FURTHER EVIDENCE SUPPORTS CEFIDEROCOL ACTIVITY AGAINST MDR GRAM-NEGATIVE PATHOGENS: DATA PRESENTED AT THE AMERICAN SOCIETY FOR MICROBIOLOGY MICROBE (ASM) MEETING

OSAKA, Japan and FLORHAM PARK, NJ, June 1, 2017 – Shionogi & Co., Ltd. (hereafter "Shionogi") will present key results of several studies for cefiderocol (S-649266), a late-stage investigational siderophore cephalosporin, at the American Society for Microbiology (ASM) Microbe in New Orleans, Louisiana, June 1-5, 2017.

Antibacterial-resistant infections, specifically those with resistance to many antibiotics, often referred to as 'superbugs,' represent an urgent global public health threat.[1] Pathogen resistance to current antibiotics is increasing worldwide and is responsible for at least 2 million illnesses and 23,000 deaths annually in the U.S.[2] The crisis has been compounded by the lack of new antibiotics and represents a significant unmet need for patients.[2] Of particular concern are the carbapenem-resistant Gram-negative pathogens: *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae (CRE). The World Health Organization (WHO) recently identified these pathogens as "Priority 1: CRITICAL" for the research and development of new antibiotics.[3]

To help address this unmet need, Shionogi is developing cefiderocol, an investigational parenteral siderophore cephalosporin antibiotic, which has a distinctive mechanism for efficiently penetrating Gram-negative pathogens and is stable against all known classes of beta- lactamases.[4-7] In surveillance studies, cefiderocol has demonstrated activity against a wide range of Gram-negative pathogens including carbapenem-resistant strains.[8]

Studies presented at the 2017 ASM Microbe meeting complement previous findings and include epidemiological, molecular mechanism, and global surveillance studies that evaluated cefiderocol, as well as other test compounds, against a wide range of Gram-negative clinical isolates collected from North America and Europe. Cefiderocol demonstrated potent activity against *P. aeruginosa*, *A. baumannii,* Enterobacteriaceae, and *Stenotrophomonas maltophilia,* including carbapenem-resistant strains of these pathogens harboring both serine and metallo-types beta-lactamases.

"We believe cefiderocol is a promising compound that will provide a potentially lifesaving intervention, and we are determined to bring this important therapeutic option to the healthcare community as soon as possible," said Dr. Tsutae Den Nagata, Chief Medical Officer. "The data presented at ASM Microbe 2017 further demonstrate cefiderocol's activity against clinically important carbapenem-resistant Gram-negative pathogens and support the positive topline results from the U.S. registrational study in a difficult-to-treat patient population with complicated urinary tract infections."

Clinical development of cefiderocol for the U.S. is ongoing with a phase 3 trial in patients with carbapenem-resistant pathogens at various infection sites (CREDIBLE-CR). Also scheduled to start in 2017 is a phase 3 trial in patients with hospital-acquired/ventilator-associated/healthcare-associated pneumonia HAP/VAP/HCAP[†] (APEKS[*]-NP[‡]). Shionogi plans to submit a new drug application (NDA) to the U.S. Food and Drug Administration (FDA) in 2017 with data from a recently completed registrational study in patients with cUTI (APEKS[*]-cUTI). Information is available at www.clinicaltrials.gov under the identifiers NCT02714595, NCT03032380, and NCT02321800, respectively.

* *Acinetobacter, Pseudomonas*, *Escherichia*, *Klebsiella and Stenotrophomonas.*
[†] Hospital-Acquired Pneumonia/Ventilator-Acquired Pneumonia/Healthcare-Associated Pneumonia.
[‡] Nosocomial Pneumonia.

"With the growing challenge of antibiotic resistance in Gram-negative pathogens, it is encouraging to see data that support cefiderocol and show that there may soon be a new treatment option available," said Barry Kreiswirth, Ph.D., Director of the Public Health Research Institute (PHRI) Tuberculosis Center at Rutgers University. "The diversity and quality of cefiderocol data presented at 2017 ASM Microbe Meeting help to further my understanding of this innovative antibiotic agent, and I am optimistic about the potential of cefiderocol for treating these life-threatening pathogens."

Shionogi continues to build on the foundation of preclinical and clinical research for cefiderocol with the goal of bringing this important antibiotic therapy to patients. The data presented at ASM add to this growing body of evidence for cefiderocol. Some key studies and findings include:

***In Vitro* Antibacterial Activity of Cefiderocol against Gram-Negative Clinical Strains Collected in North America and Europe: SIDERO-WT-2015** (poster number: SUNDAY-11)
In this study, 7054 Gram-negative clinical isolates representing 45 species were systematically collected from North America and Europe and evaluated *in vitro* with cefiderocol and a range of other test compounds. Cefiderocol demonstrated potent activity with an MIC_{90} ranging from 0.5 – 2µg/mL for the organisms tested. More than 99% of isolates had MIC values ≤4µg/mL. The potent activity of cefiderocol was observed across the clinically important Enterobacteriaceae and non-fermenters including *P. aeruginosa*, *A. baumannii* and *S. maltophilia*, including carbapenem non-susceptible isolates. These data add support to the potential of cefiderocol for treatment of these problematic pathogens.

