Conclusion. Germinant/antibiotic combinations improved survival in a rCDI mouse model compared to antibiotics alone. Germinants did not induce toxin production when combined with OMC or VAN and eliminated the spore reservoir at the end of treatment. This provides basis for further study of germinants combined with antibiotics to reduce rCDI.

Disclosures. **Warren Rose, PharmD, MPH**, **Merck** (Grant/Research Support)**Paratek** (Grant/Research Support, Advisor or Review Panel member)

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[1]; Abby L. Klauer, n/a[1]; Nicole Cotroneo[2]; Ian A. Critchley, Ph.D.[2]; Rodrigo E. Mendes, PhD[1]; [1]JMI Laboratories, North Liberty, Iowa; [2]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 comparator agents, 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 (MSCoNS, 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_{90} value of 0.03 mg/L against MSSA and 0.015 mg/L against MSSE isolates. Ertapenem MIC_{90} values were 8-fold higher against MSSA (MIC_{90}, 0.25 mg/L) and 32-fold higher against MSSE (MIC_{90}, 0.5 mg/L). Tebipenem displayed an MIC_{90} value of 0.03 mg/L against MSCoNS species other than *S. epidermidis*. This result was 8- and 32-fold lower than those of meropenem (MIC_{90}, 0.25 mg/L) and ertapenem (MIC_{90}, 1 mg/L), respectively. Tebipenem inhibited all *E. faecalis* isolates at ≤1 mg/L (MIC_{90}, 1 mg/L), with an MIC_{90} value at least 2-fold lower than meropenem (MIC_{90}, >1 mg/L) and 16-fold lower than ertapenem (MIC_{90}, >8 mg/L).

Conclusion. Tebipenem displayed potent activity against methicillin susceptible staphylococci, including MSSA, MSSE, and other MSCoNS. Tebipenem *in vitro* activity was greater than meropenem and ertapenem when tested against *E. faecalis*. These data indicate that tebipenem may be an option for treating urinary tract infections caused by these organisms or as an empiric option to provide broader coverage against Gram-negative and -positive organisms.

Organism	Cumulative % at tebipenem MIC of:								
(no. tested overall)	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1
Methicillin-susceptible *Staphylococcus aureus* (489)	0 0.0	9 1.8	325 68.3	151 99.2	4 100.0				
Methicillin-susceptible *Staphylococci epidermidis* (31)	1 3.2	22 74.2	8 100.0						
Other methicillin-susceptible coagulase-negative staphylococci (29)	4 13.8	4 27.6	17 86.2	4 100.0					
Enterococcus faecalis (31)						0 0.0	4 12.9	20 77.4	7 100.0

Disclosures. **S J Ryan Arends, PhD**, **AbbVie (formerly Allergan)** (Research Grant or Support)**GlaxoSmithKline, LLC** (Research Grant or Support)**Melinta Therapeutics, LLC** (Research Grant or Support)**Nabriva Therapeutics** (Research Grant or Support)**Spero Therapeutics** (Research Grant or Support) **Abby L. Klauer, n/a**, **Cidara Therapeutics, Inc.** (Research Grant or Support)**Spero Therapeutics** (Research Grant or Support) **Nicole Cotroneo**, **Spero Therapeutics** (Employee, Shareholder) **Ian A. Critchley, Ph.D.**, **Spero Therapeutics** (Employee, Shareholder) **Rodrigo E. Mendes, PhD**, **AbbVie** (Research Grant or Support)**AbbVie (formerly Allergan)** (Research Grant or Support)**Cipla Therapeutics** (Research Grant or Support)**Cipla USA Inc.** (Research Grant or Support)**ContraFect Corporation** (Research Grant or Support)**GlaxoSmithKline, LLC** (Research Grant or Support)**Melinta Therapeutics, Inc.** (Research Grant or Support)**Melinta Therapeutics, LLC** (Research Grant or Support)**Nabriva Therapeutics** (Research Grant or Support)**Pfizer, Inc.** (Research Grant or Support)**Shionogi** (Research Grant or Support)**Spero Therapeutics** (Research Grant or Support)

1039. Rapid Restoration of Bile Acid Compositions After Treatment with RBX2660 for Recurrent *Clostridioides difficile* Infection—Results from the PUNCH CD3 Phase 3 Trial

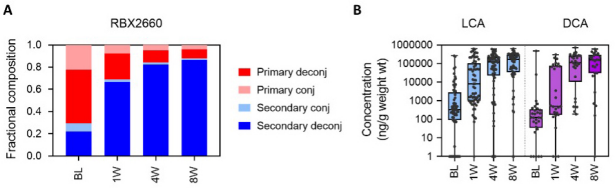
Romeo Papazyan, PhD[1]; Bryan Fuchs, PhD[1]; Ken Blount, PhD[2]; Carlos Gonzalez, MS[3]; Bill Shannon, PhD MBA[3]; [1]Ferring Research Institute, San Diego, CA; [2]Rebiotix, Inc., Roseville, Minnesota; [3]BioRankings, LLC, St. Louis, Missouri

Session: P-59. New Drug Development

Background. Microbiota-based treatments are increasingly evaluated as a strategy to reduce recurrence of *Clostridioides 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 restored 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 24 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, 3 and 6 months after receiving study treatment. A liquid chromatography tandem 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) showed large, significant increases after treatment (Figure 1B).



