ceftriaxone or their combination. The valves were then washed from any planktonic cells and the biofilm biomass was established by CFU enumeration.

***Conclusion.*** This study demonstrates that a proper *in-vitro* matching is essential in the treatment of PVE with phages. As seen here, the phage-antibiotic combination intended for treatment should be drawn according to their efficacy on suitable models, simulating the clinical settings, with the specific pathogen, the valve material, and the used phages taken into consideration.

***Disclosures.*** **Ran Nir-Paz, MD**, **BiomX** (Consultant)**Technophage** (Scientific Research Study Investigator, Advisor or Review Panel member)

### 1062. Analysis of Resistance to Oral Standard of Care Antibiotics for Urinary Tract Infections Caused By *Escherichia coli* and *Staphylococcus saprophyticus* Collected Worldwide between 2019-2020

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**Session:** P-61. Novel Agents

***Background.*** Gepotidacin (GSK2140944) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor under development for the treatment of gonorrhea and uncomplicated urinary tract infections (UTI). This study reports on the *in vitro* activity of gepotidacin and other oral antibiotics when tested against contemporary *Escherichia coli* and *Staphylococcus saprophyticus* clinical isolates collected from patients with UTIs for a gepotidacin uUTI global surveillance study as a part of the SENTRY Antimicrobial Surveillance Program.

***Methods.*** A total of 3,562 *E. coli* and 344 *S. saprophyticus* isolates were collected between 2019 and 2020 from 92 medical centers located in 25 countries. Most isolates (68%) tested were cultured from urine specimens collected from patients seen in ambulatory, emergency, family practice, and outpatient medical services. Bacterial identifications were confirmed by MALDI-TOF. Isolates were tested for susceptibility by CLSI methods at a central laboratory (JMI Laboratories). MIC results for oral antibiotics licensed for the treatment of uUTI and drug-resistant subsets were interpreted per CLSI guidelines.

***Results.*** Gepotidacin ($MIC_{50/90}$, 2/2 mg/L) displayed good activity against 3,562 *E. coli* isolates, with 98.0% of all observed gepotidacin MICs ≤4 mg/L (Table). Susceptibility (S) rates for the other oral agents tested against these isolates were: amoxicillin-clavulanate (79.6% S), ampicillin (45.6% S), ciprofloxacin (72.5%S), fosfomycin (99.0% S), mecillinam (94.1%S), nitrofurantoin (97.3% S), and trimethoprim-sulfamethoxazole (68.2% S). When tested against the drug-resistant subsets, gepotidacin maintained similar $MIC_{50/90}$ values (2/4 mg/L), except against isolates resistant to fosfomycin (2/8 mg/L). Against *S. saprophyticus* isolates, gepotidacin ($MIC_{50/90}$, 0.06/0.12 mg/L) inhibited all isolates at ≤0.25 mg/L. Most oral agents showed S results of >97% against *S. saprophyticus* isolates, except for penicillin (3.5%S).

***Conclusion.*** Gepotidacin demonstrated potent *in vitro* activity against contemporary *E. coli* and *S. saprophyticus* urine isolates. This activity was largely unaffected among isolates demonstrating drug-resistance to other oral standard of care antibiotics.

Table

| Organism (No. isolates) | No. and cumulative % of isolates inhibited at a gepotidacin MIC (mg/L) of: | | | | | | | | Gepotidacin | |
|---|---|---|---|---|---|---|---|---|---|---|
| Drug-resistant | ≤0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | $MIC_{50}$ | $MIC_{90}$ |
| *E. coli* (3,562) | 47 | 190 | 1218 | 1780 | 255 | 48 | 19 | 5 | 2 | 2 |
| | 1.3 | 6.7 | 40.8 | 90.8 | 98.0 | 99.3 | 99.9 | 100 | | |
| AMX-CLA-R (202) | 3 | 12 | 50 | 95 | 31 | 4 | 5 | 2 | 2 | 4 |
| | 1.5 | 7.4 | 32.2 | 79.2 | 94.6 | 96.5 | 99.0 | 100 | | |
| AMP-R (1,914) | 29 | 135 | 682 | 852 | 160 | 33 | 18 | 5 | 2 | 4 |
| | 1.5 | 8.6 | 44.2 | 88.7 | 97.1 | 98.8 | 99.7 | 100 | | |
| FQ-R (902) | 34 | 100 | 311 | 338 | 92 | 16 | 8 | 3 | 2 | 4 |
| | 3.8 | 14.9 | 49.3 | 86.8 | 97.0 | 98.8 | 99.7 | 100 | | |
| FOS-R (25) | 0 | 3 | 7 | 7 | 4 | 3 | 1 | | 2 | 8 |
| | 0.0 | 12.0 | 40.0 | 68.0 | 84.0 | 96.0 | 100 | | | |
| MEC-R (151) | 4 | 8 | 39 | 78 | 17 | 3 | 2 | | 2 | 4 |
| | 2.6 | 7.9 | 33.8 | 85.4 | 96.7 | 98.7 | 100 | | | |
| NIT-R (46) | 1 | 1 | 11 | 24 | 7 | 1 | 0 | 1 | 2 | 4 |
| | 2.2 | 4.3 | 28.3 | 80.4 | 95.7 | 97.8 | 97.8 | 100 | | |
| TMP-SMX-R (1,130) | 19 | 87 | 421 | 468 | 91 | 31 | 9 | 4 | 2 | 4 |
| | 1.7 | 9.4 | 46.6 | 88.1 | 96.1 | 98.8 | 99.6 | 100 | | |

