SHIONOGI PRESENTS POSITIVE CLINICAL EFFICACY TRIAL RESULTS AND *IN VITRO* DATA ON CEFIDEROCOL, AT IDWEEK 2017

OSAKA, Japan and FLORHAM PARK, NJ, October 4, 2017 – Shionogi & Co., Ltd. (hereafter "Shionogi") will present clinical trial efficacy results, as well as supportive *in vitro* data, on cefiderocol (S-649266), an investigational siderophore cephalosporin in late stage development, at IDWeek™ 2017, held October 4-8 in San Diego.

The rise of 'superbugs' means an increasing number of pathogens no longer respond to treatment with available antibiotics. Each year, antibiotic-resistant infections impact at least two million patients in the U.S.[1] As a result, antibiotic-resistant infections are responsible for more than eight million additional days in the hospital[2] and cost the U.S. healthcare system between $21 and $34 billion annually.[3] To help solve this mounting crisis, new drug development is needed, particularly for Gram-negative bacteria, identified as the biggest threats by the U.S. Centers for Disease Control and Prevention (CDC) and World Health Organization.[1,4]

Cefiderocol has a distinctive mechanism for efficiently penetrating the outer membrane of Gram-negative pathogens. In addition, cefiderocol is stable against all known classes of beta-lactamases, including both the metallo- and serine-carbapenemases.[5] The result of these two unique features provides potent activity against carbapenem-resistant strains of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia,* and Enterobacteriaceae (CRE).[6]

At IDWeek, Shionogi will share results from the APEKS*-cUTI clinical efficacy study. The poster presentation (poster number 1869), titled "Clinical Response of Cefiderocol Compared with Imipenem/Cilastatin in the Treatment of Adults with Complicated Urinary Tract Infections with or without Pyelonephritis or Acute Uncomplicated Pyelonephritis," will be presented on Saturday, October 7.

The APEKS*-cUTI study was a multinational, multicenter, double-blind, randomized trial, that showed treatment with cefiderocol met non-inferiority versus high dose of imipenem/cilastatin (IPM/CS) on the U.S. Food and Drug Administration (FDA) pre-specified composite primary endpoint of clinical cure and microbiological eradication in patients with complicated urinary tract infection (cUTI) at test of cure (TOC). The study enrolled 452 patients with cUTI, randomized 2:1 to cefiderocol and IPM/CS, with a median duration of treatment of nine days in both treatment groups. This trial was designed to evaluate the efficacy and safety of cefiderocol versus IPM/CS in hospitalized adult patients at risk for multidrug-resistant (MDR) Gram-negative infections. The study permitted enrollment of patients with complex co-morbid conditions, including renal transplant, limited the proportion of patients with acute uncomplicated pyelonephritis to less than 30 percent, and did not allow switch to oral therapy.

Key findings from the APEKS*-cUTI study included:

- Cefiderocol met non-inferiority versus IPM/CS on the FDA pre-specified primary composite endpoint of clinical cure and microbiological eradication in patients with cUTI caused by Gram-negative bacteria. In the study, 72.6 percent (183/252) of patients in the cefiderocol arm met the primary endpoint versus 54.6 percent (65/119) in the IPM/CS arm at TOC. The adjusted difference between groups was clinically meaningful at 18.58 percent (95% CI: 8.23%, 28.92%) and consistent with superiority of cefiderocol.
- The clinical response rates per pathogen at TOC for cefiderocol and IPM/CS respectively were 89.7 percent (131/146) versus 88.3 percent (68/77) for *Escherichia coli*; 89.1 percent (41/46) versus 84 percent (21/25) for *Klebsiella pneumoniae*; 73.3 percent (11/15) versus 75 percent (3/4) for *P. aeruginosa*; 100 percent (13/13) versus 100 percent (1/1) for *Proteus mirabilis*.

- Serious adverse events (SAEs) were reported for 4.7 percent (14/300) of patients who received cefiderocol and 8.1 percent (12/148) of patients who received IPM/CS.

