

sought to evaluate combinations of DAP with ampicillin (AMP), ceftazidime (CPT), and ertapenem (ERT).

**Methods.** *E. faecium* R497 harboring liaSFR mutations (DAP MIC of 16 mg/L) was evaluated in a simulated endocardial vegetation (SEV) pharmacokinetic and pharmacodynamic model over 336 hours at a starting inoculum of  $10^9$  log<sub>10</sub> CFU/g of SEV. DAP alone at 10 mg/kg/day or DAP (6, 8, 10 mg/kg/day) in combination with AMP (2 g continuous infusion), CPT 600 mg q12h or ERT 1 g q24h were evaluated. The emergence of DAP resistance was determined daily over the course of the 14-day experiment.

**Results.** DAP alone was not bactericidal and high-level DAP resistance was observed (MIC increase from 16 to 256 µg/mL) for all DAP alone regimens. Combination of DAP+AMP offered a significant reduction in log<sub>10</sub> CFU/g amounts (up to 7 log<sub>10</sub> CFU/g and to detection limits) in 24 hours in DAP10+AMP model with no further emergence of DAP resistance. Even in DAP 6 mg/kg/day with AMP (2 g), dramatic killing with no further emergence of resistance was observed. Neither CPT nor ERT in combination with DAP was effective against this strain. At higher doses of DAP (14 mg/kg/day) + CPT or ERT, a temporary (0–48 hours) CFU/g reduction was observed followed by regrowth and the further emergence of DAP resistance.

**Conclusion.** Combination of DAP + AMP offered the most encouraging results against *E. faecium* R497. A DAP dose sparing effect was noted with DAP + AMP but not with CPT or ERT. The reason for the discrepancy is unknown and is under further investigation. Further evaluation of DAP plus β-lactam therapy is warranted to discover the most optimized DAP and β-lactam therapy to improve patient outcome and prevent the emergence of resistance.

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#### 1400. Mass Balance, Metabolism, and Excretion of [<sup>14</sup>C]-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 [<sup>14</sup>C]-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 (89.1%), 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 and urine using AMS showed that [<sup>14</sup>C]-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 [<sup>14</sup>C]-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 cefepime, 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 62.5, 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 q8h for 10 days. PK samples were collected pre-dose 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) was ~6 L/h and volume of distribution ( $V_z$ ) was ~30 to 50 L. The  $t_{1/2}$  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 initial phase of ~2 hours. Minimal accumulation of VNRX-5133 was observed following q8h dosing over 10 days. In the SAD 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 q8h, VNRX-5133 demonstrated a linear and dose-proportional PK profile with low variability. No safety issues were identified.

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#### 1402. Cystatin C Improves Estimation of Vancomycin Clearance in Critically Ill Children Using a Population Pharmacokinetic Modeling Approach

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**Background.** Vancomycin (VAN) is renally eliminated and clearance (CL) correlates with glomerular filtration rate (GFR). The bedside Schwartz equation (Schwartz<sub>bed</sub>), currently used to estimate GFR in children, relies solely on creatinine (Cr) and is inaccurate in critical illness. We compared the Schwartz<sub>bed</sub> against various GFR-estimating equations that incorporate the novel biomarker cystatin C (CysC) in a population pharmacokinetic (PK) model of VAN CL in critically ill children.

**Methods.** Children 2–18 years of age receiving intravenous VAN in the Children's Hospital of Philadelphia PICU were enrolled. Three PK samples were collected during a single steady-state dosing interval in addition to VAN concentrations collected for clinical care. A sample was obtained prior to and during PK sampling for the measurement of CysC and Cr. VAN concentrations, dosing histories, and covariates (age, height, weight, sex, eGFR) were analyzed using nonlinear mixed-effects modeling with NONMEM v7.4. Model evaluation/selection was based on successful convergence, precision of the parameter estimates, the Akaike Information Criteria (AIC), and comparison of goodness-of-fit diagnostic plots of models including Schwartz<sub>bed</sub> and other published Cr- and CysC-based eGFR equations.

**Results.** We enrolled 20 subjects age 12.7 years (range: 3.9–18.2); six were female. Median VAN dosing at PK sampling was 57.4 mg/kg/day (range: 26.4–80.1). Median Cr was 0.35 mg/dL (IQR 0.3–0.5) and CysC was 0.5 mg/L (IQR 0.4–0.8); correlation between Cr and CysC was poor (0.24). Population PK data were described by a two-compartment model with allometric scaling for all parameters. The full age spectrum equation using both Cr and CysC [eGFR = 107.3/((Cr/Q<sub>cr</sub>)<sup>0.5</sup> + (CysC/Q<sub>cysc</sub>)<sup>0.5</sup>)\*0.5]; Q<sub>cr</sub> and Q<sub>cysc</sub> are normal values for age] as a covariate on CL had the largest reduction in AIC compared with Schwartz<sub>bed</sub> (ΔAIC –11.571) and provided best model fit. Typical population PK parameters (95% CI) normalized to 70 kg were 0.13 L/minute (0.11, 0.14), 24.5 L (7.7, 41.5), and 0.14 L/minute (0.01, 0.28) for CL, V<sub>1</sub>, and Q, respectively.