Abbreviations: -R, resistant per CLSI 2021; AMX-CLA, amoxicillin-clavulanate; AMP, ampicillin; FQ, fluoroquinolones; FOS, fosfomycin; MEC, mecillinam; NIT, nitrofurantoin; and TMP-SMX, trimethoprim-sulfamethoxazole.

***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) **Deborah Butler, n/a**, **GlaxoSmithKline, LLC** (Employee) **Nicole Scangarella-Oman, MS**, **GlaxoSmithKline, LLC** (Employee) **Lindsey Paustian, BS (ASCP)**, **GlaxoSmithKline, LLC** (Research Grant or Support) **Jennifer M. Streit, BS**, **GlaxoSmithKline, LLC** (Research Grant or Support)**Melinta Therapeutics, LLC** (Research Grant or Support)**Shionogi** (Research Grant or Support)**Spero Therapeutics** (Research Grant or Support) **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)

### 1063. ARGONAUT-V: Susceptibility of Multidrug-Resistant (MDR) *Pseudomonas aeruginosa* to Cefepime-Taniborbactam

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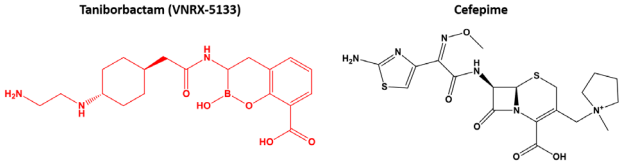
**Session:** P-61. Novel Agents

***Background.*** *P. aeruginosa* is a Gram-negative pathogen responsible for many serious infections. MDR, both intrinsic and acquired, presents major clinical challenges. Taniborbactam (formerly VNRX-5133; Fig 1) is a β-lactamase inhibitor (BLI) characterized as a bicyclic boronate, uniquely possessing activity toward all four Ambler classes of β-lactamases, both serine and metallo, with the exception of class B IMP β-lactamases. The β-lactam-BLI (BL-BLI) combination cefepime-taniborbactam (FTB; Fig 1) is currently in phase 3 clinical trials.




Structures of taniborbactam and cefepime. The β-lactamase inhibitor is in red and the β-lactam antibiotic is in black.

***Methods.*** The activity of FTB was tested against 197 well-characterized clinical *P. aeruginosa* isolates that were part of PRIMERS (Platforms for Rapid Identification of MDR-Gram-negative bacteria and Evaluation of Resistance Studies). Nearly 58% of these strains were reported as carbapenem-non-susceptible. Porin changes, efflux pumps, and/or the presence of acquired class A or class B carbapenemases were previously reported. Broth microdilution minimum inhibitory concentrations (MICs) were determined by CLSI M07 Ed. 11 methods with custom Sensititre frozen panels and interpreted using CLSI M100 Ed. 30 breakpoints. American Type Culture Collection strains were used for quality control. FEP breakpoints were provisionally used for FTB, where taniborbactam was fixed at 4 μg/mL.

***Results.*** Percent susceptibility to BL agents alone was 45.2% for imipenem (IPM), 55.8% for meropenem (MEM), 60.9% for ceftazidime (CAZ), and 67.0% for FEP. The addition of BLI to BL increased % susceptibility for MEM-vaborbactam (MVB), 56.9%; ceftolozane-tazobactam (C/T), 77.7%, CAZ-avibactam (CZA), 79.7%, and FTB, 82.7%. $MIC_{50}$s were in the susceptible range for all drugs except IPM, which was intermediate, and all $MIC_{90}$s were in the resistant range (Table 1). Taniborbactam reduced FEP MIC by 2-fold in 32% of isolates and ≥ 4-fold in 13% of isolates. Against carbapenem-non-susceptible strains, % susceptibilities were: FTB, 68.5%, CZA, 63.0%, C/T, 59.3%; and MVB, 21.3% (Table 2).

