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)

Yan Xiong, MD, PhD[1]; Wessam Abdelhady, PharmD[2]; Liang Li, PhD[2]; Raymond Schuch, PhD[3]; Cara Cassino, MD[3]; Dario Lehoux, PhD; Arnold Bayer, MD[2]; [1]Los Angeles Biomedical Research Institute, Torrance, California; [2]LABioMed at Harbor-UCLA Medical Center, Torrance, California; [3]ContraFect Corp, Yonkers, New York

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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

Stephen Barat, PhD[1]; Katyna Borroto-Esoda, PhD[1]; Mahmoud Ghannoum, PhD[2]; Elizabeth Berkow, PhD[3]; David A. Angulo, MD[1]; [1]SCYNEXIS, Inc., Jersey City, New Jersey; [2]Case Western Reserve, Cleveland, Ohio; [3]Centers for Disease Control and Prevention, Atlanta, Hawaii,

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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

Sheila Connelly, PhD[1]; Christian Furlan-Freguia, PhD[1]; Brian Fanelli, MS[2]; Nur A. Hasan, PhD[2]; Rita R. Colwell, PhD[2]; Michael Kaleko, MD, PhD[1]; [1]Synthetic Biologics Inc., Rockville, Maryland; [2]CosmosID, Inc., Rockville, Maryland

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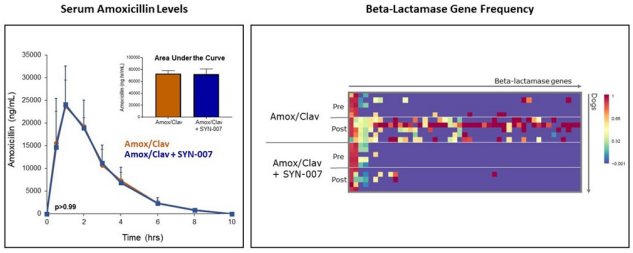
Background. Exposure of the gut microbiota to antibiotics can alter the composition of the microbiome and lead to the emergence and spread of antibiotic resistance. SYN-004 (ribaxamase) is a clinical-stage β-lactamase intended to degrade certain IV β-lactam antibiotics in the GI tract to preserve the 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

Andreas Loos; Nadine Weich; Jennifer Woo, BVSc, PhD; Guy Lalonde; Luisa Yee, PhD; Wolfgang Dummer, MD, PhD; Vu L. Truong, PhD; Aridis Pharmaceuticals, San Jose, California

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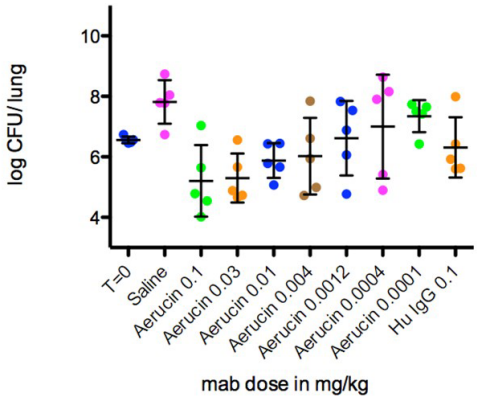
Background. Anti-bacterial monoclonal antibodies can serve as a new treatment modality for difficult to treat infections. AR-105 is a fully human IgG1 monoclonal antibody (mAb) that binds to an extracellular polysaccharide epitope of *Pseudomonas aeruginosa* (PA) and was shown to mediate *in vitro* complement-dependent 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 I 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.