A. Bile acid compositions before (BL) and up to 8 weeks after RBX2660 treatment among treatment responders. Compositions are shown as the fraction of total bile acids classified as primary or secondary conjugated or deconjugated bile acids. B. Concentrations of lithocholic acid (LCA) and deoxycholic acid (DCA) among RBX2660 treatment responders, shown with individual samples and time point group 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.

Disclosures. **Romeo Papazyan, PhD**, **Ferring Research Institute** (Employee) **Bryan Fuchs, PhD**, **Ferring Pharmaceuticals** (Employee) **Ken Blount, PhD**, **Rebiotix Inc., a Ferring Company** (Employee)

1040. Knee Explant Analysis (KnEA) Using PLG0206 in Periprosthetic Joint Infection (KnEA Study)

David Huang, MD, PhD[1]; Dana Parker, BS[2]; Nicholas Pachuda, DPM[1]; Despina Dobbins, BS[1]; Jonathan Steckbeck, PhD[1]; Kenneth Urish, MD, PhD[2]; [1]Peptilogics, Houston, Texas; [2]University of Pittsburgh, Pittsburgh, Pennsylvania

Session: P-59. New Drug Development

Background. PLG0206 is a novel engineered cationic antimicrobial peptide being evaluated for treatment of prosthetic joint infections (PJI). This study evaluated the rapid bactericidal activity of PLG0206 to decrease biofilm and planktonic bacteria on *ex vivo* infected prosthesis 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 PLG0206, 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 PLG0206.

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 PLG0206 1 mg/mL were sterilized (No. 1-5, 8-10). 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 PLG0206 demonstrated a mean 4log10 reduction (range 2 to 7).

Summary of culture and CFU log reduction among infected prosthetics exposed and not exposed to PLG0206

#	Species of culture	PLG 0206 Dose	CFU Untreated	CFU Treated	Log Reduction
1	*S. epidermidis*	1	1.00E+07	0	7.0
2	*S. epidermidis*	1	1.00E+07	0	7.0
3	*S. aureus* (MSSA)	1	No sonicate*	0	N/A
4	*S. aureus* (MRSA)	0.5	1.00E+07	0	7.0
5	*S. hemolyticus*	1	7.3E+02	0	2.9
6	*E.coli*	1	3.5E+03	60	1.8
	E.coli	1	3.5E+03	30	2.1
	Enterococcus	1	1.40E+04	80	4.1
7	*S. epidermidis*	1	1.90E+04	90	2.3
8	*H. parainfluenzae*	1	1.00E+07	0	7.0
9	*H. parainfluenzae*	1	1.00E+07	0	7.0
10	*S. aureus* (MRSA)	1	1.10E+04	0	4.0

* CFU 1.0E+07 is an estimate of untreated sonicate CFU directly from micro lab measurements.

Table: Summary of culture and CFU log reduction among infected prosthetics exposed and not exposed to PLG0206

Conclusion. Overall, these findings support the ongoing development of PLG0206 as a local irrigation solution at 1 mg/mL concentration in the wound cavity for 15 minutes in patients undergoing treatment of a PJI occurring after total knee arthroplasty.

Disclosures. **David Huang, MD, PhD**, **Peptilogics** (Employee) **Nicholas Pachuda, DPM**, **Peptilogics** (Employee) **Despina Dobbins, BS**, **Peptilogics** (Employee) **Jonathan Steckbeck, PhD**, **Peptilogics** (Employee) **Kenneth Urish, MD, PhD**, **Peptilogics** (Grant/Research Support)

1041. *In vitro* activity of tebipenem against a recent collection of fastidious organisms recovered from respiratory tract infections

S J Ryan Arends, PhD[1]; Abby L. Klauer, n/a[1]; Nicole Cotroneo[2]; Ian A. Critchley, Ph.D.[2]; Rodrigo E. Mendes, PhD[1]; [1]JMI Laboratories, North Liberty, Iowa; [2]Spero Therapeutics

Session: P-59. New Drug Development

Background. Tebipenem is under development as an oral treatment option for complicated urinary tract infections and acute pyelonephritis. This study further evaluated the *in vitro* activity of tebipenem against various fastidious organisms recovered from community-acquired respiratory tract infections (CARTIs).

