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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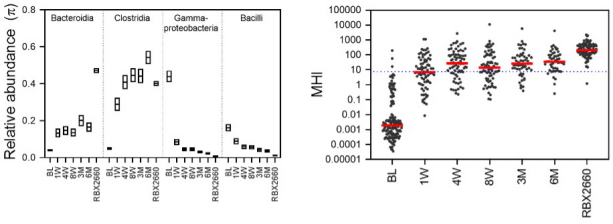
Session: P-61. Novel Agents

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

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Session: P-61. Novel Agents

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

trimethoprim-sulfamethoxazole (T/S) is considered to be the first-line therapy for *Stenotrophomonas* pneumonia. Cefiderocol (CFDC) is a new parenteral siderophore cephalosporin that is transported through the outer cell membrane as a siderophore mimic that then inhibits Gram-negative cell wall biosynthesis. CFDC has potent activity *in vitro* against *S. maltophilia*; however, little is known about its *in vivo* activity against *Stenotrophomonas* pneumonia in immunocompromised hosts. We therefore studied CFDC in comparison to TS in the persistently neutropenic rabbit model of *Stenotrophomonas* pneumonia. This rabbit model, in contrast to conventional murine models, reflects the human pattern of infection more accurately over time.

Methods. We initially studied the plasma pharmacokinetics of CFDC in non-infected and infected animals. *Stenotrophomonas* pneumonia was established by direct endotracheal inoculation of *S. maltophilia* 1×10^{10} CFUs for tracheobronchial colonization that evolved into bronchopneumonia. Experimental groups consisted of CFDC, T/S, and untreated controls (UC). Rabbits received CFDC at 120 mg/kg IV Q8h and T/S at 5 mg/kg IV Q12h. Profound persistent neutropenia was maintained with cytosine arabinoside. Treatment was continued for 10 days.

Results. There were no significant differences between non-infected and infected rabbits in CFDC pharmacokinetics. Rabbits treated with CFDC and T/S demonstrated significant decreases of residual pulmonary and BAL bacterial burden vs UC ($p\leq0.001$). CFDC achieved full clearance of *S. maltophilia* from lung tissue and BAL. This antibacterial activity coincided with significant reduction of lung weights (marker of organism-mediated pulmonary injury) in the CFDC group vs T/S and UC ($p< 0.01$). Survival was prolonged in the CFDC treatment group with 87% survival in comparison to that of T/S (25%) and UC (0%) ($p< 0.01$).

Table 1. Efficacy of Cefiderocol in Experimental *Stenotrophomonas maltophilia* Pneumonia in Persistency Neutropenic Rabbits

Experimental groups	Cefiderocol (CFDC)	Trimethoprim-sulfamethoxazole (T/S)	Untreated controls (UC)	*P* value
Pulmonary bacterial burden (Log CFU/g)	0.00 ± 0.0*	1.58 ± 0.56*	6.95 ± 0.35	*, *P≤0.001*
BAL bacterial burden (Log CFU/mL)	0.00 ± 0.0*	1.04 ± 0.56*	5.07 ± 0.59	*, *P≤0.001*
Survival median and probability (days (%))	10.8 (87.5)¶	7 (25.0)	5.5 (0.0)	¶, *P≤0.01*

* P≤0.001 Significant decrease in pulmonary tissue and BAL fluid bacterial burden in CFDC and T/S treatment group vs UC. ¶, P≤0.01 Significantly prolonged survival in CFDC group vs T/S and UC.

Conclusion. Cefiderocol is highly active in treatment of experimental *S. maltophilia* pneumonia in persistently neutropenic rabbits, thus laying the foundation for future clinical investigations against this lethal infection.

Disclosures. **Naoki Ishibashi, MD**, **Shionogi, Inc.** (Employee) **Benjamin Georgiades, n/a**, **Shionogi, Inc.** (Consultant) **Roger Echols, MD**, **Shionogi** (Consultant) **Robert A. Bonomo, MD**, **entasis** (Research Grant or Support)**Merck** (Grant/Research Support)**NIH** (Grant/Research Support)**VA Merit Award** (Grant/Research Support)**VenatoRx** (Grant/Research Support) **Yoshinori Yamano, PhD**, **Shionogi** (Employee) **Thomas J. Walsh, MD, PhD (hon)**, **Scynexis** (Consultant, Grant/Research Support)**Shionogi** (Consultant, Grant/Research Support)

1066. *In Vitro and in Vivo* Antimicrobial Activity of Cefiderocol and Comparators against *Achromobacter* spp.

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Session: P-61. Novel Agents

Background. *Achromobacter* spp. is intrinsically resistant to multiple antibiotics, and the treatment options are limited. Cefiderocol (CFDC), a siderophore cephalosporin approved in US and EU, is active against a wide variety of aerobic Gram-negative bacteria, including carbapenem-resistant strains. In this study, *in vitro* and *in vivo* antibacterial activity of CFDC against *Achromobacter* spp. was evaluated.

Methods. A total of 334 global isolates collected by IHMA from 39 countries in 2015-2019 were used. Minimum inhibitory concentrations (MICs) of CFDC and comparators were determined by broth microdilution method using iron-depleted CAMHB or CAMHB, respectively, as recommended by CLSI guidelines. *In vivo* efficacy of CFDC was compared with meropenem (MEM), piperacillin-tazobactam (PIP/TAZ), ceftazidime (CAZ), and ciprofloxacin (CIP) in a neutropenic murine lung infection model (n=5), and compared with MEM in a immunocompetent rat lung infection model (n=3-7) caused by 2 *A. xylosoxydans*. In the murine model, treatment was given 2, 5, and 8 hours post-infection, and the numbers of viable cfu in lungs were determined 24 hours post-infection. In the rat model, the humanized PK in plasma resulting from CFDC 2 g every 8 h (3-h infusion) or meropenem 1 g every 8 h (0.5-h infusion) were recreated via continuous intravenous infusion for 4 days, following which cfu in lungs were determined.

