Table 1. Baseline Patient Demographics and Characteristics

	LEF		MOX	
	PORT III patients (*n*=341)	PORT IV/V patients (*n*=121)	PORT III patients (*n*=334)	PORT IV/V patients (*n*=117)
Analysis population				
Age, years, mean (SD)	60.7 (15.3)	69.1 (14.2)	58.8 (14.3)	70.7 (12.6)
Male, *n* (%)	202 (59.2)	86 (71.1)	183 (54.8)	71 (60.7)
White, *n* (%)	277 (81.2)	92 (76.0)	277 (82.9)	96 (82.1)
Renal Status,* *n* (%)				
Normal function	148 (43.4)	34 (28.1)	166 (49.7)	25 (21.4)
Mild impairment	129 (37.8)	30 (24.8)	104 (31.1)	36 (30.8)
Moderate impairment	61 (17.9)	51 (42.1)	63 (18.9)	51 (43.6)
Severe impairment	3 (0.9)	4 (3.3)	1 (0.3)	4 (3.4)
SIRS, *n* (%)	330 (96.8)	116 (95.9)	318 (95.2)	108 (92.3)

Data for PORT I/II pts not shown.
*Normal: CrCl ≥90 mL/min; mild impairment: CrCl 60–<90 mL/min; moderate impairment: CrCl 30–<60 mL/min; severe impairment: CrCL<30 mL/min.

Table 2. TEAEs in PORT Risk Class III and IV/V Patients

	LEF		MOX	
	PORT III pts (*n*=337)	PORT IV/V pts (*n*=120)	PORT III pts (*n*=333)	PORT IV/V pts (*n*=116)
Patients with ≥1, *n* (%)				
Any TEAE	97 (28.8)	55 (45.8)	98 (29.4)	51 (44.0)
TEAE severity				
Mild	56 (16.6)	24 (20.0)	62 (18.6)	26 (22.4)
Moderate	32 (9.5)	18 (15.0)	26 (7.8)	14 (12.1)
Severe	9 (2.7)	13 (10.8)	10 (3.0)	11 (9.5)
Serious TEAE	12 (3.6)	15 (12.5)	14 (4.2)	13 (11.2)
TEAE leading to study drug discontinuation	8 (2.4)	9 (7.5)	8 (2.4)	8 (6.9)
TEAE leading to death by study Day 28	3 (0.9)	5 (4.2)	2 (0.6)	5 (4.3)
TEAE leading to death (over entire study duration)	5 (1.5)*	5 (4.2)	2 (0.6)	6 (5.2)†

TEAE=treatment-emergent adverse event.
*Two patients in the lefamulin group had a TEAE leading to death after study Day 28: one on study Day 32 and one on study Day 57.
†One patient in the moxifloxacin group had a TEAE leading to death on study Day 48.

Disclosures. **All authors:** No reported disclosures.

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665. *In vitro* Activity of Omadacycline Against Recent (2018) Bacterial Pathogens from the United States and Europe Obtained from Skin and Skin Structure, Respiratory, and Urinary Tract Infections

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Omadacycline (OMC) was FDA approved to treat acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP) for indicated organisms in 2018. Phase 2 OMC clinical trials for uncomplicated urinary tract infection (uUTI; NCT03425396) and acute pyelonephritis (NCT03757234) are ongoing. OMC is active against bacterial isolates expressing common tetracycline, penicillin, fluoroquinolone, and macrolide resistance mechanisms.

Methods. Isolates (14,000) were collected in 2018 from 31 medical centers located in the United States and 38 medical centers in Europe, including 3,458 staphylococci, 1,551 streptococci, 746 enterococci, 574 *Haemophilus* spp., and 5,690 *Enterobacterales* isolates. One isolate per patient infection episode was tested. Identifications were confirmed by MALDI-TOF MS and susceptibility testing was performed using CLSI broth microdilution methods.

Results. OMC (MIC$_{50/90}$, 0.12/0.25 mg/L) was highly active against *S. aureus* isolates from skin and skin structure infection (SSSI; 99.3% susceptible [S] including MRSA (97.7%S) and MSSA (99.9%S) (table). Similarly, OMC demonstrated potent activity against *S. aureus* isolates from respiratory tract infection (RTI; MIC$_{50/90}$, 0.12/0.25 mg/L) including MSSA (98.2%S). All *S. lugdunensis* isolates from SSSI were S (100.0%) to OMC. All *Streptococcus* anginosus group (100.0%) and 97.6% of *S. pyogenes* isolates from SSSI were S to OMC as were 98.0% of *S. pneumoniae* from RTI. No streptococci were resistant (R) to OMC. OMC (MIC$_{50/90}$, 0.12/0.25 mg/L) had potent activity against *E. faecalis* isolates from SSSI (99.0%S). OMC S against *E. cloacae* and *K. pneumoniae* isolates from SSSI was 92.1% S and 89.4% S, respectively. Similarly, 86.2% of *K. pneumoniae* isolates from RTI were S to OMC. Susceptibility of *H. influenzae* isolates from RTI to OMC was 99.8%S (no isolates were R). ≥90.0% of *E. coli* (MIC$_{50/90}$, 1/2 mg/L) and *K. pneumoniae* (MIC$_{50/90}$, 2/4 mg/L) UTI isolates were inhibited by ≤4 mg/L of OMC.