Methods. The study included a total of 2,476 fastidious organisms: *Haemophilus influenzae* (692 isolates, including fluoroquinolone-resistant, β-lactamase-positive, and β-lactamase-negative ampicillin-resistant [BLNAR]), *Haemophilus parainfluenzae* (30 isolates, including β-lactamase-positive and BLNAR), *Moraxella catarrhalis* (490 isolates), and *Streptococcus pneumoniae* (1,264 isolates, including penicillin-resistant). The isolates were collected primarily from CARTIs (90.8%) and pneumonia in hospitalized patients (PIHPs, 9.2%). Organisms were tested using reference broth microdilution methods in a central laboratory.

Results. Tebipenem had MIC_{90} values of 0.5 mg/L against *H. influenzae* and 1 mg/L against *H. parainfluenzae* isolates. All 18 BLNAR isolates from these two species were inhibited at ≤1 mg/L of tebipenem. The MIC_{90} values observed for ertapenem and meropenem was 0.25 mg/L for these organisms. Tebipenem displayed good activity against *M. catarrhalis* (MIC_{90}, 0.03 mg/L). Tebipenem inhibited 100% of *S. pneumoniae* isolates at ≤1 mg/L. Tebipenem activity (MIC_{90}, 0.12 mg/L) was 8-fold greater than ertapenem (MIC_{90}, 1 mg/L) against *S. pneumoniae* isolates.

Conclusion. Tebipenem displayed potent activity against fastidious organisms causing respiratory tract infections. Greater than 99.7% of all *Haemophilus* isolates, including all BLNAR, were inhibited at ≤1 mg/L. All *M. catarrhalis* isolates were inhibited at ≤0.03 mg/L. Although tebipenem activity correlated with penicillin resistance, all *S. pneumoniae* isolates were inhibited at ≤1 mg/L. Tebipenem *in vitro* activity was greater than ertapenem when tested against *S. pneumoniae* isolates. This data supports the possible development of tebipenem as an oral option for combating CARTIs caused by these organisms.

Table

	Cumulative % at tebipenem MIC of:										
Organism (no. tested)	**≤0.008**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**MIC_{50}**	**MIC_{90}**
Haemophilus influenzae (692)	8 1.2	21 4.2	71 14.5	184 41.0	200 70.0	117 86.9	72 97.3	17 99.7	2 100.0	0.12	0.5
BLNAR (14)					0 0.0	2 14.3	4 42.9	8 100.0		1	1
Haemophilus parainfluenzae (30)	3 10.0	3 20.0	4 33.3	9 63.3	3 73.3	2 80.0	2 86.7	4 100.0		0.06	1
BLNAR (4)							0 0.0	4 100.0		1	1
Moraxella catarrhalis (490)	11 2.2	232 49.6	247 100							0.03	0.03
Streptococcus pneumoniae (1,264)	911 72.1	28 74.3	50 78.2	133 88.8	80 95.1	59 99.8	2 99.9	1 100.0		≤0.008	0.12
Penicillin-resistant (22; MIC > 4)				0 0.0	6 27.3	15 95.5	1 100.0			0.25	0.25

BLNAR - β-lactamase-negative ampicillin-resistant

Disclosures. **S J Ryan Arends, PhD**, **AbbVie (formerly Allergan)** (Research Grant or Support)**GlaxoSmithKline, LLC** (Research Grant or Support)**Melinta Therapeutics, LLC** (Research Grant or Support)**Nabriva Therapeutics** (Research Grant or Support)**Spero Therapeutics** (Research Grant or Support) **Abby L. Klauer, n/a**, **Cidara Therapeutics, Inc.** (Research Grant or Support)**Spero Therapeutics** (Research Grant or Support) **Nicole Cotroneo**, **Spero Therapeutics** (Employee, Shareholder) **Ian A. Critchley, Ph.D.**, **Spero Therapeutics** (Employee, Shareholder) **Rodrigo E. Mendes, PhD**, **AbbVie** (Research Grant or Support)**AbbVie (formerly Allergan)** (Research Grant or Support)**Cipla Therapeutics** (Research Grant or Support)**Cipla USA Inc.** (Research Grant or Support)**ContraFect Corporation** (Research Grant or Support)**GlaxoSmithKline, LLC** (Research Grant or Support)**Melinta Therapeutics, Inc.** (Research Grant or Support)**Melinta Therapeutics, LLC** (Research Grant or Support)**Nabriva Therapeutics** (Research Grant or Support)**Pfizer, Inc.** (Research Grant or Support)**Shionogi** (Research Grant or Support)**Spero Therapeutics** (Research Grant or Support)

