

SHIONOGI ANNOUNCES SUBMISSION OF CEFIDEROCOL MARKETING AUTHORISATION APPLICATION

OSAKA, Japan & AMSTERDAM, NL Apr 1, 2019 –Shionogi & Co., Ltd (hereafter “Shionogi”) announces that the Marketing Authorisation Application (MAA) submission for cefiderocol, a novel siderophore cephalosporin, has been accepted for review by the European Medicines Agency (EMA). The CHMP has granted cefiderocol accelerated assessment indicating that this medication is expected to be of major public health interest, particularly from the point of view of therapeutic innovation. Shionogi is seeking an indication for the treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options.

Cefiderocol has shown *in vitro* activity against all the Gram-negative species that were identified by the WHO as being the highest priority for finding new treatments.^{1,2} These include the critical carbapenem-resistant Gram-negative non-fermenters *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, as well as difficult-to-treat carbapenem-resistant *Enterobacteriaceae*. Cefiderocol has been developed to meet a significant unmet need in an area where mortality is high. No antibiotics are currently available that address all three major carbapenem-resistant mechanisms.

“We are pleased to announce the MAA submission for cefiderocol which is an important milestone in the regulatory process.” said Dr. John Keller Senior Vice President Global Business Division and Head of European and US operations Shionogi.

AMR (Antimicrobial Resistance) is a major health burden that urgently needs to be addressed. In the US and Europe alone, approximately 56,000 people die of antibiotic-resistant infections every year^{3,4} 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 Cefiderocol - An Investigational Antibiotic Agent

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.⁶ This mechanism allows cefiderocol to overcome resistance due to porin channel mutations as well as achieving higher concentrations in the periplasmic space where it can then bind to receptors and inhibit cell wall synthesis in the bacterial cells⁷ 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.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*, *P. aeruginosa*, *Enterobacteriaceae*, and *S. maltophilia*.¹ Cefiderocol has poor *in vitro* activity against Gram-positive or anaerobic bacteria.

Cefiderocol is currently in clinical development. The APEKS-cUTI study was successfully completed in 2017. It was a multinational, multicenter, double-blind trial, which enrolled 452 patients with a complicated urinary tract infection (cUTI). This trial was designed to evaluate the efficacy and safety of cefiderocol in this population versus imipenem/cilastatin in hospitalized adult patients at risk for multidrug-resistant Gram-negative infection.^{9,10,11} *The Lancet Infectious*

Diseases journal has published the clinical results from this trial.¹²

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.

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/>.

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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² WHO. WHO publishes list of bacteria for which new antibiotics are urgently needed <https://www.who.int/en/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed>

³ CDC. Antibiotic / Antimicrobial Resistance (AR / AMR). Available at: <https://www.cdc.gov/drugresistance/index.html>
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⁴ European Commission. EU Action on Antimicrobial Resistance. Available at: http://ec.europa.eu/health/amr/antimicrobial-resistance_en Last accessed March 2019

⁵ O'Neill, J. *et al.* Review on antimicrobial resistance. Tackling drug-resistant infections globally: final report and recommendations. 2016

⁶ Ito A, Nishikawa T., Masumoto S, et al. Siderophore Cephalosporin Cefiderocol Utilizes Ferric Iron Transporter Systems for Antibacterial Activity against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother.* 2016;60(12):7396-7401.

⁷ Tillotson GS. Trojan Horse Antibiotics—A Novel Way to Circumvent Gram-Negative Bacterial Resistance? *Infectious Diseases: Research and Treatment.* 2016;9:45-52 doi:10.4137/IDRT.S31567

⁸ Ito-Horiyama T, Ishii Y, Ito A, et al. Stability of Novel Siderophore Cephalosporin S-649266 against Clinically Relevant Carbapenemases. *Antimicrob Agents Chemother.* 2016;60(7):4384-4386.

⁹ [Press release on January 12, 2017](#)

SHIONOGI ANNOUNCES POSITIVE TOP-LINE RESULTS FOR CEFIDEROCOL PIVOTAL cUTI CLINICAL TRIAL

¹⁰ [Press release on April 25, 2017](#)

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

¹¹ [Press release on October 5, 2017](#)

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

¹² [Press release on October 25, 2018](#)

Pivotal Trial Results for Shionogi's Cefiderocol Published in *The Lancet Infectious Diseases*