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SHIONOGI ANNOUNCES PUBLICATION OF TWO STUDIES IN *THE LANCET INFECTIOUS DISEASES* HIGHLIGHTING THE EFFICACY AND SAFETY OF CEFIDEROCOL FOR THE TREATMENT OF INFECTIONS DUE TO AEROBIC GRAM-NEGATIVE BACTERIA IN ADULTS WITH LIMITED TREATMENT OPTIONS

- Shionogi announces publication of data from two of its clinical trials; APEKS-NP and CREDIBLE-CR in the journal *The Lancet Infectious Diseases*
- APEKS-NP demonstrated that cefiderocol is an effective and well tolerated treatment option for Gram-negative nosocomial pneumonia infections, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and Enterobacterales, in critically ill patients including those who are at risk of multi-drug resistant (MDR) infection[1]
- CREDIBLE-CR provides descriptive evidence that cefiderocol is an option for the treatment of high-risk, critically ill patients with carbapenem-resistant (CR) Gram-negative infections, including *P. aeruginosa*, *A. baumannii*, Enterobacterales and metallo-beta-lactamase expressing organisms[2]
- These clinical data build on *in vitro* data highlighting cefiderocol's extensive coverage against all Gram-negative pathogens considered of critical priority by the WHO – carbapenem-resistant *A. baumannii*, *P. aeruginosa* and Enterobacterales[3,4]
- 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,[5] so new and effective treatment options are urgently needed

OSAKA, Japan and AMSTERDAM, NL, 13 October 2020 – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President & CEO: Isao Teshirogi, Ph.D.) (hereafter "Shionogi") today announces the back to back publication of two studies in *The Lancet Infectious Diseases* journal highlighting the efficacy and safety of cefiderocol against some of the most difficult-to-treat Gram-negative bacterial infections, including nosocomial pneumonia (NP), bloodstream infections (BSI), sepsis, and complicated urinary tract infections (cUTI).[1,2]

APEKS-NP was a Phase 3 clinical trial designed to compare the efficacy and safety of cefiderocol versus high-dose, extended-infusion meropenem (2g, q8h, 3-hour infusion) in critically ill patients with hospital-acquired, ventilator-associated, or healthcare-associated pneumonia (HAP, VAP, and HCAP, respectively) caused by a broad range of Gram-negative bacteria, like *Acinetobacter baumannii*, *Pseudomonas*

aeruginosa, and Enterobacterales, including patients at risk of MDR infections. The study successfully met the primary endpoint of non-inferiority in all-cause mortality (ACM) at Day 14 with 12.4% for the cefiderocol arm (18/145) and 11.6% for the meropenem arm (17/146; adjusted treatment difference 0.8% [95% CI –6.6 to 8.2]) in the modified intention-to treat-population (mITT population). Cefiderocol was well tolerated, and its safety profile was consistent with that of other cephalosporins and/or carbapenems.

The CREDIBLE-CR trial was a small non-inferential Phase 3 open label, pathogen-focused trial designed to assess the efficacy and safety of cefiderocol or best available therapy (BAT) for the treatment of a diverse range of serious CR infections including CR non-fermenters and carbapenemase producers consisting of NP, BSI, sepsis, and cUTI. BAT was combination therapy in 71% (27/38) of cases with 28 different BAT regimens being used, whereas 83% (66/80) of cefiderocol treatment was monotherapy. Two thirds (66% [25/38]) of the BAT regimens contained colistin.[2]

The results of the CREDIBLE-CR study provided descriptive evidence of the efficacy and safety of cefiderocol in CR Gram-negative infections in a highly heterogeneous patient population frequently presenting with complex comorbidities. The clinical and microbiological outcomes were generally similar between cefiderocol and BAT, except for metallo-beta-lactamases infections where cefiderocol was substantially better (cefiderocol: 75% and 44%; BAT: 29% and 14%, respectively). There was an observed mortality difference between treatment arms in the subset of patients with *Acinetobacter* spp. infections, likely linked to imbalances in risk factors at baseline. There was no mortality difference observed in *P. aeruginosa* or Enterobacterales without *Acinetobacter* spp. co-infection. No deaths were attributed to cefiderocol-related adverse events as examined by investigators assessing the mortality imbalance.[2]

“The patient population in the CREDIBLE-CR study represents a real clinical scenario with the highest unmet need and provides descriptive evidence that cefiderocol may be a treatment option for physicians treating such critically ill patients,” commented Professor Matteo Bassetti, Lead Author and Head of the Infectious Diseases Clinic, San Martino Hospital, Genoa, Italy.

“From the results of APEKS-NP and CREDIBLE-CR studies, we believe that cefiderocol becomes a new option for the treatment of patients at risk of multi-drug resistant Gram-negative infections”, said Takuko Sawada, Director and Executive Vice President, Senior Vice President of Integrated Disease Care Department of Shionogi.

Cefiderocol received European Commission (EC) marketing authorisation for the treatment of infections due to aerobic Gram-negative bacteria in adults with limited treatment options under the brand name

FETCROJA® in April 2020 and is now commercially available in the UK. Shionogi remains committed to making the drug available further in Europe as quickly as possible.[6]

Cefiderocol is the first treatment which provides coverage against all Gram-negative pathogens considered of critical priority by the WHO – carbapenem -resistant *A. baumannii, P. aeruginosa,* and Enterobacterales.[3,4]

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. Infections caused by carbapenem-resistant Gram-negative bacteria are often associated with a high mortality rate.[7] If no action is taken, antibiotic resistance is predicted to kill 10 million people every year by 2050, at a cumulative cost to global economic output of 100 trillion USD.[5]

About FETCROJA® (cefiderocol)

Cefiderocol is a 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.[8] 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.[9] Cefiderocol has also demonstrated *in vitro* activity against certain bacteria that contain very problematic resistant enzymes such as ESBLs, AmpC, serine- and metallo-carbapenemases.[10,11] 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 *Stenotrophomonas maltophilia.*[12] 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: *E. coli, K. pneumoniae, P. mirabilis, P.*

aeruginosa, and *E. cloacae* complex.[13]

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.[14]

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

About Shionogi

Shionogi & Co., Ltd. is a 142-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/
Shionogi B.V. is the European headquarters of Shionogi & Co., Ltd. For more information on Shionogi B.V., please visit www.shionogi.eu.

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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