1397. Comparative Efficacy of Human-Simulated Epithelial Lining Fluid (ELF) Exposures of Tezolidin (TZD) Against Meticillin-resistant Staphylococcus Aureus (MRSA) in Neutropenic (I-) vs. Immunecompetent (I+) Murine Models of Pneumonia

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Background. TZD is an oxazolidinone with potent activity against Gram-positive pathogens, including MRSA. Limited data currently exist on the efficacy of TZD in the presence of neutropenia. Herein, we investigate the comparative efficacy of human-simulated ELF exposures of TZD against MRSA in I- and I+ murine models of pneumonia.

Methods. Four MRSA isolates with TZD broth microdilution MICs of 0.5 mg/L were studied. BALB/c mice in I- groups were made neutropenic with cyclophosphamide. Lungs of I- mice were inoculated intranasally with bacterial suspensions of 10^6 CFU/mL; a higher inoculum of 10^7 CFU/mL was required to induce infection in I+ mice. Single daily doses of TZD simulating human ELF exposures after doses of 200 mg q24h were determined in both I+ (40 mg/kg) and I- (32 mg/kg) models. Three I- mice. Single daily doses of TZD simulating human ELF exposures after doses of 200 mg q24h were determined in both I+ (40 mg/kg) and I- (32 mg/kg) models. Three I- mice.

Results. The average bacterial burdens at 0 hour were 5.86 ± 0.21 and 8.10 ± 0.24 log CFU/lungs, respectively. Mean changes in bacterial density are reported in the table. No I+ control mice survived past 48 hours.

| Change in Log CFU/lungs (Mean ± SD) |
|-----------------------------------|
| I-                                |
| 24 hours                          |
| Control                           | 2.06 ± 0.62 |
| TZD                               | -1.18 ± 0.58 |
| 48 hours                          |
| Control                           | 2.54 ± 0.31 |
| TZD                               | -1.99 ± 0.90 |
| 72 hours                          |
| Control                           | 2.95 ± 0.60 |
| TZD                               | -2.78 ± 0.74 |

ND, no data.

Conclusion. Human-simulated ELF exposures of TZD demonstrated substantial and sustained efficacy in both I- and I+ murine models of pneumonia. These preclinical data utilizing clinically achievable bronchopulmonary exposures suggest that the efficacy of TZD for treatment of MRSA lung infections is not compromised by neutropenic status of the host. Further validation of these findings in patients is warranted.

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1398. β-Lactam Probability of Target Attainment (PTA) and Penetration into Epithelial Lining Fluid (ELF) Based on Multiple Bronchaleolar Lavage (BAL) Sampling Time Points in a Swine Pneumonia Model

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Background. Defining ELF concentrations is desired for antibiotics developed for pneumonia. For ethical reasons, BAL sampling in humans is routinely done at a single time point, thereby creating ambiguity in the precise ELF profile. It is unknown if additional sampling of the ELF would lead to more accurate estimates of exposure. The swine pneumonia model was used to characterize the full ELF profiles (5-BAL) of two β-lactams for comparison with models employing 1 BAL (1B) and 2-BAL (2B) sampling time points only.

Methods. Sixteen ventilated swine were infected with Pseudomonas aeruginosa to establish pneumonia and then treated for 72 hours with cefotaxime/tazobactam (C/T) 50 mg/kg q8h (n = 8) or piperacillin/tazobactam (TZP) 200 mg/kg q8h (n = 8). Plasma and BAL concentrations were measured in each swine at 1, 2, 4, 6, and 8 hours after the first dose. Urea correction was used to calculate ELF values. Cefotaxime and piperacillin plasma and ELF data were fitted to a two compartment model using the nonparametric adaptive grid program in Pmetrics. Hypothetical models were refitted after randomly selecting either 1B or 2B sampling time points from each swine. A 5,000 subject Monte-Carlo simulation was performed for each model to define PTA (60% free time above the MIC) and ELF penetration [area under the curve in ELF (AUC_{ELF})] vs. free AUC_{plasma}. The KS-test was used to analyze distribution differences, reporting maximum vertical deviation (D) as percent difference. D < 20% was defined as negligible.

Results. Thirty-two 1B/T and 34 TZP plasma samples and 29 and 32 BAL samples were available for the full model, respectively; 1B and 2B sampling models used eight and 16 BAL samples. All models adequately fitted the data. C/T PTA at 4 mg/L was 95%, 90%, 88%, 85%, 82%, 78%, 75%, and 72% for the full, 1B, and 2B models. TZP PTA at 16 mg/L was 55%, 46.8, and 46.7%, respectively, C/T median [interquartile range] penetration differences were negligible between the full (65% [25–109]) and 1B (72% [45–125], D = 15%) or 2B models (62% [32–111], D = 6%). TZP penetration differences were also minimal within the full (32% [9–67]) and 1B (17% [5–49], D = 18%) or 2B models (27% [9–44], D = 15%).

