1038. In Vitro Activity of Tebipenem, an Orally Available Carbapenem Agent, Against a Collection of Surveillance Gram-Positive Clinical Isolates S J Ryan Arends, PhD; Abby L. Klauer, n/a; Nicole Cotromone*; Ian A. Critchley, Ph.D.; Rodrigo E. Mendes, PhD; JMI Laboratories, North Liberty, Iowa; Spero Therapeutics

Session: P-59. New Drug Development

Background. Tebipenem, an orally bioavailable carbapenem administered as a pro-drug, completed a phase 3 clinical trial for evaluating its safety and efficacy for the treatment of complicated urinary tract infection and acute pyelonephritis. The purpose of this study was to investigate the in vitro activity of tebipenem and comparators, including ertapenem and meropenem, against a recent collection of Gram-positive isolates associated with clinical infections.

Methods. The susceptibility of 580 Gram-positive organisms were tested, including: methicillin-susceptible Staphylococcus aureus (MSSA, 489 isolates), methicillin-susceptible Staphylococcus epidermidis (MSSE, 31), other methicillin-susceptible coagulase-negative staphylococci (MSSCoNS, 29), and vancomycin-susceptible Enterococcus faecalis (31). The isolates were collected primarily from pneumonia in hospitalized patients (498 isolates; 85.9%), urinary tract infections (42 isolates; 7.2%), and bloodstream infections (38 isolates; 6.6%). Organisms were tested using reference broth microdilution methods in a central laboratory.

Results. Tebipenem had an MIC<sub>90</sub> value of 0.03 mg/L against MSSA and 0.015 mg/L against MSSE isolates. Ertapenem MIC<sub>90</sub> values were 8-fold higher against MSSA (MIC<sub>90</sub> 0.25 mg/L) and 32-fold higher against MSSE (MIC<sub>90</sub> 0.5 mg/L). Tebipenem displayed an MIC<sub>50</sub> value of 0.03 mg/L against MSSCoNS species other than S. epidermidis. This result was 8- and 32-fold lower than those of meropenem (MIC<sub>50</sub> 0.25 mg/L) and ertapenem (MIC<sub>50</sub> 1 mg/L), respectively. Tebipenem inhibited all E. faecalis isolates at ≤1 mg/L (MIC<sub>50</sub> 1 mg/L), with an MIC<sub>50</sub> value at least 2-fold lower than meropenem (MIC<sub>50</sub> >1 mg/L) and 16-fold lower than ertapenem (MIC<sub>50</sub> >8 mg/L).

Conclusion. Tebipenem displayed potent activity against methicillin susceptible staphylococci, including MSSA, MSSE, and other MSSCoNS. Tebipenem in vitro activity was greater than meropenem and ertapenem when tested against MSSA, MSSE and other MSCoNS. Tebipenem against Gram-positive bacteria appears promising, and further testing is warranted.

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1039. Rapid Restoration of Bile Acid Compositions After Treatment with RBX2660 for Recurrent Clostridium difficile Infection—Results from the PUNCH CD3 Phase 3 Trial Romeo Papazyan, PhD; Bryan Fuchs, PhD; Ken Blount, PhD; Carlos Gonzalez, MS; Bill Shannon, PhD MBA; Ferring Research Institute, San Diego, CA; *Rebiotix, Inc., Roseville, Minnesota; +BioRankings, LLC, St. Louis, Missouri

Session: P-59. New Drug Development

Background. Microbiota-based treatments are increasingly evaluated as a strategy to reduce recurrence of Clostridium difficile infection (rCDI), and their proposed mechanisms include restoration of the microbiota and microbiota-mediated functions, including bile acid metabolism. RBX2660—a broad-consortium investigational live biotherapeutic—has been evaluated in >600 participants in 6 clinical trials, with consistent reduction of rCDI recurrence. Here we report that fecal bile acid compositions were significantly reduced in treatment-responsive participants in PUNCH CD3—a Phase 3 randomized, double-blinded, placebo-controlled trial of RBX2660.

Methods. PUNCH CD3 participants received a single dose of RBX2660 or placebo between 2 to 72 hours after completing rCDI antibiotic treatment. Clinical response was the absence of CDI recurrence at eight weeks after treatment. Participants voluntarily submitted stool samples prior to blinded study treatment (baseline), 1, 4 and 8 weeks, and 3 and 6 months after receiving study treatment. A liquid chromatography with mass-spectrometry method was developed to extract and quantify 33 bile acids from all participant fecal samples received up to the 8-week time point. Mean bile acid compositions were fit to a Dirichlet multinomial distribution and compared across time points and between RBX2660- and placebo-treated participants.

Results. Clinically, RBX2660 demonstrated superior efficacy versus placebo (70.4% versus 58.1%). RBX2660-treated clinical responders' bile acid compositions shifted significantly from before to after treatment. Specifically, primary bile acids predominated before treatment, whereas secondary bile acids predominated after treatment (Figure 1A). These changes trended higher among RBX2660 responders compared to placebo responders. Importantly, median levels of lithocholic acid (LCA) and deoxycholic acid (DCA) among RBX2660 treatment responders, shown with individual samples and time point median with interquartile ranges.

Conclusion. Among PUNCH CD3 clinical responders, RBX2660 significantly restored bile acids from less to more healthy compositions. These clinically correlated bile acid shifts are highly consistent with results from a prior trial of RBX2660.

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1040. Knee Explant Analysis (KnEa) Using PLG2026 in Periprosthetic Joint Infection (KnEa Study) David Huang, MD, PhD; Dana Parker, BS; Nicholas Pachuda, DPM; Despina Dobkins, BBS; Jonathan Stickbeck, PhD; Kenneth Urish, MD, PhD; Peptilogics, Houston, Texas; University of Pittsburgh, Pittsburgh, Pennsylvania

Session: P-59. New Drug Development

Background. PLG2026 is a novel engineered cationic antimicrobial peptide being evaluated for treatment of prosthetic joint infections (PJI). This study evaluated the rapid bactericidal activity of PLG2026 to decrease biofilm and planktonic bacteria on ex vivo infected prostheses following removal from patients with chronic PJI.

Methods. De-identified infected prosthetics were removed from nine patients with PJI, despite chronic suppressive oral antibiotics, during a 2-stage revision procedure. Removed prosthetics were then submersed ex vivo to an expected clinical exposure of PLG2026, 1 mg/mL, for ~15 minutes. Upon completion of the 15-minute exposure, the treated explant was placed into buffer and sonicated. The sonication solution was then plated for bacterial analysis including colony forming unit (CFU) enumeration. Remaining explanted implants from the same patient served as a control and was processed similarly but without exposure to PLG2026.

Results. As shown in the Table, both Gram-positive and Gram-negative bacteria were identified from removed prosthetics during a 2-stage revision procedure of chronic PJI. Eight of ten infected prosthetics treated ex vivo to PLG2026 1 mg/mL were sterilized (No. 1–5, 6). Of the two infected prosthetics that were not sterilized (No. 6 and 7), one was polymicrobial (No. 6) and the other was monomicrobial (No. 7). Collectively, infected prosthetics exposed to PLG2026 demonstrated a mean 4log10 reduction (range 2 to 7).

Summary of culture and CFU log reduction among infected prosthetics exposed and not exposed to PLG2026.