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 RXB2660, standardized microbiota-based drug, for recurrent CDI.

Methods. This prospective, multicenter, open-label Phase 2 study enrolled subjects with recurrent CDI. Participants CDI isolates have received up to 2 doses of RXB2660 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 RXB2660. Stool samples were tested for VRE using bile esculin azide agar with and without 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 CDI population provides additional support that microbiota-based formulations, such as RXB2660 may have additional benefit beyond reducing the recurrence of CDI. Additional study is needed to confirm the role of microbiome restoration on VRE clearance.

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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 unacceptable 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 strains MW2 was induced by the IV administration of 1 × 10^9 to 2 × 10^9 cfu in aortic-catherized rabbits. At 24-hour post-infection, animals were randomized into one of the 13 groups: (1) vehicle controls given one daily (QD); 2–13) DAP alone (at 4 mg/kg or QD × 4 d; 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, cfu/g of tissue (±SD).

Results. Treatment with DAP alone caused ~2–3 log, cfug/ml reduction in MRSA densities in all target tissues vs. vehicle control groups (~6–log, cfug/ml). In general, DAP plus CF-301 given as a single dose trended towards 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 regimens.

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672. Activity of Ibexafungerp (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. Ibexafungerp is a novel IV/oral glucon synthase inhibitor (triterpenoid) antimicrobial with activity against Candida, Aspergillus, and Pneumocystis spp., in Phase 3 development.

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

Results. In vitro and in vivo studies demonstrated that ibexafungerp is active against C. auris, including MDR strains. The MIC mode for ibexafungerp was 1 μg/mL and the MBC and MIC for CF-301 were 0.5 and 1 μg/mL, respectively. Many echinocandin-resistant isolates were concurrently susceptible to ibexafungerp. Furthermore, ibexafungerp has been shown to reduce biofilm thickness. In animal models of C. auris infection, treatment with ibexafungerp resulted in improved survival and reduced fungal burden in both the marine model of disseminated infection and the guinea pig model as compared in vitro. In humans, two patients with difficult to treat C. auris candidemias were enrolled in the CARES study and responded positively to oral ibexafungerp with eradication of the infection.

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

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

Conclusion. Oral amoxiclav disrupted the gut microbiome in dogs and resulted in the emergence of β-lactamase genes. SYN-007 diminished amoxiclav-mediated microbiome disruption and attenuated emergence of β-lactamase genes. SYN-007 did not interfere with amoxiclav systemic absorption indicating that the β-lactamase was not released in the upper small intestine, the site of oral amoxicillin absorption. Antibiotic resistance was measured as the percentage of β-lactamase-positive strains at the end of treatment for prevention of the gut microbiome disruption 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.

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

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**Background.** Anti-bacterial monoclonal antibodies can serve as a new treatment modality for difficult to treat infections. AR-105 is a fully human IgG1 monoclonal antibody (mAb) that binds to an extracellular polysaccharide epitope of *Pseudomonas aeruginosa* (PA) and was shown to mediate in vitro complement-dependent opsonophagocytic killing. AR-105 is currently being tested in a global Phase 2 clinical trial as an adjunctive treatment to standard of care antibiotics in ventilator-associated pneumonia patients. Here we present pre-clinical efficacy and clinical safety data for AR-105.

**Methods.** Efficacy in nonclinical studies against PA pneumonia was tested in prophylactic and therapeutic mouse models, either as a stand-alone therapy or in combination with antibiotics. Mice were dosed intranasally or by intravenous infusion with AR-105 post or prior to infection with PA and survival or lung bacteriology were monitored. In a clinical Phase 1 open-label study, 16 healthy volunteers received 2, 8, or 20 mg/kg of AR-105. Adverse events, immunogenicity, and pharmacokinetic (PK) profiles were evaluated for up to 84 days following administration.

**Results.** In the animal models, AR-105 reduced lung bacterial counts in a dose-dependent manner, and improved survival (80% in the treated group vs. 0% in the control group). Combination of AR-105 with antibiotics was more effective than monotherapy. In the Phase 1 study, no serious adverse events (AE) were observed in any cohort. Few AE were deemed related to the investigational drug, and all were mild and transient. AR-105 was found to be well tolerated in healthy volunteers with no anti-drug antibodies (ADA) detected. The PK profile was comparable with other human IgG1 mAbs, exhibiting a serum half-life of approximately 20 days.