Cefiderocol Susceptibility against Globally Isolated Meropenem Non-Susceptible Gram-Negative Bacteria Containing Serine and Metallo-Carbapenemase Genes (poster number: SUNDAY-25)
In a separate study, 1221 meropenem non-susceptible strains of Enterobacteriaceae, *A. baumannii*, and *P. aeruginosa*, were evaluated to determine the MIC of cefiderocol and a range of other test compounds. All isolates were PCR genotyped to detect specific carbapenemases including KPC, VIM, IMP, NDM, and OXA types. The MIC_{90} of cefiderocol against 74 KPC-producing Enterobacteriaceae was 2µg/mL. The MIC_{90} of cefiderocol against 72 metallo-type carbapenemase producers including Enterobacteriaceae, *A. baumannii*, and *P. aeruginosa* was 4µg/mL. The MIC_{90} of cefiderocol was 1µg/mL against 679 OXA producers including 649 *A. baumannii* and 30 Enterobacteriaceae. Overall, cefiderocol demonstrated potent *in vitro* activity irrespective of the presence of serine or metallo-type carbapenemases.

Anti-Acinetobacter Activity of Cefiderocol (S-649266), a Novel Siderophore Cephalosporin: Bactericidal Activity Due to Penicillin-binding Proteins Inhibition and Antibacterial Activity against Globally Collected Clinical Isolates (poster number: SATURDAY-115)
A. baumannii is recognized to be one of the most difficult-to-treat pathogens. This study investigated antibacterial activity and mode of action of cefiderocol against 1148 globally collected clinical isolates of *A. baumannii*. Cefiderocol displayed robust activity with an MIC_{90} of 1µg/mL compared to an MIC_{90} of >64µg/mL for meropenem and cefepime and other test compounds. The MIC_{90} for colistin and ciprofloxacin were 4µg/mL and >8µg/mL respectively. These data indicate that cefiderocol should be promising for the treatment of *A. baumannii*, including carbapenem-resistant strains.

***Stenotrophomonas maltophilia* in United States Hospitals between 2010 and 2015** (poster number: SATURDAY-113)
S. maltophilia is highly resistant to most classes of antibiotics, including carbapenems. Trimethoprim/sulfamethoxazole (TMP/SMX) and minocycline are most active *in vitro* and TMP-SMX is considered the treatment of choice, although increasing resistance is reported. This study investigated 10,194 unique patients with positive *S. maltophilia* cultures from 2010 to 2015 in the United States using the Premier healthcare database. Occurrence was identified in inpatients (83%) and outpatients and from various infection sites, but most frequently respiratory. TMP/SMX and

minocycline were the most active antimicrobials tested, but about 25% of patients received either TMP-SMX or minocycline. These findings suggest that treatment of *S. maltophilia* represents an unmet need.

Additional *in vitro* cefiderocol molecular and surveillance data are also being presented (poster numbers: FRIDAY-16, FRIDAY-177, SATURDAY-114, SUNDAY-110, SUNDAY-208, and SUNDAY-352).

Cefiderocol—an investigational antibiotic agent[4]
Cefiderocol is a siderophore cephalosporin with a novel mechanism for efficiently penetrating the outer cell membrane of Gram-negative pathogens. 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.[5] This Trojan horse strategy 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.[6] In addition, cefiderocol is stable against all known classes of beta-lactamases, including both the metallo- and serine-carbapenemases.[7] Data from global surveillance studies for cefiderocol demonstrated potent in vitro activity against a wide spectrum of Gram-negative pathogens including carbapenem-resistant *A. baumannii, P. aeruginosa*, Enterobacteriaceae, and *S. maltophilia*.[8]

About Shionogi
Shionogi & Co., Ltd. is a 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 well-being of the patients we serve." Shionogi's research and development currently target two therapeutic areas: infectious diseases, and pain/CNS disorders. For over 50 years, Shionogi has developed and commercialized innovative oral and parenteral anti-infectives. In addition, Shionogi is engaged in new research areas, such as obesity/geriatric metabolic disease and oncology/immunology. Contributing to the health and quality of life of patients around the world through development in these therapeutic areas is Shionogi's primary goal. For more details, please visit www.shionogi.co.jp/en/. For more information on Shionogi Inc., the U.S.-based subsidiary of Shionogi & Co., Ltd., headquartered in Florham Park, NJ, USA, please visit www.shionogi.com. For more information on Shionogi Ltd., the UK-based subsidiary of Shionogi & Co. Ltd., headquartered in London, England, 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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