Consultant, Consulting fee. **S. Puttagunta**, Iterum Therapeutics: Employee and Shareholder, Salary.

1394. A Translational Pharmacokinetic Rat Model of Cerebral Spinal Fluid (CSF) and Plasma Concentrations of Cefepime

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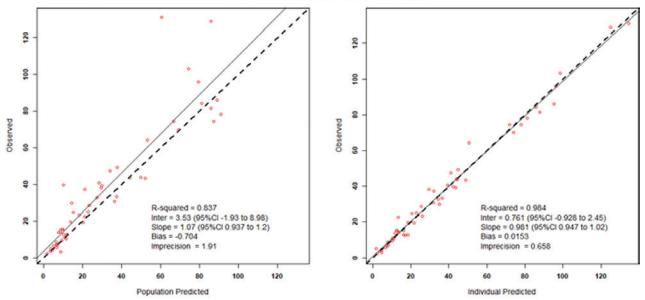
Background. For treatment of central nervous system infections caused by GNB, adequate cefepime concentrations are required in the cerebral spinal fluid (CSF) and brain. However, high plasma cefepime exposures have resulted in neurotoxicity. There is a need to understand the real-time pharmacokinetic (PK) relationship between plasma and CSF concentrations as serial CSF sampling is not regularly performed.

Methods. Male Sprague-Dawley rats received cefepime via an internal jugular vein catheter. A total daily dose of 150 mg/kg/day was administered as a single injection every 24 hours for 4 days. Plasma samples (mean n = 5 per rat) was obtained via a second dedicated catheter, with up to five samples obtained on a single concentration–time curve. CSF sampling occurred via an intracisternal catheter, with up to two samples taken every 24 hours. Cefepime in plasma and CSF were quantified via LC–MS/MS. PK analyses were conducted using Pmetrics for *R*. Multiple physiologic compartmental models were fit, with the ultimate model selected by Akaike score and rule of parsimony. Each rat's concentrations were predicted from the final model, and predictive performance was evaluated with bias and imprecision of the population and Bayesian posterior prediction models. PK parameters were estimated, and PK exposures during the first 24 hours (i.e., AUC_{0-24}, $CMAX_{0-24}$, $CMIN_{0-24}$) were calculated for each rat from Bayesian posteriors.

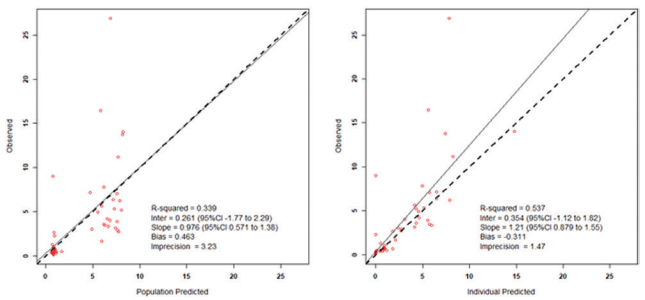
Results. Eleven rats contributed PK data. A three-compartment model fit the data well [Figure 1: Plasma, Population (a) and Bayesian (b); Figure 2: CSF, Population (a) and Bayesian (b)]. Population median parameter values (CV%) for rate constant (Ke), volume central compartment (V1), volume CSF compartment (V3), rate to/from central/peripheral compartment (KCP, KPC), rate to/from central/CSF compartment (K13, K31) were: 5.04 $hour^{-1}$ (43.4%), 0.069 L (39.24%), 0.28 $hour^{-1}$ (52.11%), 17.42 $hour^{-1}$(34.83%), 0.32 $hour^{-1}$ (165.3), 0.31 $hour^{-1}$ (79.89), respectively. Noncompartmental analysis of the Bayesian posteriors revealed a plasma median half-life, AUC_{0-24}, $CMAX_{0-24}$, and $CMIN_{0-24}$ of 2.6 hours, 158.1 mg hour/L, 189.3 mg/L, and 0.0003 mg/L from the first dose.

Conclusion. Cefepime transit to the CSF is rapid and highly predictable in the rat model. This model will be highly useful for understanding neurotoxicity outcomes for cefepime.

Figures 1a and 1b. Plasma.
Observed vs. Predicted Plots for the Population (a) and Individual (b).



