Seltzer, Nabriva (previous employee and salary): Employee and Shareholder, Salary. **G. H. Talbot**, Nabriva Therapeutics: Board Member, Consultant and Shareholder, Consulting fee and stock options, board fees. **L. B. Gasink**, Nabriva: Employee, Salary.

2387. Selecting *Clostridium difficile* Infection (CDI) Outcome Measures Relevant to Public Health Concerns: Experience From a Ridinilazole (RDZ) Phase 2 Trial

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Background. CDC recognizes CDI as an immediate public health threat requiring urgent and aggressive action. Recurrent CDI (rCDI) occurs in up to 30% following initial therapy and 65% following a second recurrence. Perturbation by prior antibiotic use diminishes host colonization resistance allowing *C. difficile* to overgrow. Current CDI therapy with vancomycin (VAN) or metronidazole causes further collateral damage to the gut microbiota (GUT) priming patients for rCDI. Novel antibacterial agents are needed to tackle this life-threatening infection through (1) effectively treating initial CDI, (2) minimizing rCDI and (3) preventing collateral damage to GUT. A phase 2 trial with RDZ points to optimal selection of endpoints to capture these different benefits.

Methods. Randomized double-blind phase 2 study to compare 10 days RDZ 200 mg BID to VAN 125 mg QID. The primary endpoint was SCR defined as cure with no recurrence to 30 days post end of treatment. Fecal samples from all patients were collected at baseline, days 5, 10, 25 and 40 and at recurrence and changes to the microbiome were assessed.

Results. While clinical cure rates with RDZ and VAN were similar, RDZ-treated patients had a lower recurrence rate. As a result, in the primary efficacy analysis of 69 patients, 24 of 36 (66.7%) on RDZ vs. 14 of 33 (42.4%) on VAN had SCR (treatment difference 21.1%, 90% CI 3.1–39.1) establishing non-inferiority of RDZ ($P = 0.0004$) and also showing statistical superiority at the prespecified 10% level. Improved SCR with RDZ was associated with limited GUT impact vs. substantial GUT perturbation seen on VAN; both therapies reduced *C. difficile* to below the limit of detection.

Conclusion. SCR captures the impact of a therapy on both initial cure of CDI and rCDI. Applicable in randomized studies, it avoids methodological issues associated with recurrence as a separate endpoint. Moreover, by capturing impact on rCDI, it can assess superiority of novel therapies over existing agents with high cure rates. SCR should be a preferred measure of CDI treatment outcomes, and will be the primary endpoint in Phase 3 trials of RDZ. These trials will also evaluate GUT effects, so capturing three important determinants of public health impact: initial CDI, GUT and rCDI.

Disclosures. **R. Vickers**, Summit Therapeutics: Employee, Salary and Stock options. **S. Chowdhury**, Summit Therapeutics Inc.: Employee and Shareholder, Salary and Shareholder.

2388. Efficacy of Humanized Cefiderocol Exposures Over 72 Hours Against a Diverse Group of Gram-Negative Isolates in the Neutropenic Murine Thigh Infection Model

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Background. Previous pharmacodynamic (PD) assessments conducted over a 24 hours dosing period have revealed that cefiderocol humanized exposures produced predictable bacterial kill against MDR Gram-negatives with MICs ≤4 mg/L. Our current aim was to evaluate the sustainability of cefiderocol *in vivo* activity over 72 hours against MDR pathogens. *A. baumannii* (AB, $n = 4$), *P. aeruginosa* (PSA, $n = 2$), *K. pneumoniae* (KP, $n = 4$) and *E. coli* (EC, $n = 2$) displaying cefiderocol MICs of 0.5–16 mg/L were used in the neutropenic murine thigh model.

Methods. Mice received either humanized exposures of cefiderocol equivalent to the clinical dose [2g q8h 3h inf.] or cefepime (FEP) reflective of a 2g q8h 3h inf or vehicle. Efficacy was determined as the change in log CFU at 24, 48 and 72h compared with 0 hours controls. MICs were determined on organisms recovered from both the control and treatment animals.

Results. In AB, PSA and Enterobacteriaceae (EB) displaying MICs 0.5–8 ($n = 9$), infected mice given cefiderocol showed reductions of 0.5–3 log CFU at 72 hours. The killing profile observed among these 9 isolates followed a similar trend, demonstrating an initial reduction in bacterial burden at 24 hours which was sustained at 48 hours and 72 hours. As expected based on the PD profile of cefiderocol, no killing was seen with the AB isolate (MIC = 16). While cefiderocol exposure resulted in the killing of the FEP-resistant phenotype of the EB, mice receiving FEP displayed growth similar to controls. Infection with the remaining 2 organisms (EC 462, MIC = 1; KP 531, MIC = 4) resulted in a cumulative increase in bacterial burden over the study duration resulting in 1–2 logs growth following cefiderocol exposure over 72 hours. Retest MICs revealed an increase (≥2 dilutions) compared with control in only 1 animal (1/54 samples or 1.8%) observed in EC 462 at 72 hours. Additional samples from this group (2/3) remained unchanged throughout the study duration. Importantly, the retest MIC for this sample did not exceed the MIC of 4 mg/L.

