# SHIONOGI ANNOUNCES DATA DEMONSTRATING POTENT IN VITRO ACTIVITY OF CEFIDEROCOL AGAINST THE MOST CRITICAL PRIORITY GRAM-NEGATIVE BACTERIAL PATHOGENS

- Potent *in vitro* activity of cefiderocol has been demonstrated against the most difficult-to-treat Gram-negative bacteria, including multidrug-resistant strains, collected from across Europe

- Cefiderocol has shown broad activity against a global collection of Gram-negative bacteria even in the presence of serine- and metallo-carbapenemase-encoding genes, which can contribute to carbapenem resistance

- According to WHO, development of new antibiotics against carbapenem-resistant strains of *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Enterobacteriaceae* is a critical priority[1]

**OSAKA, Japan and AMSTERDAM, Netherlands APRIL 15, 2019 –** Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President & CEO: Isao Teshirogi, Ph.D.) and Shionogi B.V. the European subsidiary of Shionogi & Co., Ltd respectively, (hereafter "Shionogi") today announces key data for cefiderocol, a late-stage investigational, novel siderophore cephalosporin, presented at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), in Amsterdam, Netherlands, April 13-16, 2019. The data in these presentations suggest cefiderocol shows a high potential for treating infections caused by the most difficult to treat Gram-negative (GN) bacteria collected from across Europe, including multidrug-resistant strains.[2,3]

The *in vitro* activity of cefiderocol was evaluated against GN bacteria collected from across Europe and the activity was compared with comparator agents in a multi-national surveillance study,[2] which demonstrated not only the potent activity of cefiderocol against carbapenem-resistant isolates of *Enterobacteriaceae*, but also against the more difficult-to-treat carbapenem-resistant non-fermentative bacteria, *A. baumannii* and *P. aeruginosa*. In this study, 99.2% of GN isolates had minimum inhibitory concentrations (MIC) of ≤4 mg/L.[a]

In separate studies, the susceptibility profile of cefiderocol was evaluated against a global collection of only carbapenem-resistant GN bacteria.[3,4] In these studies, the *in vitro* activity against the European isolates and the presence of carbapenemase genes were evaluated. Cefiderocol showed antibacterial activity against 95.5% of carbapenem-resistant GN isolates at ≤4 mg/L. The study also evaluated regional differences in carbapenemase gene distribution. Significant differences were seen in carbapenemase gene profile across bacterial species between regions and especially between EU countries; yet cefiderocol showed the potential to be effective against *Enterobacteriaceae, A. baumannii*, and *P. aeruginosa* regardless of the presence of serine- and metallo-carbapenemase-encoding genes.

[a] The approved CLSI breakpoint for cefiderocol is defined as 4 mg/L

Similar results were seen at a national level in a study conducted in the UK, with cefiderocol demonstrating activity at low concentrations against multi-drug-resistant carbapenemase-producing *P. aeruginosa* and *A. baumannii*.[5] The relevance of *in vitro* to clinical efficacy has yet to be determined.

*"Increasing resistance in Gram-negative bacteria complicates treatment, especially where it compromises carbapenems, which are the 'go-to' antibiotics for difficult infections. The enzymes responsible for this resistance - carbapenemases - are diverse. Different types predominate in different countries and species, adding to the challenge,"* said Professor David Livermore, Professor of Medical Microbiology, University of East Anglia.

*"In the lab, cefiderocol stays active against Enterobacteriaceae with any of the common carbapenemases. What's more it's also active against Pseudomonas and Acinetobacter with carbapenemases. Pseudomonas is inherently difficult as most antibiotics are not effective against this critical pathogen, and Acinetobacter has unique carbapenemases that evade all the inhibitors available so far. We found cefiderocol to be almost universally active,"*

Professor Livermore continued, *"Overall, it's this breadth of cefiderocol's potential coverage against carbapenemase producers that's so interesting. The UK doesn't have the high prevalence of carbapenemases producers that you see in Italy, Greece, Brazil and – above all – India, but we do have diversity …. and that makes a single, widely active, agent attractive."*

John Keller, Senior Vice President Global Business Division and Head of European and US Operations Shionogi commented, "*Shionogi is excited to share these important data at ECCMID, which suggests the potential activity of cefiderocol against some of the most challenging pathogens identified by the World Health Organization. Antimicrobial resistance is a major health burden and we are committed to developing effective treatments to address this growing threat*."

Notably, in addition to these results, data from several external susceptibility studies will also be presented at ECCMID, showing activity of cefiderocol against multidrug-resistant Gram-negative pathogens from Italy, Spain, Germany and the UK.

**About Cefiderocol - An Investigational Antibiotic Agent**

Cefiderocol is a parenteral siderophore cephalosporin with a novel mechanism for penetrating the outer cell membrane of Gram-negative pathogens including multidrug-resistant 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.[6] 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.[7] These mechanisms allows cefiderocol to achieve higher concentrations in the periplasmic space where it can bind to receptors and inhibit cell wall synthesis in the bacterial cells.[8] 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*, *Pseudomonas aeruginosa*, *Enterobacteriaceae*, and *Stenotrophomonas maltophilia*.[9] Cefiderocol has poor *in vitro* activity against Gram-positive or anaerobic bacteria.

Two Phase III studies are ongoing in patients with HAP/VAP/HCAP† (APEKS-NP‡) and with carbapenem-resistant pathogens at various infection sites (CREDIBLE-CR). Information is available at www.clinicaltrials.gov under the identifiers NCT02714595 and NCT03032380, respectively.

Cefiderocol is not currently commercially available.

**About Gram-negative infections**

The increasing resistance of many infections caused by Gram-negative bacteria to existing therapies, including carbapenem-resistant Enterobacteriaceae and non-fermenting species such as *P. aeruginosa, A. baumannii,* and *S. maltophilia*, means there is a critical need for new, effective therapies.[9,10,11,12] There are an increasing number of Gram-negative pathogens resistant to multiple antibiotics, making them difficult to treat and resulting in high mortality rates.[13] In the U.S., at least 2 million people are infected with antibiotic-resistant bacteria, and at least 23,000 people die as a result each year.[14] In the EU, about 25 000 patients die from an infection with the selected multidrug-resistant bacteria.[15] The World Health Organization have identified carbapenem-resistant strains of *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii* as the top priority in the research and development of new antibiotics.[1]

**About Shionogi**

Shionogi & Co., Ltd. ("Shionogi") 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." 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, please visit http://www.shionogi.co.jp/en/. Shionogi B.V. is the European subsidiary of Shionogi & Co., Ltd. based in Amsterdam, Netherlands. For more information on Shionogi B.V., please visit http://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.

† Hospital-Acquired Pneumonia/Ventilator-Acquired Pneumonia/Healthcare-Associated Pneumonia.
‡ Nosocomial Pneumonia.

**For further information, contact:**

**Shionogi & Co., Ltd.**
Corporate Communications
Telephone: +81-6-6209-7885
Fax: +81-6-6229-9596

**Shionogi Europe Media Contact**
Russell Stapley
European Marketing Director
+44 (0) 7741 626375
russell.stapley@shionogi.eu



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