Conclusion. These data suggest that antibiotic ELF models constructed from a single BAL point result in similar exposure estimates to full ELF profiles.

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1399. Efficacy of Daptomycin Combination with β-Lactams for Daptomycin-resistant Enterococcus faecium Infection Among Adults in an Inpatient Setting

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Background. Daptomycin (DAF) is one of the mainstays treatments for Enterococcus faecium infections. However, development of resistance threatens its continued viability as a treatment option. Although the mechanisms of DAP resistance in enterococci are not fully comprehended, they are associated with alterations in cell envelope phospholipids assembly which leads to repulsion of the drug from cell exterior and diversion from the cell septum. Previous data suggest that combination of DAP with β-lactams has the potential to improve patient outcomes. In this investigation, we
1400. Mass Balance, Metabolism, and Excretion of [14C]-Plazomicin in Healthy Human Subjects

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Background. Plazomicin is a next-generation aminoglycoside (AG) with a structure that protects it from common AG resistance mechanisms in Enterobacteriaceae, and with in vitro activity against extended spectrum β-lactamase-producing and carbapenem-resistant Enterobacteriaceae. The purpose of this study was to evaluate the metabolism and excretion of plazomicin in healthy human subjects.

Methods. Six healthy male subjects were administered a single 30-minute intravenous infusion of 15 mg/kg [14C]-plazomicin (~100 µCi/dose). Following administration, blood (and plasma), urine, and feces were collected for 7 days. Total radioactivity was analyzed by liquid scintillation counting; plazomicin concentration was analyzed by a validated liquid chromatography-tandem mass spectrometry method; and metabolite profiling was conducted by accelerator mass spectrometry (AMS).

Results. The majority of the total administered radioactivity was recovered in urine (88.1%), with negligible amounts (<0.2%) excreted in feces. Radioactivity was rapidly eliminated, with ~56% of the total radioactivity recovered in urine within the first 4 hours postdose and >85% recovered in urine by 48 hours postdose. Analysis of nonradiolabeled plazomicin demonstrated that 97.5% of the dose was recovered as unchanged parent drug in urine by the end of the last sampling interval. Metabolite profiling of plasma at 10 hours using AMS showed that plazomicin was the only definable peak present, accounting for 94.3% and 93.6%, respectively, of the total carbon content.

Conclusion. Mass balance was achieved for [14C]-labeled and for nonradiolabeled plazomicin as the majority of the administered dose was recovered in urine, with negligible amounts in the feces. Plazomicin was eliminated as unchanged drug by the kidneys and thus did not appear to be metabolized to any appreciable extent. No metabolites were detected by AMS and plazomicin was the only definable peak present in plasma and urine.

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1401. A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Pharmacokinetics of Single and Repeat Doses of VNRX-5133 in Healthy Subjects

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Background. VNRX-5133 is a novel, non-β-lactam, β-lactamase inhibitor with potent and selective direct inhibitory activity against serine- and metallo-β-lactamases. VNRX-5133, combined with the β-lactam antibiotic ceftazidime, is being developed for the treatment of serious infections due to multidrug-resistant Gram-negative bacteria, including ESBL-producing organisms and carbapenem-resistant Enterobacteriaceae and Pseudomonas aeruginosa. This study evaluated the safety and pharmacokinetics (PK) of VNRX-5133 after single and multiple intravenous (IV) doses.

Methods. This was a Phase 1, randomized, single-center, double-blind, placebo-controlled, sequential group study in healthy subjects. In a single ascending dose (SAD) phase, subjects received 6.25, 125, 250, 500, 1000, and 1500 mg VNRX-5133 via a 2-hour IV infusion. In a multiple ascending dose (MAD) phase, subjects received 250, 500, and 750 mg VNRX-5133 q48h for 10 days. PK samples were collected predose and at frequent intervals. Safety was assessed from adverse events (AEs), laboratory tests, physical examination, vital signs, and electrocardiogram (ECG).

Results. All subjects completed the SAD (n = 48) and the MAD phases (n = 36). VNRX-5133 plasma exposure exhibited dose proportionality and linearity. Total clearance (CL) and volume of distribution (Vz) were 250 – 50 L. The t1/2 based on a noncompartmental analysis was ~6.5 hours. Modeling of VNRX-5133 plasma concentrations showed that the PK fit a 2-compartment model with most of the drug exposure accounted for within the phase of ~2 hours. Minimal accumulation of VNRX-5133 was observed following q48h dosing over 10 days. In the MAD phase, AEs occurred in four subjects (33.3%) with placebo and seven (19.4%) with VNRX-5133. In the MAD phase, AEs occurred in three subjects (33.3%) with placebo and eight (29.6%) with VNRX-5133. The most common AEs with VNRX-5133 were headache (11.1%), nausea (7.4%), and constipation (7.4%).

Conclusion. After single doses of 62.5–1,500 mg and multiple doses of 250–750 mg q48h, VNRX-5133 demonstrated a linear and dose-proportional PK profile with low variability. No safety issues were identified.

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