Conclusion. OMC was highly active against bacterial pathogens associated with ABSSSI, CABP, and UTI including staphylococci (97.7%-100.0%S), streptococci (97.6%-100.0%S), *E. faecalis* (99.0%S). *E. cloacae* (92.1%S), *K. pneumoniae* (86.2%-89.4%S), and *E. coli*.

Organism (no. of isolates)	Infection type	MIC$_{50}$	MIC$_{90}$	%S	%R	FDA Breakpoint Applied
S. aureus (1,475)	SSSI	0.12	0.25	99.3	0.2	ABSSSI
MRSA (432)	SSSI	0.12	0.25	97.7	0.7	ABSSSI
MSSA (1,043)	SSSI	0.12	0.25	99.9	0.0	ABSSSI
S. aureus (699)	RTI	0.12	0.25	95.3	2.9	CABP[a]
MRSA (248)	RTI	0.12	0.5	89.9	7.3	CABP[a]
MSSA (451)	RTI	0.12	0.25	98.2	0.4	CABP
S. lugdunensis (29)	SSSI	0.06	0.06	100.0	0.0	ABSSSI
S. anginosus gr (13)	SSSI	0.06	0.12	100.0	0.0	ABSSSI
S. pyogenes (125)	SSSI	0.06	0.12	97.6	0.0	ABSSSI
S. pneumoniae (794)	RTI	0.06	0.12	98.0	0.0	CABP
E. faecalis (101)	SSSI	0.12	0.25	99.0	0.0	ABSSSI
H. influenzae (512)	RTI	0.5	1	99.8	0.0	CABP
E. cloacae (89)	SSSI	2	4	92.1	3.4	ABSSSI
K. pneumoniae (141)	SSSI	2	8	89.4	5.7	ABSSSI
K. pneumoniae (290)	RTI	2	8	86.2	7.9	CABP
K. pneumoniae (275)	UTI	2	4	--	--	
E. coli (865)	UTI	1	2	--	--	

[a] Omadacycline CABP breakpoint for MSSA applied for comparison purposes.

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666. Efficacy and Safety of Cefiderocol According to Renal Impairment in Patients With Complicated Urinary Tract Infection (cUTI) in a Phase 2 Study

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Cefiderocol, a novel siderophore cephalosporin with broad activity against Gram-negative bacteria, requires dose adjustment in patients with renal impairment or augmented renal clearance, similarly to other β-lactams. The efficacy and safety of cefiderocol were assessed according to degree of renal impairment as part of a pivotal study vs. imipenem–cilastatin (IPM/CS) in patients with cUTI (NCT02321800).

Methods. A total of 448 randomized adults with cUTI received cefiderocol (2 g) or IPM/CS (1 g / 1 g), IV, q8h, for 7–14 days (safety population), with 371 patients in the microbiological intent-to-treat (Micro-ITT) population. Dose adjustments were made based on body weight (to enable IPM/CS blinding) and creatinine clearance (CrCL). The composite (clinical and microbiological) outcome at a test of cure (TOC; 7 days after treatment cessation) was analyzed by CrCL subgroup. Adverse events (AEs) according to renal subgroup were monitored throughout the study.

Results. A treatment difference in the composite outcome at TOC in favor of cefiderocol vs. IPM/CS was observed across renal subgroups (table), with greater differences in moderate and severe groups, consistent with that observed in the overall population (*n* = 371; 18.0%, 95% confidence interval: 7.5; 28.5). The incidence of AEs in the cefiderocol group was comparable across all renal subgroups. Conversely, AE incidence increased with the degree of impairment in the IPM/CS group (table).

Conclusion. In contrast to IPM/CS, the efficacy of cefiderocol was maintained across all renal function subgroups with no increase in the rate of AEs. These findings underscore the efficacy and safety of cefiderocol in patients with renal impairment and support the adequacy of the dose adjustment.

Table.