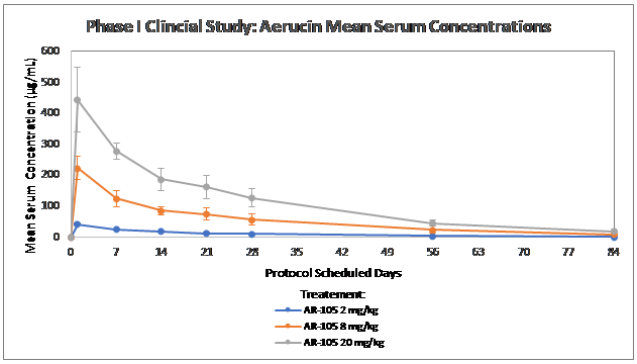
Conclusion. AR-105 was confirmed to be effective in PA pneumonia animal models, either as stand-alone therapeutic or in combination with antibiotics. In the Phase 1 clinical study, AR-105 was shown to be safe and well-tolerated, with a PK profile similar to that of other IgG1 mAbs. AR-105 is a promising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

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



PK Characteristics of Aerucin by Dose Level

Parameter Statistics	Aerucin 2.0 mg/kg (N=5)	Aerucin 8.0 mg/kg (N=6)	Aerucin 20.0 mg/kg (N=5)
Cmax (µg/mL)			
Mean	42.6737	223.5833	443.7230
SD	4.3644	37.0869	104.3782
Tmax (h)			
Mean	25.4	26.3	25.8
SD	0.89	1.51	0.84
t½ (h)			
Mean	426.3954	470.3799	498.2121
SD	98.3213	144.0327	87.1815
AUC(0-last) (µg*h/mL)			
Mean	19551.3567	97177.3962	249106.7305
SD	3454.7592	35656.1818	60768.8219
AUC(0-inf) (µg*h/mL)			
Mean	21195.2689	114797.6332	264250.3780
SD	2813.3058	35896.9289	67372.4678
Cl (L/h)			
Mean	8.6783	5.9588	6.3568
SD	0.9851	1.4862	1.8183
λz (1/h)			
Mean	0.0017	0.0016	0.0014
SD	0.0005	0.0005	0.0003
MRT (h)			
Mean	459.6475	425.2518	509.9929
SD	117.7048	143.5832	59.5586
Vdss (mL)			
Mean	3936.2764	2382.1174	3218.2642
SD	946.5306	427.3122	858.6019



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

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

James M. Kidd, PharmD; Kamilia Abdelraouf, PhD; David P. Nicolau, PharmD; Hartford Hospital, Hartford, Connecticut

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Background. WCK 5222 combines cefepime (FEP) with zidebactam (ZID), a bicycloacyl hydrazide β-lactam enhancer which binds PBP2 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 ≥64 mg/L 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 10^7–10^8 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 mg/L for all isolates, while ZID and WCK 5222 MICs ranged from 4–512 and 4–32 mg/L, respectively. Mean bacterial growth for all isolates at 0 hour was 6.68 $\log_{10}$ CFU/lungs. Mean changes ± SD in bacterial density at 24 hours compared with 0 hour controls for 12 isolates with WCK5222 MIC ≤16 mg/L were 2.08 ± 1.09, 1.09 ± 0.98, −0.92 ± 1.45, and −2.13 ± 0.75, for control, FEP, ZID, and WCK5222, respectively. Against these isolates, ZID yielded >1 $\log_{10}$ CFU/lungs reduction in 7/12, while activity was enhanced with WCK5222, producing >1 $\log_{10}$ CFU/lungs reduction in 11/12 and >2 $\log_{10}$ CFU/lungs reduction in 9/12. All isolates showed growth or stasis on FEP.

Conclusion. Human-simulated bronchopulmonary exposures of WCK5222 is effective against MDR PSA at MIC up to 16 mg/L in a neutropenic murine model. These data support the clinical development of WCK5222 for the treatment of pseudomonal lung infections, but further studies of PSA with high WCK5222 MIC are necessary to delineate the susceptibility breakpoint.

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

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)

Thomas Lodise, PharmD, PhD[1]; Sam Colman, MSc[2]; Elizabeth Alexander, MD, MSc., FIDSA[3]; Daniel Stein, MD[3]; David Fitts, MPH, PhD[3]; Lisa Goldberg, MS[3]; Jennifer Schranz, MD[3]; [1]Albany College of Pharmacy and Health Sciences, Albany, New York; [2]Covance Market Access Services, Inc., Gaithersberg, Maryland; [3]Nabriva Therapeutics US, Inc., King of Prussia, Pennsylvania

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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 antibiotic 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