| | AMK | ATM | C/T | CAZ | CZA | FEP | FTB | IPM | MEM | MVB | TZP | TOB |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CLSI Susceptible Breakpoint | ≤16 | ≤8 | ≤4/4 | ≤8 | ≤8/4 | ≤8 | ≤8* | ≤2 | ≤2 | * | ≤16/4 | ≤4 |
| $MIC_{50}$ | 4 | 8 | 0.5 | 4 | 2 | 4 | 4 | 4 | 1 | 1 | 8 | 0.5 |
| $MIC_{90}$ | >32 | >16 | >8 | >16 | >8 | >16 | >8 | >4 | >4 | >4 | >64 | >8 |
| %S | 87.3 | 53.8 | 77.7 | 60.9 | 79.7 | 67.0 | 82.7* | 45.2 | 55.8 | 56.9 | 56.9 | 78.7 |

$MIC_{50}$ and $MIC_{90}$ values (μg/mL) and percent susceptibility (%S) for all P. aeruginosa strains (n=197). AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime-avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem-vaborbactam; TZP, piperacillin-tazobactam; TOB, tobramycin. *The breakpoints for FEP and MEM alone were provisionally applied to FTB and MVB, respectively. Tazobactam, avibactam, and taniborbactam were fixed at 4 μg/mL, while vaborbactam was fixed at 8 μg/mL. Breakpoints from CLSI M100, 31st ed, 2021.

MIC50 and MIC90 values (μg/mL) and percent susceptibility (%S) for all P. aeruginosa strains (n=197). AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime-avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem-vaborbactam; TZP, piperacillin-tazobactam; TOB, tobramycin. *The breakpoints for FEP and MEM

alone were provisionally applied to FTB and MVB, respectively. Tazobactam, avibactam, and taniborbactam were fixed at 4 μg/mL, while vaborbactam was fixed at 8 μg/mL. Breakpoints from CLSI M100, 31st ed, 2021.

| | AMK | ATM | C/T | CAZ | CZA | FEP | FTB | IPM | MEM | MVB | TZP | TOB |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CLSI Susceptible Breakpoint | ≤16 | ≤8 | ≤4/4 | ≤8 | ≤8/4 | ≤8 | * | ≤2 | ≤2 | * | ≤16/4 | ≤4 |
| $MIC_{50}$ | 4 | >16 | 4 | >16 | 8 | >16 | 8 | >4 | >4 | >4 | >64 | 1 |
| $MIC_{90}$ | >32 | >16 | >8 | >16 | >8 | >16 | >8 | >4 | >4 | >4 | >64 | >8 |
| %S | 76.8 | 25.0 | 59.3 | 30.5 | 63.0 | 40.7 | 68.5 | 0.0 | 19.4 | 21.3 | 23.0 | 61.0 |

$MIC_{50}$ and $MIC_{90}$ values (μg/mL) and percent susceptibility (%S) for the subset of carbapenem-non-susceptible P. aeruginosa strains (n=108). AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime-avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem-vaborbactam; TZP, piperacillin-tazobactam; TOB, tobramycin. *The breakpoints for FEP and MEM alone were provisionally applied to FTB and MVB, respectively. Tazobactam, avibactam, and taniborbactam were fixed at 4 μg/mL, while vaborbactam was fixed at 8 μg/mL. Breakpoints from CLSI M100, 31st ed, 2021.

MIC50 and MIC90 values (μg/mL) and percent susceptibility (%S) for the subset of carbapenem-non-susceptible P. aeruginosa strains (n=108). AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime-avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem-vaborbactam; TZP, piperacillin-tazobactam; TOB, tobramycin. *The breakpoints for FEP and MEM alone were provisionally applied to FTB and MVB, respectively. Tazobactam, avibactam, and taniborbactam were fixed at 4 μg/mL, while vaborbactam was fixed at 8 μg/mL. Breakpoints from CLSI M100, 31st ed, 2021.

***Conclusion.*** Compared to MVB, CZA, and C/T, FTB demonstrated the greatest activity against the 197 *P. aeruginosa* strains tested, including many carbapenem-non-susceptible strains. Pending completion of clinical development, FTB may be a promising therapeutic option for MDR *P. aeruginosa* infections.