	Renal subgroup, CrCL mL/min			
	>80 (Normal)	>50–80 (Mild)	30–50 (Moderate)	<30 (Severe)
Composite outcome at TOC, Micro-ITT population, n/N (%)				
Cefiderocol (n=250)	97/124 (78.2)	49/78 (62.8)	30/41 (73.2)	5/7 (71.4)
IPM/CS (n=119)	31/51 (60.8)	22/41 (53.7)	11/23 (47.8)	1/4 (25.0)
Difference (95% CI)	17.4 (2.2; 32.7)	9.2 (–9.5; 27.8)	25.3 (0.8; 49.9)	46.4 (na)
AEs, safety population, n/N (%)				
Cefiderocol (n=298)	62/152 (40.8)	35/89 (39.3)	22/49 (44.9)	3/8 (37.5)
IPM/CS (n=148)	26/63 (41.3)	27/50 (54.0)	18/28 (64.3)	5/7 (71.4)

na: not available

Disclosures. **All authors:** No reported disclosures.

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667. Preclinical Pharmacokinetic and Pharmacodynamic Characterization of EDP-938, a Novel and Potent NonFusion Replication Inhibitor of Respiratory Syncytial Virus

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Respiratory syncytial virus (RSV) infection presents a significant health challenge in young children, elderly and immunocompromised patients. To date, there are no effective treatments available. EDP-938 was designed to meet this unmet medical need and is currently in Phase 2 clinical trials. Herein we report its pre-clinical pharmacokinetic (PK) and pharmacodynamic (PD) properties.

Methods. The pharmacokinetics of EDP-938 following single intravenous and oral doses were determined in mice, rats, dogs, and monkeys. *In vitro* cellular permeability and metabolic stability were assayed using Caco-2 cells and human liver microsomes, respectively. *In vivo* pharmacodynamic efficacy of EDP-938 was conducted in the African green monkey model, in which animals experimentally challenged with RSV were orally dosed twice daily with 100 mg/kg EDP-938 for 6 days starting 24 hours prior to infection.

Results. EDP-938 was well absorbed in the preclinical species with oral bioavailability values ranging from 27.1% in dogs, 35.4% in mice, 35.7% in rats, and 39.5% in monkeys, after a single oral dose when formulated in 0.5% methylcellulose. EDP-938 showed a moderate *in vitro* permeability of 3.6×10^{-6} cm/sec in Caco-2 cells. Based on the outcome of these absorption studies, EDP-938 was projected to have good oral absorption in humans. EDP-938 had low intrinsic clearance of 5 mL/minute/mg in human liver microsomes. Moreover, EDP-938 demonstrated potent antiviral efficacy in an African green monkey model of RSV infection. In untreated monkeys the RSV RNA viral load in the bronchoalveolar lavage fluid peaked at 10^6 copies/mL on day 5 post-infection, by comparison in animals treated with EDP-938 the viral load was below the limit of detection by day 3 post-infection. The PK/PD modeling suggested that plasma trough concentrations $\geq 10 \times EC_{90}$ led to >4-log viral load reduction in EDP-938 treated monkeys.

Conclusion. The favorable preclinical PK and PD properties of EDP-938 support its further clinical development as a novel treatment for RSV infection.

Disclosures. All authors: No reported disclosures.

668. Quality of Life Changes in Patients with *Clostridium difficile* Infection (CDI): A Randomized, Double-Blind Trial of Ridinilazole (RDZ) Compared with Vancomycin (VAN)

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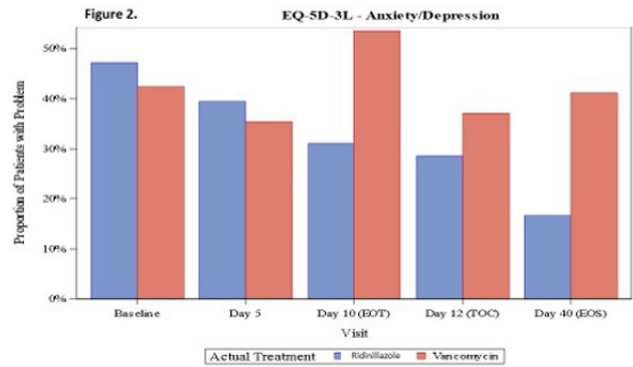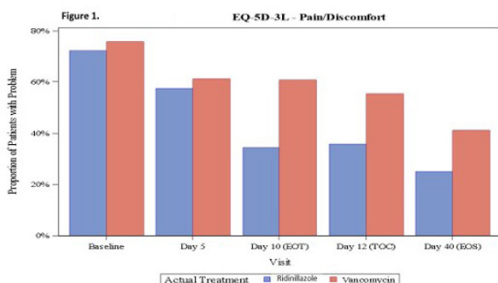
Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. *C. difficile* is the most frequent hospital-acquired bacteria in the United States. CDI is associated with significant morbidity and mortality, and a 46% lower mean EQ-5D index of Health-Related Quality of Life (HRQoL) compared with the general population. However, data on the impact of antibiotic treatment for CDI on HRQoL are lacking.

