Press Release

Shionogi to Present New Data at European Congress of Clinical Microbiology and Infectious Diseases 2019

OSAKA, Japan and FLORHAM PARK, N.J., Apr 4, 2019 – Shionogi & Co., Ltd. (Head Office: Osaka, Japan; President and CEO: Isao Teshirogi, Ph.D.) and Shionogi Inc., the U.S. subsidiaries of Shionogi & Co., Ltd respectively, (hereafter "Shionogi") today announced 12 data presentations taking place at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), being held April 13-16, 2019 in Amsterdam.

Eight posters will be presented on cefiderocol, a late-stage investigational, novel siderophore cephalosporin. Cefiderocol has broad Gram-negative antimicrobial activity against all the critical Gram-negative pathogens the World Health Organization has identified as being the highest priority for finding new treatment options.*

Data for XOFLUZA™ (baloxavir marboxil), a first-in-class, single-dose oral medicine for the treatment of influenza, will be presented in two oral presentations and two posters.

Presentations will include data on these Shionogi agents from company-sponsored or investigator-initiated investigational studies.

"We look forward to sharing findings from several large-scale surveillance studies conducted in Europe and North America, in which cefiderocol demonstrated potent *in vitro* activity against problematic Gram-negative bacteria. We believe these data further support the clinical profile of cefiderocol in treating serious and life-threatening infections," said Dr. Tsutae Den Nagata, Chief Medical Officer, Shionogi. "In addition, the XOFLUZA data to be presented add to the growing body of evidence of the drug's robust efficacy and utility against influenza, which remains a global public health concern."

The details for the presentations are as follows:

Cefiderocol

Poster #P1851: Cefiderocol *in vitro* activity against Gram-negative clinical isolates collected in Europe: result from SIDERO-CR-2014/2016 (Abstract #740)
Presenter: Masakatsu Tsuji
Date and time: April 15, 13:30-14:30
Session title and location: PS106 - Cefiderocol *in vitro*; paper poster area

Poster #P1852: Cefiderocol *in vitro* activity against Gram-negative clinical isolates collected in Europe: result from three SIDERO-WT surveillance studies between 2014-2017 (Abstract #739)

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Presenter: Masakatsu Tsuji
Date and time: April 15, 13:30-14:30
Session title and location: PS106 - Cefiderocol *in vitro*; paper poster area

Poster #P1853: Cefiderocol susceptibility and geographical analysis against globally isolated meropenem non-susceptible Gram-negative bacteria containing serine- and metallo-carbapenemase gene (Abstract #737)
Presenter: Masakatsu Tsuji
Date and time: April 15, 13:30-14:30
Session title and location: PS106 - Cefiderocol *in vitro*; paper poster area

Poster #P1854*: In vitro* and *in vivo* activity of cefiderocol against *Burkholderia cepacia* complex clinical isolates (Abstract #733)
Presenter: Masakatsu Tsuji
Date and time: April 15, 13:30-14:30
Session title and location: PS106 - Cefiderocol *in vitro;* paper poster area

Poster #P1855: *In vitro* antibacterial activity of cefiderocol against an international collection of carbapenem-non-susceptible Gram-negative bacteria isolated from respiratory, blood, skin/soft tissue and urinary sources of infection: SIDERO-WT-2014-2016 (Abstract #6281)
Presenter: Sean Nguyen
Date and time: April 15, 13:30-14:30
Session title and location: PS106 - Cefiderocol *in vitro*; paper poster area

Poster #P1857: Characterization of isolates showing high MICs to cefiderocol from global surveillance study SIDERO-CR-2014/2016 (Abstract #2832)
Presenter: Akinobu Ito
Date and time: April 15, 13:30-14:30
Session title and location: PS106 - Cefiderocol *in vitro*; paper poster area

Poster #P0911: Prevalence and treatment of *Stenotrophomonas maltophilia* among adult patients in United States hospitals between 2010 and 2015 (Abstract #6069)
Presenter: Bin Cai
Date and time: April 14, 12:30-13:30
Session title and location: PS057 - Infection due to *Pseudomonas aeruginosa* and other non-fermenters – many challenges; paper poster area

Poster #P1803: Distribution of Gram-negative pathogens by infection site among hospitalised adult

patients in United States hospitals between 2010 and 2015 (Abstract #6234)
Presenter: Bin Cai
Date and time: April 15, 12:30-13:30
Session title and location: PS101 - Clinical epidemiology of infections due to MDR Gram-negatives; paper poster area