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**1064. Treatment Success in Reducing Recurrent *Clostridioides difficile* Infection with Investigational Live Biotherapeutic RBX2660 Is Associated with Microbiota Restoration: Consistent Evidence from a Phase 3 Clinical Trial**

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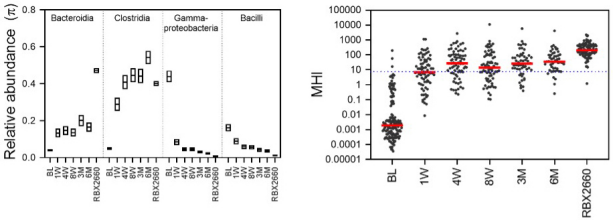
**Session:** P-61. Novel Agents

***Background.*** Several investigational microbiota-based live biotherapeutics are in clinical development for reducing recurrence of *Clostridioides difficile* infection (rCDI), including RBX2660 a liquid suspension of a broad consortium of microbiota, which includes Bacteridetes and Firmicutes. RBX2660 has been evaluated in >600 participants in 6 clinical trials. Here we report that RBX2660 induced significant shifts to the intestinal microbiota of treatment-responsive participants in PUNCH CD3—a Phase 3 randomized, double-blinded, placebo-controlled trial.

***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. Samples were extracted and sequenced using shallow shotgun methods. Operational taxonomic unit (OTU) data were used to calculate relative taxonomic abundance, alpha diversity, and the Microbiome Health Index (MHI)—a biomarker of antibiotic-induced dysbiosis and restoration.

***Results.*** Clinically, RBX2660 demonstrated superior efficacy versus placebo (70.4% versus 58.1%). From before to after treatment, RBX2660-treated clinical responders' microbiome diversity shifted significantly (Mann-Whitney), and so did microbiome composition (Generalized Wald Test). Post-treatment changes were characterized by increased Bacteroidia and Clostridia and decreased Gammaproteobacteria and Bacilli, changes and were durable to at least 6 months. Repeated measures analysis confirmed that shifts were greater among RBX2660 responders compared to placebo responders (DMRepeat). The majority of responders' MHI values shifted from a range common to antibiotic dysbiosis to a range common in healthy populations.

Figure 1




Left panel. Mean relative abundance taxonomic class level at timepoints for participants in PUNCH CD3 before and after RBX2660 treatment, and for doses of RBX2660 administered in PUNCH CD3. The four taxonomic classes that change most from before to after treatment are shown with the mean and confidence intervals based on fitting OTU data to a Dirichlet multinomial distribution. Right panel, MHI biomarker for the same time points and investigational product groups, shown as median (red) and individual samples. A previously calculated threshold of MHI = 7.2 is shown (dotted line), above which MHI values predict healthy, below which MHI values predict antibiotic-induced dysbiosis.

***Conclusion.*** Among PUNCH CD3 clinical responders, RBX2660 significantly restored microbiota from less to more healthy compositions, and this restoration was durable to at least 6 months. These clinically-correlated microbiome shifts are highly consistent with results from multiple prior trials of RBX2660.

***Disclosures.*** **Ken Blount, PhD**, **Rebiotix Inc., a Ferring Company** (Employee) **Dana M. Walsh, PhD**, **Rebiotix** (Employee)

**1065. Efficacy of Cefiderocol in Experimental *Stenotrophomonas maltophilia* Pneumonia in Persistently Neutropenic Rabbits**

Vidmantas Petraitis, MD[1]; Ruta Petraitiene, MD[1]; Povilas Kavaliauskas, MSc[1]; Ethan Naing, MD[2]; Andrew Garcia, MS[1]; Naoki Ishibashi, MD[3]; Benjamin Georgiades, n/a[4]; Roger Echols, MD[5]; Robert A. Bonomo, MD[6]; Yoshinori Yamano, PhD[7]; Thomas J. Walsh, MD, PhD (hon)[8]; [1]Weill Cornell Medicine of Cornell University, New York, NY; [2]Transplantation–Oncology Infectious Disease Program, Translational Research Laboratory, Division of Infectious Diseases, Weill Cornell Medicine, New York, NY 10065, US, New York, NY; [3]Pharmaceutical Research Division, Osaka, Osaka, Japan; [4]Shionogi, Inc., Florham Park, New Jersey; [5]Infectious Disease Drug Development Consulting LLC, Easton, Connecticut; [6]Louis Stokes Cleveland VA Medical Center, Cleveland, OH; [7]Shionogi & Co., Ltd., Osaka, Osaka, Japan; [8]Weill Cornell Medicine, New York, NY

**Session:** P-61. Novel Agents

***Background.*** *Stenotrophomonas maltophilia* causes lethal pneumonia, bacteremia, and sepsis in immunocompromised patients. As a standard of care,