SHIONOGI & CO., LTD.

Shionogi Presents Results of the First Clinical Efficacy Trial and In Vitro Data on Cefiderocol (S-649266), a Siderophore Cephalosporin

Osaka, Japan, April 22, 2017 - Shionogi & Co., Ltd. today announced it will present for the first time clinical trial efficacy results, as well as supportive *in vitro* data, on cefiderocol (S-649266), an investigational siderophore cephalosporin in late stage development with activity against a broad range of Gram-negative pathogens, including those highly resistant to currently available agents such as colistin and carbapenem-resistant strains of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae (CRE) and *Stenotrophomonas maltophilia*, at the 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), held in Vienna, Austria, April 22 - 25, 2017.

Key findings for cefiderocol reported during oral sessions on April 22 and 24 at ECCMID include the following:

APEKS-cUTI Study (Late Breaker) (abstract #7582)
The APEKS*-cUTI study was a multinational, multicenter, double-blind, randomized trial, that showed treatment with cefiderocol met non-inferiority versus 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). In the study, 72.6% (183/252) of patients in the cefiderocol arm met the primary endpoint vs 54.6% (65/119) in the IPM/CS arm. The weighted difference between groups was 18.58 percent (95% CI: 8.23%, 28.92%), consistent with superiority of cefiderocol. 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 with cUTI, with or without pyelonephritis, or acute uncomplicated pyelonephritis at TOC (approximately 7 days following the end of treatment). 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.

Highlights of key results of the APEKS*-cUTI study include:

- 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. The difference between groups at TOC was 18.58 percent (95% CI: 8.23%, 28.92%), consistent with superiority of cefiderocol.
- Cefiderocol's per patient microbiologic response at TOC was 73.0 percent versus 56.3 percent in the

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IPM/CS group. Although the study was a non-inferiority study, the difference between groups at TOC was 17.25 percent (95% CI: 6.92%, 27.58%), consistent with superiority of cefiderocol.

- Cefiderocol was well tolerated in the study, with adverse events reported for 40 percent of patients in the cefiderocol arm versus 50 percent of patients in the IPM/CS arm. Only 1 percent of cefiderocol treated patients were discontinued due to drug-related adverse events.
- Serious adverse events (SAEs) were reported for 4.7 percent of patients who received cefiderocol and 8.1 percent of patients who received IPM/CS.

"We are very excited by the results of the APEKS*-cUTI trial as it enrolled more-difficult-to-treat patients than other recent cUTI studies. We believe cefiderocol is a promising compound that will help save patient lives and we are determined to bring this important therapeutic option quickly to the healthcare community," said Dr. Tsutae Den Nagata, Chief Medical Officer.

Additional *in vitro* cefiderocol data presented during poster session titled “cefiderocol” on April 24 highlight the following:

SIDERO-WT 2014 European Region (poster #1314)
A separate surveillance study SIDERO-WT-2014 evaluated the *in vitro* activity of cefiderocol and comparator agents against 4,966 strains of Gram-negative clinical isolates systematically collected from Europe. In this study, cefiderocol exhibited potent antibacterial activity with MIC_{90} of 1 mg/L. Cefiderocol demonstrated equally potent activity against the non-fermenters (*Pseudomonas aeruginosa, Acinetobacter baumannii and Stenotrophomonas maltophilia* as well as the broad group of Enterobacteriaceae) with more than 99.3 percent of all isolates having MIC values ≤4 mg/L. In subsets of carbapenem non-susceptible isolates of Enterobacteriaceae (N=125) and non-fermenters (N=1070), cefiderocol inhibited 96.0 and 98.0 percent at ≤4 mg/L, respectively, demonstrating the potential of cefiderocol for treating infections caused by these problematic organisms.

SIDERO-CR 2014/2016 (poster #1316)
The surveillance study SIDERO-CR-2014/2016 showed cefiderocol exhibited potent *in vitro* activity against a collection of 1,873 strains of highly-resistant Gram-negative bacteria, including carbapenem-resistant strains, from across the globe (53% from Europe, 21% Latin America, 12% from North America and 14% ROW). Against CRE, MIC_{90} of cefiderocol was 4 mg/L, while MIC_{90} of comparator agents ceftazidime-avibactam, ceftolozane-tazobactam and colistin were >64, >64 and >8 mg/L, respectively. Against MDR non-fermenters, MIC_{90} of cefiderocol was 1 mg/L, while MIC_{90} of the same comparators were >64, >64 and 4 mg/L, respectively.

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Cefiderocol Activity against *Stenotrophomonas maltophilia* (poster #1313)
Antibacterial activity of cefiderocol was tested against *Stenotrophomonas maltophilia*, an increasingly important pathogen which is intrinsically resistant to carbapenems and other broad spectrum beta-lactam antibiotics. With a MIC_{50}/MIC_{90} of 0.063/0.25 mg/L, cefiderocol demonstrated growth inhibition of all 645 strains, which were collected in the SIDERO-WT 2014 and SIDERO-CR 2014/2016 studies, at 4 mg/L or less, including isolates with decreased susceptibility to colistin. Comparator agents, including ceftazidime-avibactam, ceftolozane-tazobactam and meropenem were not effective (MIC_{50}/MIC_{90}: 8/64, 8/>64, >64/>64 mg/L, respectively).

Additional *in vitro* data of cefiderocol activity against MDR pathogens is being presented in oral (abstract #1383 and #3177) and poster (poster #1312 and #1315) presentations.

Cefiderocol—an investigational antibiotic agent[1]
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.[2] 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.[3] In addition, cefiderocol is stable against all known classes of beta-lactamases, including both the metallo- and serine-carbapenemases.[4] 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,* and Enterobacteriaceae and *Stenotrophomonas maltophilia.*[5]

About the regulatory pathway of cefiderocol
Cefiderocol is currently in clinical development and recently completed a US registrational study in patients with cUTI (APEKS*-cUTI). An additional Phase 3 trial in patients with carbapenem-resistant pathogens at various infection sites (CREDIBLE-CR) is ongoing. In 2017 Shionogi will initiate a Phase 3 HAP/VAP/HCAP† (APEKS*-NP‡) clinical trial. The Company plans to submit a new drug application to the U.S. FDA in 2017 and to the EMA in 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

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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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