Conclusion. These data show that for isolates demonstrating kill at 24 hours, cefiderocol efficacy was unchanged over the 72 hours treatment period. Despite the MDR profile of the pathogens tested their phenotypic profile remained largely unchanged and adaptive resistance during therapy was not observed.

Disclosures. **M. Tsuji**, Shionogi & Co., Ltd.: Employee, Salary. **Y. Yamano**, Shionogi & Co., Ltd.: Employee, Salary.

2389. Effect of Rezafungin on QT Interval in Healthy Subjects

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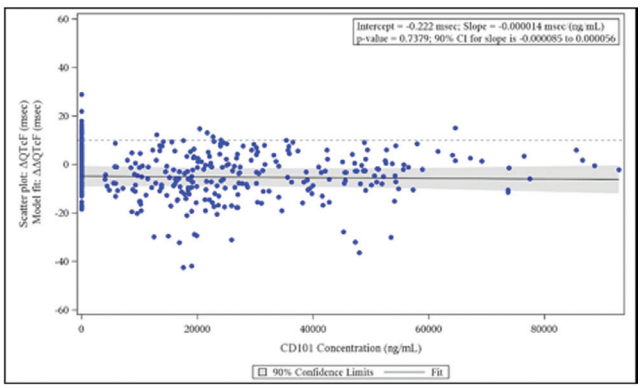
Background. Rezafungin (RZF), a novel, once-weekly echinocandin for treatment and prophylaxis of invasive fungal infections, successfully met safety and efficacy endpoints in Phase 2 and is advancing to Phase 3 studies. RZF is the first echinocandin to undergo a definitive QT evaluation.

Methods. This Phase 1, single-center, randomized, double-blind, comparative study evaluated the effects of RZF on the QTcF (corrected using Fridericia's formula) interval), heart rate, and other cardiac parameters. There were three dose groups, RZF (600 mg or 1,400 mg IV), IV placebo, and oral moxifloxacin (positive control). The 600 mg (therapeutic) and 1400 mg (supratherapeutic) doses were selected to achieve exposures approximating those after multiple doses of the highest dosage regimen assessed in the Phase 2 study (400 mg once weekly) and exposures ~2.5-fold higher, respectively. The primary endpoint was based on an analysis of change of QTcF from Baseline (ΔQTcF) as a function of RZF plasma concentration, to derive the estimated mean placebo-adjusted change of QTcF from Baseline (ΔΔQTcF) for the RZF dose groups at the geometric mean Cmax for each dose level. The outcome was defined by a comparison of the upper bounds of the 2-sided 90% CIs within 10 ms.

Results. 60 subjects were enrolled and completed the study. Demographics included: sex (43.3% male) and age (median age 34.0 years; ranging from 20 to 51 years) approximately evenly distributed by treatment. A linear regression model best fit the data, as shown in Figure 1. From this model, the estimated mean ΔΔQTcF at the Cmax for both of the RZF doses had upper bounds <10 ms. The mean ΔΔQTcF at each time point by dose, showed all 1-sided 95% upper bounds to be <10 ms, thus supporting the conclusion of the primary analysis. Assay sensitivity was established for moxifloxacin. No clinically significant effects on any of the cardiac parameters tested (RR, QRS, HR) were observed. RZF was generally well tolerated. All adverse events (AE) were mild to moderate in severity with no discontinuations due to AEs.

Conclusion. Rezafungin, in single IV doses up to 1,400 mg, does not prolong the QT interval. This finding supports the clinical safety and continued development of RZF.

Figure 1: Rezafungin for Injection Regression Analysis: Scatter Plot of Change of QTcF from Baseline (ΔQTcF) for Rezafungin and Placebo Subjects versus Rezafungin Concentration; and Linear Model Slope and 2-sided 90% Confidence Bounds of the Slope Representing Placebo-adjusted Change of QTcF from Baseline (ΔΔQTcF) (msec)



Disclosures. **S. Flanagan**, Cidara Therapeutics: Employee and Shareholder, Salary and stock options. **A. Jandourek**, Cidara Therapeutics: Consultant, Consulting fee. **T. Sandison**, Cidara Therapeutics: Employee, Salary.

