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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 preclinical 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 x 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 ≥10 × 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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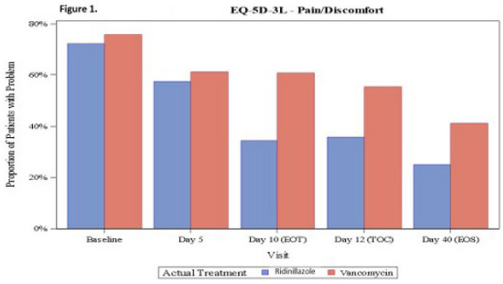
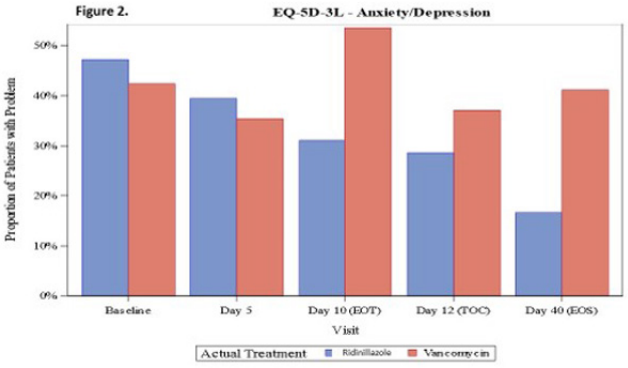
Background. *C. difficile* is the most frequent hospital-acquired bacteria in the United States. CDI is associated with significant morbidity and mortality, and a 46% lower mean EQ-5D index of Health-Related Quality of Life (HRQoL) compared with the general population. However, data on the impact of 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.





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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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.

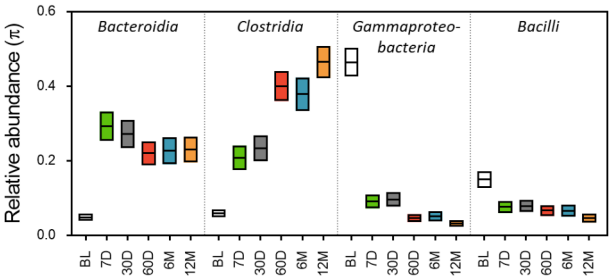

Figure 1. Relative taxonomic abundance at the class level among treatment responders (π, Dirichlet multinomial with confidence limits)

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

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

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Background. Vancomycin-resistant *Enterococcus* (VRE) infection is frequently associated with immunocompromised and critically ill patients. VRE carriers are at increased risk for infection due to VRE colonization and they pose a risk as a transmission source. VRE infection and *Clostridium difficile* infection (CDI) share common risk factors, including disruption of the intestinal microbiome. Thus, therapeutic approaches that decolonize VRE would be valuable. Herein, we report on stool VRE clearance in a cohort analysis from a Phase 2 open-label study of RBX2660, standardized microbiota-based drug, for recurrent CDI.

Methods. This prospective, multicenter, open-label Phase 2 study enrolled subjects with recurrent CDI. Participants received up to 2 doses of RBX2660 delivered via enema with doses 7 days apart. Patients were requested to voluntarily submit stool samples at baseline and at 7, 30 and 60 days, 6, 12, and 24 months after the last administration of RBX2660. Stool samples were tested for VRE using bile esculin azide agar with 6 µg/mL vancomycin and gram staining. Vancomycin resistance was confirmed via blood agar and etest.

Results. Stool samples were available for 143 patients. Twenty-one patients were VRE-positive at the first test (baseline or 7 day). Of the 19 VRE-positive patients that provided additional samples at later timepoints, 18 (94.7%) converted to negative as of the last available follow-up (30 or 60 days and 6, 12, or 24 months). The remaining patient remained positive at all follow-ups.

Conclusion. This cohort analysis of VRE-positive patients within an rCDI population provides additional support that microbiota-based formulations, such as RBX2660, may have additional benefit beyond reducing the recurrence of CDI. Additional study is needed to confirm the role of microbiome restoration on VRE clearance.