**Conclusion.** AR-105 was confirmed to be effective in PA pneumonia animal models, either as stand-alone therapeutic or in combination with antibiotics. In the Phase 1 clinical study, AR-105 was shown to be safe and well-tolerated, with a PK profile similar to that of other IgG1 mAbs. AR-105 is a promising drug candidate for therapy of PA pneumonia.

**AR-105 (Aerucin) reduces Bacterial Lung Counts in a Prophylactic Mouse Model**

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675. **Efficacy of Human-Simulated Bronchopulmonary Exposures of Cefepime and Zidebactam (WCK 5222) Against Multidrug-Resistant (MDR) *Pseudomonas aeruginosa* (PSA) in a Neutropenic Murine Pneumonia Model**

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**Background.** WCK 5222 combines cefepime (FEP) with zidebactam (ZID), a bicycloacyl hydrazide β-lactam enhancer which binds βP2 in PSA and inhibits class A and C β-lactamases. The *in vivo* efficacy of human-simulated bronchopulmonary exposures of WCK 5222 against MDR PSA, a recalcitrant pneumonia-causing pathogen with few treatment options, was investigated in a neutropenic murine pneumonia model.

**Methods.** Thirteen clinical isolates of MDR PSA with FEP MIC 264 μg/mL were studied in neutropenic CD-1 mice. FEP, ZID, and WCK 5222 MICs were measured by broth microdilution in triplicate. For *in vivo* experiments, lungs were intranasally inoculated with 10<sup>8</sup>−10<sup>9</sup> CFU/mL bacterial suspensions. Human-simulated regimens (HSR) of FEP and ZID alone and in combination which achieved epithelial lining fluid (ELF) exposures in mice approximating human ELF exposures after doses of 2 g FEP/1 g ZID as a 1 hour infusion at steady state were developed. For each regimen, groups of 6 mice were dosed subcutaneously 2 hours after inoculation for 24 hours, then sacrificed. Vehicle-dosed control mice were sacrificed at the start (0 hour) and end (24 hours) of the dosing period. Lungs were aseptically harvested and bacterial CFU/lungs were determined.

**Results.** FEP MIC was >64 μg/mL for all isolates, while ZID and WCK 5222 MICs ranged from 4–512 and 32–64 μg/mL, respectively. Mean bacterial growth for all isolates at 0 hour was 6.68 log<sub>10</sub> CFU/lungs. Mean changes ± SD in bacterial density at 24 hours compared with 0 hour controls for 12 isolates with WCK222 MIC ≤16 μg/mL were 2.08 ± 1.09, 1.09 ± 0.98, −0.92 ± 1.45, and −2.13 ± 0.75, for control, FEP, ZID, and WCK2222, respectively. Against these isolates, ZID yielded >1 log<sub>10</sub> CFU/lungs reduction in 7/12, while activity was enhanced with WCK2222, producing >1 log<sub>10</sub> CFU/lungs reduction in 11/12 and >2 log<sub>10</sub> CFU/lungs reduction in 9/12. All isolates showed growth or stasis on FEP.

**Conclusion.** Human-simulated bronchopulmonary exposures of WCK2222 is effective against MDR PSA, at MIC up to 16 μg/mL in a neutropenic murine model. These data support the clinical development of WCK2222 for the treatment of pseudomonal lung infections, but further studies of PSA with high WCK2222 MIC are necessary to delineate the susceptibility breakpoint.

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676. **Health-Related Quality of Life (HRQoL) as Measured by the 12-Item Medical Outcomes Study Short-Form (SF-12) Among Adults With Community-Acquired Bacterial Pneumonia (CABP) Who Received Either Lefamulin (LEF) or Moxifloxacin (MOX) in Two Phase 3 Randomized, Double-Blind, Double-Dummy Clinical Trials (LEAP 1 and 2)**

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**Background.** Interest in patient health experience as part of a benefit–risk assessment for new drug approvals is increasing. Patient-centeredness, a key metric in the 2010 Affordable Care Act, is also a growing area of focus in healthcare. LEF, a new anti-biotic in development for treating adults with CABP, was noninferior to MOX based on clinical response endpoints in LEAP 1 and 2. HRQoL was prospectively incorporated and evaluated in both studies via SF-12, a well-known survey that measures general health status in 8 domains (physical function, role limitations due to physical