2390. Avibactam Sensitizes NDM *Klebsiella pneumoniae* to Innate Immune Killing by Human Cathelicidin LL-37, Serum, Neutrophils, and Platelets

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Background. Avibactam (AVI) is a broad-spectrum intravenous non-β-lactam/β-lactamase inhibitor with no reported activity against metallo-β-lactamases such as New Delhi metallo-β-lactamases (NDM). Structural similarities between β-lactamases and bacterial penicillin-binding proteins (PBPs) have led investigators to explore and confirm the hypothesis that AVI may interact with PBPs of several Gram-negative and -positive bacterial species. Potent synergy has also been observed between AVI and peptide antibiotics such as polymyxin B. We hypothesized that sub-bacteriostatic concentrations of AVI may bind PBPs to weaken cell wall integrity and enhance lysis by the membrane attack complex of complement and by endogenous cationic antimicrobial peptides (AMPs) such as human cathelicidin LL-37. Sensitization to endogenous AMPs could improve killing by neutrophils and platelets that release these effectors upon degranulation.

Methods. Using NDM *K. pneumoniae* (NDM-KP) as a model, we performed LL-37 kill curves and killing assays with human serum, neutrophils and platelets in the presence or absence of AVI 4 μg/mL against NDM-KP.

Results. AVI alone lacked *in vitro* activity against NDM-KP. Addition of AVI to a physiological achievable concentration of LL-37 (2 mM) was bactericidal and resulted in an 8-$\log_{10}$ reduction (below detection limit) in recoverable NDM-KP CFU at 6 and 24 h; no bactericidal activity was seen in bacteria treated with LL-37 or AVI alone ($P < 0.0001$). AVI pretreatment dramatically sensitized NDM-KP to neutrophil and platelet killing ($P < 0.0001$ and $P < 0.01$, respectively). AVI also sensitized NDM-KP to 20% human serum, resulting in 8-$\log_{10}$ reduction in recoverable NDM-KP CFU within 6 h ($P < 0.0001$), an effect abrogated by heat treatment to inactivate complement.

Conclusion. AVI demonstrates potent synergy with peptide antibiotics and the innate immune system *in vitro*. Since AVI alone has scant direct antimicrobial activity and no direct inhibitory effect on metallo-β-lactamases, it is less likely to increase selective pressures toward antibiotic resistance. The use of AVI in combination with other antibiotics against drug-resistant bacterial pathogens warrants further study.

Disclosures. **G. Sakoulas**, Allergan: Consultant and Speaker, Consulting fee and Speaker honorarium. Sunovion: Speaker, Speaker honorarium. The Medicines Company: Speaker, Consulting fee. Paratek Pharmaceuticals: Consultant, Consulting fee. Cidara Therapeutics: Scientific Advisor, None. Arsanis Pharmaceuticals: Scientific Advisor, None.

2391. Liposomal Vancomycin and Cefazolin Combinations for *S. aureus* Biofilms

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Background. Biofilms are sophisticated communities of matrix-encased and surface-attached bacteria that exhibit a distinct and specific resistant/tolerant phenotype to almost all antibacterial agents, with activity reduced 10- to 1,000-fold. Interestingly, this augmented resistance rapidly reverts when bacteria detach from the biofilm and return to a planktonic state. However, in this *in vitro* pharmacokinetic and pharmacodynamic (PK/PD) model we are able to expose biofilms to shear rates that are consistent with human interface and mimic antibiotic penetration and diffusion pathways from serum antibiotic concentration in humans.

Methods. Methicillin-susceptible ATCC 29213 and MRSA 494 strains were evaluated. Initial susceptibility tests were performed by broth microdilution method. Time kill studies were performed to identify synergy patterns for liposomal and commercial antibiotics. Biofilm eradication was investigated using antibiotics vancomycin (VAN) (commercial) vs. liposomal VAN (VAN-L) (Patent#17-1460) and also combination of VAN- cefazolin (commercial) vs. liposomal vancomycin and liposomal cefazolin (CFZ-L) (Patent# 17-1460) in biofilms for strain MRSA 494. Biofilms were generated overnight using the BioFlux Microfluidic system (Fluxion BioSciences) at constant and continuous shear rates to optimize biofilm attachment and creation. Perfusion of antibiotic solutions (free peak concentration) was applied over a 24 h time period. Time lapse pictures were recorded to determine antibiotic biofilm eradication rates over 18h of incubation and pictures were analyzed using Bioflux Montage software.