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

671. Impact of Dose-Administration Strategies of the Antistaphylococcal Lysin Exebacase, (CF-301), in Addition to Daptomycin (DAP) in an Experimental Infective Endocarditis (IE) Model due to Methicillin-Resistant Staphylococcus aureus (MRSA)

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Background. MRSA infections, especially involving the endovascular system (e.g., IE), are associated with unacceptably high morbidity and mortality rates. The use of bacteriophage-derived lysin, which acts as direct lytic agents, represents a novel adjunctive approach against virulent Gram-positive bacteria, such as MRSA. The current study examined the efficacy of DAP alone or DAP plus CF-301administered on a single day using various dosing regimens, in a rabbit model of MRSA IE.

Methods. Aortic valve IE due to MRSA strain MW2 was induced by the IV administration of ~1×10^5–2×10^5 cfu in aortic-catheterized rabbits. At 24-hour post-infection, animals were randomized into one of the 13 groups: (1) vehicle controls given once daily (QD); 2–13) DAP alone (at 4 mg/kg iv QD × 4d; this dose yields significant but modest clearance of MRSA in experimental IE); DAP + CF-301 (given as an IV dose on the first day of DAP treatment only by 5–10 min slow bolus at (mg/kg): 0.70 QD, 0.35 Q12h, 0.23 Q8h, 0.35 QD, 0.175 Q12h, 0.117 Q8h, 0.09 QD, 0.045 Q12h, 0.03 Q8h, 0.06 QD, 0.03 Q12h or 0.03 QD. At 24 hours after the last DAP dose, three target organs were quantitatively cultured (cardiac vegetations; kidneys and spleen). Data for each organ were calculated as mean $\log_{10}$ cfu/g of tissue (±SD).

Results. Treatment with DAP alone caused ~2–3 $\log_{10}$ cfu/g reduction in MRSA densities in all three target tissues vs. vehicle controls. All CF-301 doses given in addition to DAP, even at the lowest CF-301 dose (0.03 mg/kg), significantly reduced MRSA densities further in all target tissues vs. DAP alone (~3 $\log_{10}$ cfu/g) and vehicle control groups (~6 $\log_{10}$ cfu/g). In general, DAP plus CF-301 given as a single dose trended toward better microbiologic efficacy than CF-301 given at Q12h or Q8h, although this difference was not statistically significant.

Conclusion. These results demonstrate that CF-301, given at multiple dose strategies and at different dose regimens, in addition to sublethal DAP, had significant efficacy in further decreasing MRSA densities in relevant target tissues in the IE model (vs. DAP alone and untreated controls). DAP plus a single dose of CF-301 trended to better efficacy than when it was administered in fractionated dose-strategies.

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

672. Activity of Ibrexafungerp (Formerly SCY-078) Against *Candida auris*: *In vitro*, *In Vivo*, and Clinical Case Studies of Candidemia

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Background. *Candida auris* is a growing global threat; a pathogen associated with high mortality (up to 60%), multidrug resistance, the ability to spread from person-to-person and surface-to-person, presenting high risk for outbreaks in healthcare facilities. Ibrexafungerp is a novel IV/oral glucan synthase inhibitor (triterpenoid) antifungal with activity against *Candida*, *Aspergillus,* and *Pneumocystis* spp., in Phase 3 development.

Methods. *In vitro* studies tested ibrexafungerp against >100 clinical isolates of *C. auris*. Other *in vitro* studies evaluated the effects of ibrexafungerp against *C. auris* biofilms. *In vivo* activity against *C. auris* was evaluated using a disseminated murine model and a cutaneous infection guinea pig model. In humans, an ongoing open-label trial of ibrexafungerp for treatment of patients with infections caused by *C. auris* (the CARES study) has been initiated in the United States and India.

Results. *In vitro* and *in vivo* studies demonstrated that ibrexafungerp is active against *C. auris*, including MDR strains. The MIC mode for ibrexafungerp was 1 µg/mL and the MIC_{50} and MIC_{90} were 0.5 and 1 µg/mL, respectively. Many echinocandin-resistant *C. auris* isolates have shown susceptibility to ibrexafungerp. Furthermore, ibrexafungerp has been shown to reduce biofilm thickness. In animal models of *C. auris* infection, treatment with ibrexafungerp resulted in improved survival and reduced fungal burden in both the murine model of disseminated infection and the guinea pig model of cutaneous infection as compared with untreated controls. In humans, two patients with difficult to treat *C. auris* candidemias were enrolled in the CARES study and responded positively to oral ibrexafungerp with eradication of the infection.

