CNS disorders, cardiovascular diseases and gastroenterology. Shionogi's research and development currently target two therapeutic areas: infectious diseases, and pain/CNS disorders.

For more information on Shionogi & Co., Ltd., please visit https://www.shionogi.com/global/en/

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, 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.

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