Results. MIC values demonstrated a 2-fold reduction for liposomal vancomycin vs. commercial vancomycin. Also, combination of liposomal VAN MIC in presence of CFZ-L showed a 15.87-fold reduction in comparison to commercial VAN for 494. Overall, our biofilm results demonstrated a 43.6% improved eradication using VAN-L and CFZ-L combination in comparison to commercial VAN-CFZ combination. We also observed 5.7% improved eradication using VAN-L vs. commercial VAN.

Conclusion. Liposomal form of VAN and CFZ combinations are a promising approach to improved efficacy and reduced VAN resistance in *S. aureus* biofilms.

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2392. Fosfomycin Utilization and Outcomes in a Large VA Medical Center Over a Decade

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Background. Urinary tract infection (UTI) is one of the most common infectious diagnoses and in 2007 accounted for 10.5 million primary care visits in the US Advancing age and comorbidities, such as chronic kidney disease (CKD) and diabetes, affect antimicrobial prescribing habits. Sulfamethoxazole/trimethoprim (SMX-TMP), nitrofurantoin, and fosfomycin are first-line recommendations for uncomplicated cystitis. In an aging male population with potential allergies or contraindications to the above, fosfomycin is a potential option for treatment.

Methods. A retrospective chart review of fosfomycin prescribing habits at a large VA academic medical center. Patients were selected based on fosfomycin prescription in both inpatient and outpatient settings from January 1, 2004 to December 5, 2017. Data reviewed included indication, organism(s), susceptibility, duration of treatment, CKD, and clinical success. Treatment success was defined as no representation with UTI symptoms for 30 days.

Results. 117 cases of UTI in which fosfomycin was used were identified with a median patient age of 70 years old and 90% male. Twenty-five were uncomplicated cystitis, 49 complicated cystitis, and 34 catheter associated infections. Treatment success was obtained in 92% of the uncomplicated cystitis cases, 76% in complicated cystitis cases, and 67% in catheter associated UTIs. In half of all the cases an ESBL bacterium was isolated and 79% were successfully treated with fosfomycin. The most common pathogen identified was *E. coli* 58/118 (49%), followed by *Klebsiella* 25/118 (21%).

Conclusion. Fosfomycin is an antibiotic recommended for simple cystitis due to its safety profile, less collateral damage (gut flora disturbance), and low resistance as currently known. This review displays the largest ESBL cohort identified in the literature and uniquely used in a predominant male population. These findings suggest that ESBL producing bacteria can be treated successfully with fosfomycin in a male population as well as uncomplicated cystitis. However, caution should be used with catheterized patients as treatment was less effective regardless of isolated bacteria.

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

2393. Evaluation of Antifungal Treatment in a Neutropenic Mouse Model of Scedosporiosis

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Background. Scedosporiosis is a rare fungal infection with high mortality rates. Because clinical trials are hard to conduct, we developed a murine model for evaluating the efficacy of currently used antifungals in treating scedosporiosis.

Methods. MIC of isavuconazole (ISAV), posaconazole (POSA), voriconazole (VORI), and micafungin (MICA) were determined against 9 clinical isolates of *Scedosporium apiospermum, S. boydii* and *Lomentospora prolificans* using the CLSI M38 method. ICR mice were immunosuppressed with cyclophosphamide (200 mg/kg) and cortisone acetate (500 mg/kg) on days −2, +3, and +8 relative to intratracheal infection with 3.0×10^7 cells of *S. apiospermum*. For survival studies, treatment with placebo (vehicle control), ISAV (110 mg/kg, tid, po), POSA (30 mg/kg, tid, po), VORI (40 mg/kg, qd, po), MICA (3 or 10 mg/kg, qd, ip) or a combination of MICA (10 mg/kg) + ISAV (110 mg/kg) began 16 h post infection and continued for 7 days. For fungal burden studies, dosing began 8 h post infection and continued for 3 days. Mice were sacrificed on day +4. Survival and tissue fungal burden (by qPCR) served as efficacy endpoints.

Results. *S. apiospermum* was the most susceptible to all 4 antifungals with MICA MIC of 0.25 μg/mL and azole MICs of 1 μg/mL. *S. boydii* was also susceptible to MICA (0.125–0.5 μg/mL) but with variable susceptibility to azoles (1–16 μg/mL). In contrast, *L. prolificans* strains were resistant (MICA MIC 2–4 μg/mL and azole MIC >16 μg/mL). *S. apiospermum* DI16-478 was used to test *in vivo* efficacy. Only MICA (10 mg/kg) treatment prolonged survival of mice ($n = 10$) vs. placebo (median survival time = 8 days for MICA vs. 5 for placebo, $P < 0.03$ by log rank) and reduced fungal burden in lungs (primary target organ), brains and kidneys ($P \leq 0.02$, by Wilcoxon