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

Richard Vickers, PhD, R&D[1] and Sumita Chowdhury, MD MPH, R&D[2]; [1]Summit Therapeutics, Abingdon, UK, [2]Summit Therapeutics, Cambridge, Massachusetts

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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

Sean Stainton, PharmD[1]; Marguerite Monogue, PharmD[1]; Masakatsu Tsuji, PhD[2]; Yoshinori Yamano, PhD[2]; Roger Echols, MD, FIDSA[3] and David P. Nicolau, PharmD, FCCP, FIDSA[1]; [1]Center for Anti-Infective Research & Development, Hartford Hospital, Hartford, Connecticut, [2]Shionogi & Co., Ltd., Osaka, Japan, [3]ID3C, Easton, Connecticut

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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

Shawn Flanagan, PhD[1]; Daniel B. Goodman, MD[2]; Pallavi Rao, BSN, RN[1]; Alena Jandourek, MD[1]; Terry O'Reilly, MD, CPI[3] and Taylor Sandison, MD, MPH[1]; [1]Cidara Therapeutics, San Diego, California, [2]Cardiocore, Inc., Rockville, Maryland, [3]Celerion, Inc, Tempe, Arizona

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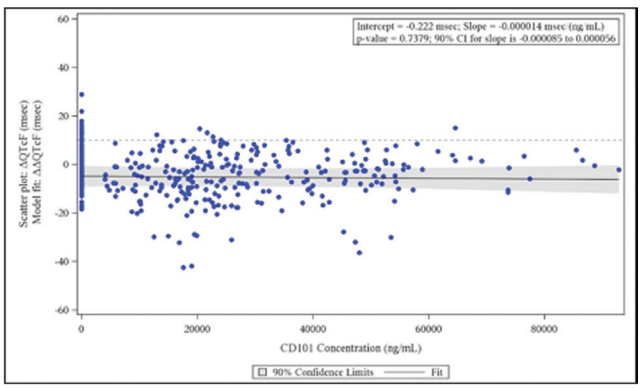
Background. Rezafungin (RZF), a novel, once-weekly echinocandin for treatment and prophylaxis of invasive fungal infections, successfully met safety and efficacy endpoints in Phase 2 and is advancing to Phase 3 studies. RZF is the first echinocandin to undergo a definitive QT evaluation.

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

Erlinda Rose Ulloa, MD, MSc[1]; Nicholas Dillon, PhD, MS[2]; George Sakoulas, MD[3] and Victor Nizet, MD[4]; [1]The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, [2]Pediatrics, University of California-San Diego, La Jolla, California, [3]University of California San Diego School of Medicine, San Diego, California, [4]Pediatrics and Pharmacy, University of California San Diego, La Jolla, California

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