1042. Safety of Investigational Microbiota-Based Live Biotherapeutic RBX2660 in Individuals with Recurrent *Clostridioides difficile* Infection: Data from Five Prospective Clinical Studies

Tricia Braun, PharmD[1]; Beth Guthmueller, AS[2]; Adam J. Harvey, PhD[1]; [1]Rebiotix, A Ferring Company, Roseville, Minnesota; [2]Rebiotix Inc, A Ferring Company, Victoria, Minnesota

Session: P-59. New Drug Development

Background. Microbiota-based treatments have shown promise to reduce recurrence, morbidity, and mortality for recurrent *Clostridioides difficile* infections (rCDI), but consistent and reliable safety data are needed to support regulatory approvals and broaden patient access. Here we provide cumulative safety data from 5 prospective clinical studies evaluating RBX2660—a standardized, microbiota-based investigational live biotherapeutic—for reducing rCDI.

Methods. This analysis included three Phase 2 (PUNCH CD, PUNCH CD2, PUNCH CD Open Label) and two Phase 3 trials (PUNCH CD3, PUNCH CD3-OLS *ad hoc* analysis). Participants were ≥18 years old with documented rCDI who completed standard-of-care oral antibiotic therapy prior to treatment with RBX2660. PUNCH CD3-OLS allowed participants with comorbidities of irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD). Depending on the trial, assigned study treatment was 1 or 2 doses of RBX2660 (or placebo), administered rectally. Participants whose CDI recurred within 8 weeks were eligible for additional RBX2660 treatment. Treatment-emergent adverse events (TEAEs) were recorded for at least 6 months following last study treatment; CD2 and CD Open Label recorded TEAEs for 24 months.

Results. Among 620 participants who received at least one RBX2660 dose (assigned treatment or after recurrence), 324 (52.3%) received 1, 270 (43.5%) received 2, 14 (2.3%) received 3, and 12 (1.9%) received 4. 83 participants received blinded placebo only. A total of 1980 TEAEs were reported from 432 (69.7%) RBX2660-treated participants, compared to 174 TEAEs in 50 (60.2%) placebo-only treated participants. Most TEAEs were mild or moderate in severity, with diarrhea common in all treatment groups. No potentially life-threatening TEAEs were considered related to RBX2660. Study discontinuation due to TEAEs was minimal (< 1%) with none related to RBX2660. There were no reported infections for which the causative pathogen was traced to RBX2660.

Conclusion. Across five clinical studies with consistent investigational product, RBX2660 was well-tolerated in rCDI participants. In aggregate, this data provides compelling and consistent safety data for RBX2660.

Disclosures. **Tricia Braun, PharmD**, **Rebiotix, a Ferring Company** (Employee) **Beth Guthmueller, AS**, **Rebiotix Inc, A Ferring Company** (Employee) **Adam J. Harvey, PhD**, **Rebiotix, A Ferring Company** (Employee)

1043. Activity of Mecillinam Against Enterobacterales Isolates Collected From Patients With Urinary Tract Infections (UTIs) in the USA During 2019

Stephen Hawser, PhD[1]; Ian Morrissey[2]; Anne Santerre Henriksen, MS[3]; [1]IHMA, Monthey, Valais, Switzerland; [2]IHMA Europe, Monthey, Valais, Switzerland; [3]Maxel Consulting ApS, London, England, United Kingdom

Session: P-59. New Drug Development

Background. Mecillinam is a β-lactam antibiotic that exerts its antibacterial activity by binding to penicillin-binding protein 2. In the USA, intravenous (IV) mecillinam is in development for the treatment of complicated UTIs in the hospital setting and as step-down therapy transitioning from IV mecillinam to oral pivmecillinam so that patients can continue treatment at home. To support the clinical development of mecillinam in the USA for the treatment of both complicated and uncomplicated UTI, this observational study investigated the activity of mecillinam against Enterobacterales isolates from patients with UTI in the USA, collected during 2019.

Methods. This study evaluated the activity of mecillinam and other antimicrobial agents against 1075 selected Enterobacterales clinical isolates collected from patients with UTI in the USA during 2019. Antibiotic activity (minimum inhibitory concentration [MIC]) was determined by Clinical & Laboratory Standards Institute (CLSI) agar dilution methodology, and susceptibility was interpreted according to CLSI guidelines.

Results. Among the selected 1075 isolates, producers of extended-spectrum beta-lactamase (ESBL) represented 9.6% of *Escherichia coli* and 50% of *Klebsiella pneumoniae*. Ninety-five percent of the isolates tested were susceptible to mecillinam (Table 1). The MIC_{50} and MIC_{90} values for mecillinam were 0.25 and 2 μg/mL, respectively. Fosfomycin MIC_{50} and MIC_{90} were 1 and 32 μg/mL, respectively (97.6% of isolates