Methods. RDZ is a novel, narrow-spectrum antibiotic with targeted activity against *C. difficile*, under development for the treatment of CDI and prevention of recurrence. We evaluated HRQoL prospectively with the EQ-5D-3L in 69 patients enrolled in a Phase 2 randomized, double-blind trial comparing RDZ ($n = 36$) with VAN ($n = 33$). EQ-5D-3L was obtained at five time points (baseline, days 5, 10, 12, and 40) with summary index values calculated using US weights (Shaw 2005) evaluating raw scores for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and visual analog scale (VAS) scores.

Results. As early as Day 5, CDI patients on RDZ had significant improvements in mean change from baseline in index scores ($P = 0.008$) and VAS scores ($P = 0.01$) but no significant improvements were seen in patients on VAN. Time to resolution of diarrhea also occurred sooner with RDZ with a hazard ratio 1.19 in favor of RDZ (90% CI: 0.76, 1.87). Mean changes in index scores in the VAN group took longer to improve significantly compared with baseline and became higher on VAN on Day 12 and Day 40. Treatment-related improvements in pain/discomfort and anxiety/depression are shown in Figures 1 and 2. The mean change from baseline in EQ-5D-3L domains showed the highest (significant) improvements in the pain/discomfort domain for both treatment groups across all time points. However, by Day 40, anxiety/depression improved significantly more with RDZ than with VAN ($P = 0.039$).

Conclusion. We believe this is the first study to document improvements in HRQoL after antimicrobial treatment for CDI. Patients receiving ridinilazole experienced greater improvements in HRQoL sooner than those on VAN. Anxiety/depression and pain/discomfort improved significantly with treatment. HRQoL should be evaluated in Phase 3 interventional studies for CDI. These results will need to be validated in the ongoing Phase 3 randomized, double-blind, global trials comparing RDZ to VAN for the treatment of CDI.

Figure 1.

Figure 2.

Disclosures. All authors: No reported disclosures.

669. Twelve-Month Durability of Microbiota-Based Therapy RBX2660 for Prevention of Recurrent *Clostridium difficile* Infection

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Recurrent *Clostridium difficile* infections (rCDI) are a public health threat with insufficient treatment options at present. Two Phase 2 clinical studies have reported the efficacy of RBX2660, a standardized, stabilized microbiota-based drug, in preventing rCDI. For one of these trials, we report herein the durability of clinical response (lack of CDI recurrence) and microbiome restoration to 12 months after RBX2660 treatment.

Methods. Data were drawn from an interim analysis of a multicenter, open-label Phase 2 study in which participants with multi-recurrent rCDI received up to 2 doses of RBX2660 delivered via enema 7 days apart; this analysis includes data to 12 months after treatment, with follow-up ongoing. Efficacy was defined as the absence of CDI recurrence to 56 days after the last dose; and durability is defined as a continued lack of reported recurrence. Participant stool samples collected prior to and at 1, 7, 30, 60 days and 6 and 12 months after treatment were sequenced using a shallow shotgun method, with only treatment responders reported herein. Operational taxonomic unit (OTU) data were used to calculate relative abundance at the class level and Microbiome Health Indices.

Results. This study included 149 RBX2660-treated participants and 110 historical control patients, in the United States and Canada. As previously reported, the efficacy of RBX2660 in preventing rCDI (79.9%; 119/149) was higher than CDI-free rates in the historical control group (51.8%, 57/110; $P < 0.001$). Of 109 participants who had a 6-month follow-up, 97.2% (106/109) remained CDI-free, and no new CDI recurrences were reported at 12 months. Among treatment responders, the microbiome composition was restored after treatment to predominance by *Bacteroidia-* and *Clostridia-*class bacteria, and these compositions remained stable to 12 months after treatment among participants who provided samples.

Conclusion. RBX2660, a microbiota-based drug, was efficacious for preventing rCDI, with clinical and microbiome restoration durability to at least 12 months after treatment. The follow-up of efficacy, safety, and microbiome restoration are ongoing.
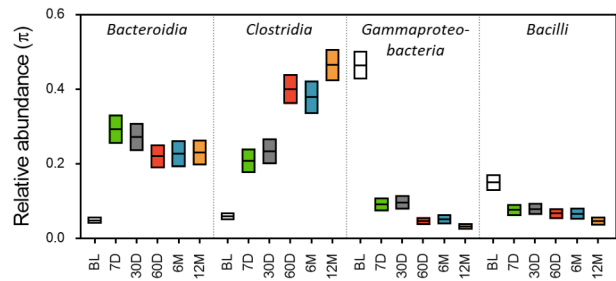

Figure 1. Relative taxonomic abundance at the class level among treatment responders (π, Dirichlet multinomial with confidence limits)

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670. VRE Clearance in Patients with Recurrent *Clostridium difficile* Infection Following Treatment with Microbiota-Based Drug RBX2660

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM