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SHIONOGI

NOVEL SIDEROPHORE CEPHALOSPORIN S-649266
PRE-Clinical results suggest potent activity
against multidrug-resistant gram-negative pathogens

PHILADELPHIA, PA (October 9, 2014) S-649266, an investigational parenteral siderophore cephalosporin, exhibits marked potency against Gram-negative bacteria, including multidrug-resistant (MDR) pathogens, in pre-clinical studies. S-649266 has demonstrated active penetration into bacteria and stability to beta-lactamases that hydrolyze carbapenem antibiotics, according to results presented at IDWeek 2014.

The increase of MDR bacteria has been called a “crisis” by the President’s Council of Advisors on Science and Technology.1 Pathogen resistance to current antibiotics is increasing worldwide2 and is responsible for 2 million illnesses and 23,000 deaths annually in the U.S.3

S-649266 is a new parenteral siderophore cephalosporin antibiotic discovered by Shionogi & Co., Ltd. It has unique structural features that exploit the way Gram-negative bacteria acquire iron which is necessary for growth. S-649266 binds to free iron, and is actively transported across the outer membrane with the iron. This “Trojan Horse” strategy allows S-649266 to enter the periplasmic space where it binds to penicillin-binding proteins (PBPs) and disrupts cell wall synthesis. In addition to improved transportation into bacterial cells, S-649266 is highly stable to a variety of beta-lactamases.

“Multidrug-resistant bacteria continue to increase and with these difficult to treat infections come increased morbidity, mortality and costs not just in dollars but in an overall societal cost due to the impact of these problematic infections,” said Richard P. Wenzel, Professor of Medicine at Virginia Commonwealth University and former President of the International Society for Infectious Diseases.

“S-649266 has many of the criteria needed to be of value in this ongoing fight, we await clinical results with anticipation.”

Important findings reported at IDWeek 2014 include:

- In vitro activity of S-649266 was evaluated against clinical isolates of Gram-negative bacteria, including MDR strains, under culture conditions that mimic human infection. Compared with other cephalosporins and carbapenems, S-649266 showed robust in vitro activity against Pseudomonas aeruginosa, Acinetobacter baumannii and Enterobacteriaceae including MDR strains. Against carbapenemase producers, S-649266 was more active than meropenem and cefepime.
- S-649266 was shown to be 10-1,000 times more stable to carbapenemase than ceftazidime, cefepime and meropenem.
- In rat lung infection studies designed to evaluate the bactericidal activity of S-649266 under pharmacokinetic conditions mimicking human free plasma concentrations S-649266 was shown to exhibit potent bactericidal activity at 2g, q8h with a 3 hour infusion against target pathogens such as carbapenem resistant Klebsiella pneumoniae.
“Opinion leaders we’ve been working with in the U.S., Europe, and Japan believe the efficient use of the iron uptake system may allow S-649266 to be an effective approach to treat Gram-negative bacterial infections that are not able to be treated by available antibiotics,” said Dr. Tsutae Den Nagata, Chief Medical Officer, Shionogi. “S-649266 is the most advanced product in our anti-infective development portfolio. We are looking forward to the next stage of its development.”

S-649266 was also featured in an oral presentation and nine posters at the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in September. Phase II clinical development is underway; Phase III is expected to start during 2015. Shionogi is currently developing S-649266; GSK has an option to jointly develop this compound with Shionogi.

**Shionogi Leadership in Anti-Infective Development**

For over 50 years, Shionogi has developed and commercialized innovative oral and parenteral anti-infectives. Sulfamethoxazole was discovered by Shionogi and launched in 1959. In 1982, Shionogi launched in Japan its first cephalosporin Shiomarin™ (moxalactam), a third-generation cephalosporin for the treatment of respiratory tract infections, sepsis, urinary tract infections, abdominal/pelvic infections, genitourinary infections and purulent meningitis. Shionogi is also the originator of Doribax® (doripenem for injection), a carbapenem anti-bacterial for the treatment of complicated intra-abdominal infections and complicated urinary tract infections (U.S. indications). Tivicay® (dolutegravir), an anti-HIV agent Shionogi discovered and co-developed with ViV Healthcare, was approved for marketing by the Food and Drug Administration in 2013, and by the European Commission in 2014.

**About Shionogi**

Shionogi & Co., Ltd. is a major research-driven pharmaceutical company dedicated to placing the highest value on patients. Shionogi’s research and development currently targets two therapeutic areas: infectious diseases, and pain/CNS disorders. In addition, Shionogi is engaged in new research areas such as obesity/geriatric metabolic disease and oncology/immunology. Contributing to the health 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](http://www.shionogi.co.jp). 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](http://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](http://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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