XOFLUZA (baloxavir marboxil)
Oral presentation #O0817: Clinical, virologic and safety outcomes in otherwise healthy adolescent patients with acute influenza: sub-group analyses in adolescent population from the CAPSTONE-1 phase III clinical trial (Abstract #3691)
Presenter: Simon Portsmouth
Date and time: April 15, 14:06-14:16
Session title and location: OS166 - New therapeutic strategies in viral infections; Hall M

Oral presentation #O0819: Treatment emergent influenza virus variants with reduced baloxavir susceptibility: impact on clinical and virologic outcomes in otherwise healthy outpatients with acute influenza (Abstract #2849)
Presenter: Takeki Uehara
Date and time: April 15, 14:30-14:40
Session title and location: OS166 - New therapeutic strategies in viral infections; Hall M

Poster #P0765: Delayed oral dosing of baloxavir marboxil in combination with a neuraminidase inhibitor ameliorates virus-induced infiltration of inflammatory cells into lungs and protected lung function in mice lethally infected with influenza A virus (Abstract #4353)
Presenter: Keita Fukao
Date and time: April 14, 12:30-13:30
Session title and location: PS050 - New therapeutic approaches in viral infections; paper poster area

Poster #P1122: Baloxavir demonstrates clinical and virologic efficacy in high-risk patients with influenza B infection: CAPSTONE-2 Study (Abstract #3801)
Presenter: Simon Portsmouth
Date and time: April 14, 13:30-14:30
Session title and location: PS066 - Respiratory viral epidemiology; paper poster area

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About Cefiderocol

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.[1] 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.[2] These mechanism 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.[3] 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*.[4] 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.

About Gram-negative Infections

The availability of effective therapies against Gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae and non-fermenting species such as *P. aeruginosa*, *A. baumannii* and *S. maltophilia*, is an important unmet medical need.[4-8] There are an increasing number of Gram-negative pathogens resistant to multiple antibiotics, making them difficult to treat and resulting in high mortality rates.[9] 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[10]. In the EU, about 25 000 patients die from an infection with the selected multidrug-resistant bacteria[11]. 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.[5]

About XOFLUZA™ (baloxavir marboxil)

XOFLUZA, discovered by Shionogi, has a novel mechanism of action that inhibits cap-dependent endonuclease in the polymerase acidic (PA) protein (in the United States Prescribing Information, this enzyme is stated as polymerase acidic endonuclease), an enzyme essential for viral replication. The regimen for XOFLUZA is a single oral dose to treat uncomplicated influenza, which is different from all currently available antiviral treatments. In non-clinical studies, XOFLUZA demonstrated an antiviral effect against a wide range of influenza viruses including oseltamivir-resistant strains and avian strains (H7N9, H5N1).[12-14] XOFLUZA was approved and is now available in Japan for the treatment of influenza Types A and B in adults and paediatric patients.[15] Shionogi submitted a NDA

for XOFLUZA in Taiwan on June 29, 2018, for the treatment of influenza in patients 12 years of age and older.[16]

Shionogi and the Roche Group, which includes Genentech in the U.S., have a license and collaboration agreement to further develop and commercialize XOFLUZA globally. Under the terms of this agreement, Roche Group holds worldwide rights to XOFLUZA excluding Japan and Taiwan, which will be retained exclusively by Shionogi & Co., Ltd. XOFLUZA is currently available across the U.S. for the treatment of acute, uncomplicated influenza in people 12 years of age or older.[17] The U.S. Food and Drug Administration (FDA) has accepted a supplemental New Drug Application for XOFLUZA for the treatment of influenza in individuals at high-risk for influenza-related complications 12 years and older. The Prescription Drug User Fee Act (PDUFA) date for an FDA decision is November 4, 2019. For more information, please refer to the XOFLUZA website.

Roche is now conducting a Phase III development program including paediatric populations, and hospitalised patients with severe influenza and will further assess the potential to reduce transmission in otherwise healthy patients. Shionogi is conducting a post-exposure Phase III prophylaxis study in Japan in the 2018/2019 north hemisphere flu season.

About Influenza

Seasonal and pandemic influenza remain a major public health concern, and novel influenza drugs that will offer significant improvement over current therapy are urgently needed. Globally, annual epidemics result in three-to-five million cases of severe disease, millions of hospitalizations and up to 650,000 deaths worldwide.[18-22]

About Shionogi

Shionogi & Co., Ltd. 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, cardiovascular diseases and gastroenterology. Our pipeline is focused on infectious disease, pain, CNS and oncology. For more information on Shionogi & Co., Ltd., visit www.shionogi.co.jp/en. Shionogi Inc. is the U.S. subsidiary of Shionogi & Co., Ltd. based in N.J. For more information on Shionogi Inc., please visit https://www.shionogi.com/.

Forward-Looking Statements

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.

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

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