Results. CFDC showed *in vitro* activity with $MIC_{50/90}$ of 0.06/0.5 µg/mL against 334 *Achromobacter* spp. Only 7 isolates (2.1%) had MICs > 4 µg/mL. These were the lowest values among all compound tested (Table). In the murine model, CFDC caused > 1.5 $\log_{10}$ decrease of viable cfu in lungs at 100 mg/kg dose (%*f*T >MIC: < 50%) from baseline control against both of strains (CFDC MIC: 0.5 and 2 µg/mL) ($P< 0.05$). No decrease of cfu in lungs was observed for the comparators at 100 mg/kg (MEM, PIP/TAZ, CAZ, and CIP MICs were >16, >64, >32, and >8 µg/mL, respectively). In the rat model, humanized CFDC dosing reduced the viable cfu by >1 $\log_{10}$ CFU/lung compared with baseline controls ($P< 0.05$). MEM showed no significant activity.

In vitro activity of CFDC and comparator agents against Achromobacter spp.

Drug	MIC (µg/mL) against 334 *Achromobacter* spp.		
	MIC range	MIC_{50}	MIC_{90}
Cefiderocol	≤0.03 - >64	0.06	0.5
Cefepime	1 - >32	32	> 32
Ceftazidime	1 - >32	8	32
Ceftazidime-avibactam	1 - >16	4	16
Ciprofloxacin	0.5 - >8	4	> 8
Colistin	≤0.25 - >8	2	4
Imipenem-relebactam	0.25 - >16	1	2
Meropenem	≤0.12 - >16	0.25	8
Meropenem-vaborbactam	≤0.06 - >16	0.25	4
Tigecycline	≤0.03 - 8	1	4
Trimethoprim-sulfamethoxazole	≤0.25 - >32	0.5	4

334 Achromobacter spp. isolates collected from 2015 and 2019. The majority of isolates tested were A. xylosoxidans (312/334; 93.4%), followed by A. insolitus (11/334; 3.3%), Achromobacter sp. (8/334; 2.4%), A. denitrificans (2/334; 0.6%), and A. piechaudii (1/334; 0.3%).

Conclusion. CFDC showed potent *in vivo* efficacy reflecting *in vitro* activity against *A. xylosoxidans*. The results suggested that CFDC has the potential to be an effective therapeutic option for *Achromobacter* spp. infections.

Disclosures. **Ryuichiro Nakai, MSc**, **Shionogi TechnoAdvance Research & Co., Ltd.** (Employee) **Ayaka makino, BSc**, **Shionogi TechnoAdvance Research & Co., Ltd.** (Employee) **Toriko Yoshitomi, -**, **Shionogi TechnoAdvance Research & Co., Ltd.** (Employee) **Rio Nakamura, BSc**, **Shionogi TechnoAdvance Research & Co., Ltd.** (Employee) **Meredith Hackel, PhD MPH**, **IHMA** (Employee)**Pfizer, Inc.** (Independent Contractor) **Miki Takemura, MS**, **SHIONOGI & CO., LTD.** (Employee) **Daniel F. Sahm, PhD**, **IHMA** (Employee)**Pfizer, Inc.** (Independent Contractor) **Yoshinori Yamano, PhD**, **Shionogi** (Employee)

1067. Identifying and Assaying New Potential Molecular Targets in Fungi Following a Novel Strategy Based on Binding Site (Dis)Similarities with Proteins of the Human Pharmacolome

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Session: P-61. Novel Agents

Background. Invasive fungal infections account for a high burden of morbidity and mortality. This is aggravated because of the toxicity and resistance problems associated to current antifungal drugs, which in whole target only a handful of fungal molecules. In this scenario, new target identification and drug design, together with drug repurposing, represent promising strategies.

Methods. We aim to identify and test *in vitro* potential new therapeutic targets in fungi. Our strategy consists in identifying fungal proteins with active sites (meaning the set of residues lining the binding pocket) that are similar, but not identical!, to sites of proteins from the human pharmacolome. A high structural similarity with a human counterpart allows validation of the fungal target using cross-reactive inhibitors of the human protein. On the other hand, a few amino acid differences in the binding pocket produce local topological and chemical changes that create a "design space" for new specific inhibitors of the fungal target.

Results. Applying our own bioinformatics approach and taking advantage of the >200 available crystal structures of proteins of the human pharmacolome in complex with inhibitors, we have identified ca. 30 proteins in several fungal species of the genera *Histoplasma*, *Candida*, *Criptococcus*, *Aspergillus* and *Fusarium*, whose binding sites share at least 70% amino acid identity with their similar binding pockets in human pharmaceutical targets. So far we have assayed *in vitro*, in seven different fungal species, ca. 60 known inhibitors of around twenty of the orthologous human proteins. Some of the tested inhibitors have been previously assayed in different species in drug repurposing screenings, while others, to our knowledge, have not been yet tested. Over a dozen of these compounds, targeting eight different protein targets, showed IC50 values in the micromolar order in one or across several species. In general, yeasts were more significantly affected than molds.

Conclusion. Our results point to new potential fungal targets that can be exploited for the design of new antifungal agents. Ongoing work by our group aims to identify, by virtual screening, specific inhibitors for several of these potential targets.

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