Conclusion. These data demonstrate that ibrexafungerp possess potent *in vitro* and *in vivo* activity as well as promising clinical activity. Therefore, continued clinical evaluation of ibrexafungerp as an option to treat *C. auris* infections is warranted.

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

673. Novel Delayed-Release Formulation of an Oral β-Lactamase Prevents Gut Microbiome Damage and Attenuates Antibiotic Resistance Caused by Oral Amoxicillin/Clavulanate without Interfering with Amoxicillin Systemic Absorption in Dogs

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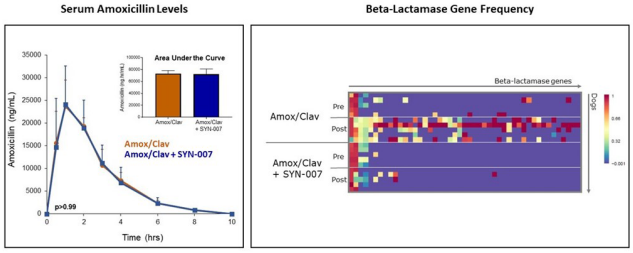
Background. Exposure of the gut microbiota to antibiotics can alter the composition of the microbiome and lead to the emergence and spread of antibiotic resistance. SYN-004 (ribaxamase) is a clinical-stage β-lactamase intended to degrade certain IV β-lactam antibiotics in the GI tract to preserve the gut microbiome. In a phase 2b clinical study, ribaxamase significantly reduced *C. difficile* infection in patients treated with IV ceftriaxone. A new delayed-release ribaxamase formulation, SYN-007, intended for use with oral β-lactams, was evaluated in dogs that received oral amoxicillin plus the β-lactamase inhibitor, clavulanate (amox/clav).

Methods. SYN-007 was engineered for release in the lower small intestine, distal to the site of antibiotic absorption. Dogs received amox/clav (40 mg/kg amox/5.7 mg/kg clav, PO, TID) +/- SYN-007 (10 mg, PO, TID) for 16 doses. Amoxicillin serum levels were measured by LC/MS/MS after the first and last doses. DNA, isolated from feces collected before and after antibiotic treatment, was analyzed by whole-genome shotgun sequencing using CosmosID, Inc. metagenomics software.

Results. Serum amoxicillin levels were not significantly different +/- SYN-007 after the first and last doses of amox/clav. Microbiome analyses revealed that amox/clav disrupted the gut microbiome resulting in loss of some species and overgrowth of other taxa. SYN-007 attenuated changes to gut microbiome composition. Amox/clav exposure resulted in the emergence of many, mainly TEM β-lactamase genes that was reduced with SYN-007.

Conclusion. Oral amox/clav disrupted the gut microbiome in dogs and resulted in the emergence of β-lactamase genes. SYN-007 diminished amox/clav-mediated microbiome disruption and attenuated emergence of β-lactamase genes. SYN-007 did not interfere with amox systemic absorption indicating that the β-lactamase was not released in the upper small intestine, the site of oral amoxicillin absorption. Antibiotic inactivation represents a potential new treatment paradigm for preservation of the gut microbiome and reduction of antibiotic resistance. SYN-007 has the potential to expand β-lactamase-mediated microbiome protection to oral as well as IV β-lactam antibiotics.



Left panel: Serum Amoxicillin PK curves were not significantly different between amoxicillin/clavulanate alone (Amox/Clav) and amoxicillin/clavulanate+SYN-007 (Amox/Clav+SYN-007) cohorts (n=5 each) after 16 doses of antibiotic. **Right panel:** Heat map of beta-lactamase gene frequency prior to and after amoxicillin/clavulanate +/- SYN-007. Amoxicillin/clavulanate exposure resulted in emergence of many beta-lactamase genes, mainly TEM beta-lactamases, while SYN-007 reduced the emergence of beta-lactamase genes.

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

674. Pre-Clinical and Phase I Safety Data for Anti-*Pseudomonas aeruginosa* Human Monoclonal Antibody AR-105

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