"Results from the APEKS*-cUTI trial support the findings of non-clinical studies and reinforce the value of cefiderocol by demonstrating efficacy in a difficult to treat patient population with complicated urinary tract infections," said Dr. Tsutae "Den" Nagata, Chief Medical Officer, Shionogi. "There is a clear, unmet need for new anti-infectives to battle the growing problem of drug-resistant bacteria and cefiderocol has the potential to be an important treatment option."

Additional *in vitro* cefiderocol data presented during poster sessions on Friday, October 6 at IDWeek include:

***In Vitro* Activity of Cefiderocol against Globally Collected Carbapenem-Resistant Gram-Negative Bacteria Isolated from Urinary Tract SIDERO-CR-2014/2016** (poster number: 1199)
Cefiderocol inhibited the growth of 97.5 percent of clinical isolates at 4 µg/mL or less including CRE, MDR *P. aeruginosa*, MDR *A. baumannii*, and *S. maltophilia*. The MIC_{90} values of comparator antibiotics ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem, were >64 µg/mL. The carbapenem-resistant Gram-negative isolates included 226 Enterobacteriaceae, 44 *A. baumannii*, 45 *P. aeruginosa*, 7 *S. maltophilia,* and 1 *Burkholderia cepacia* isolated from urinary tract sources collected globally from 2014 to 2016.These results support cefiderocol as a promising candidate for the treatment of serious cUTI caused by carbapenem-resistant Gram-negative bacteria.

***In Vitro* Activity of Cefiderocol against Gram-Negative Clinical Isolates Collected from Urinary Tract SIDERO-WT-2014/SIDERO-WT-2015** (poster number: 1229)
Cefiderocol inhibited the growth of 99.8 percent of all clinical isolates at 4 µg/mL or less in this study. Cefiderocol exhibited *in vitro* activity against 2,306 strains of Gram-negative bacteria. The cefiderocol MIC_{90} value was 2 µg/mL for carbapenem non-susceptible (CarbNS) non-fermenters including *P. aeruginosa*, and *A. baumannii* and 2 µg/mLfor CarbNS Enterobacteriaceae. The MIC_{90} of comparators against CarbNS Enterobacteriaceae including cefepime, ceftolozane-tazobactam, and meropenem was >64 µg/mL, >8 µg/mL for colistin and ciprofloxacin and 4 µg/mL for ceftazidime-avibactam. The isolates in the study included a total of 1,887 Enterobacteriaceae and non-fermenters including 106 *A. baumannii,* 294 *P. aeruginosa*, and 11 *S. maltophilia* isolated from urinary tract sources collected in the U.S. from 2013 to 2016. These findings indicate that cefiderocol may have the potential for treating cUTI infections caused by these problematic organisms, including isolates resistant to colistin.

Additional *in vitro* and *in vivo* data on cefiderocol and its activity against MDR pathogens are being presented (poster numbers: 1230, 1512, 1520 and 1524).

Cefiderocol—an investigational antibiotic agent
Cefiderocol is a siderophore cephalosporin with a novel mechanism for efficiently penetrating the outer cell membrane of aerobic 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.[7] 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.[8] 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-carbapenemases.[5] 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*.[6] Cefiderocol has poor *in vitro* activity against Gram-positive or anaerobic bacteria.

About the regulatory pathway of cefiderocol
Cefiderocol is currently in clinical development and has completed a U.S. registrational study in patients with cUTI (APEKS*-cUTI). Additionally, a Phase 3 trial in patients with carbapenem-resistant pathogens at various infection sites (CREDIBLE-CR) is ongoing. In 2017 Shionogi also initiated a Phase 3 HAP/VAP/HCAP[†] (APEKS*-NP[‡]) clinical trial. The company plans to submit a New Drug Application to the U.S. FDA. A marketing authorization application to the EMA is planned for 2018. Information is available at www.clinicaltrials.gov under the identifiers NCT02321800, NCT02714595 and NCT03032380, respectively.

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

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