Figures 2a and 2b. CSF.
Observed vs. Predicted Plots for the Population (a) and Individual (b).



Disclosures. **J. Liu**, Merck: Grant fund from Merck, Research grant.

1395. Defining the Magnitude of AUC:MIC Driver for Efficacy of the β-Lactamase Inhibitor VNRX-5133 When Combined with Cefepime Against KPC- and VIM/NDM-Producing Enterobacteriaceae and *P. aeruginosa*

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Background. VNRX-5133 is a cyclic boronate β-lactamase inhibitor (BLI) in clinical development with cefepime for treatment of infections caused by ESBL- and carbapenemase producing Enterobacteriaceae and *P. aeruginosa*. It is a new generation broad-spectrum BLI with direct inhibitory activity against serine-active site and emerging metallo-β-lactamases (e.g., VIM/NDM). In previous *in vivo* and *in vitro* studies, the PK-PD driver of efficacy of VNRX-5133 was defined as AUC:MIC. Described herein are *in vitro* studies to assess the magnitude of VNRX-5133 exposure (AUC:MIC) required to restore efficacy of cefepime against a broad collection of KPC- and VIM/NDM-producing Enterobacteriaceae (ENT) and *P. aeruginosa* (PSA) clinical isolates.

Methods. Dose-fractionation studies, consisting of four VNRX-5133 exposures fractionated into regimens administered every 4, 8, 12 and 24 hours, were performed in an *in vitro* infection model with simulated 2 g q8h dosing of cefepime against NDM-1 producing *E. coli*. A Hill-type model described the relationship between change in log_{10} CFU at 24 hours and VNRX-5133 exposure (AUC:MIC), where cefepime MIC was determined with 4 µg/mL VNRX-5133. To evaluate variability of efficacy enabled by VNRX-5133 between isolates as well as between Serine-BL and Metallo-BL producers, dose-ranging studies were completed for eight isolates (seven ENT and one PSA) producing KPC or VIM/NDM metallo-β-lactamases.

Results. The PK-PD exposure parameter AUC:MIC accurately described the efficacy of VNRX-5133 in rescuing cefepime activity against KPC and VIM/NDM carbapenemase-producing isolates of ENT and PSA. The AUC:MIC ratios associated with net bacterial stasis, 1-, and 2-log_{10} reductions in bacterial burden from baseline were 6.1, 18.4 and 45, respectively, for a collection of five VIM/NDM- and three KPC-producing isolates with cefepime MICs ranging from 4–8 µg/mL with no significant differences observed between Ser-BL and MBL producers.

Conclusion. These data confirm the equivalent *in vitro* activity of cefepime/VNRX-5133 against organisms producing serine- and metallo-β-lactamases and provides an initial PK-PD target for VNRX-5133 efficacy when used in combination with cefepime for the treatment of ESBL- and carbapenemase-producing ENT and PSA infections.

Disclosures. **D. Daigle**, VenatoRx Pharmaceuticals Inc.: Employee and Shareholder, Salary. **S. Vernacchio**, VenatoRx Pharmaceuticals Inc.: Employee and Shareholder, Salary. **L. Xerri**, VenatoRx Pharmaceuticals Inc.: Employee and Shareholder, Salary. **D. Pevear**, VenatoRx Pharmaceuticals Inc.: Employee, Salary.

1396. Predictions of Isavuconazonium Sulfate Dosage in Patients Aged 6 Months: <18 Years by Physiologically Based Pharmacokinetic Modeling

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Background. Best practice to establish dosage regimens for "first-in-pediatric" clinical trials requires knowledge of efficacious and safe exposures in adults.

Methods. Pediatric equivalent doses were predicted for patients aged 6 months and <18 years using physiologically based pharmacokinetic (PBPK) modeling, and compared with predictions by allometric scaling. All simulations were completed using PK-Sim®, which implements a whole-body PBPK model with 15 organs and appropriate maturation of anatomical and physiological parameters for children. The adult PBPK model was built using knowledge of drug physico-chemistry and clearance partitioning (CYP3A4, CYP3A5, glomerular filtration). PK data following IV (40, 80, 160 mg 60-minute infusion) and oral (100, 200, 400 mg capsule) doses in adults were used for initial model development. This model was validated by matching observed adult concentrations after multiple oral 200 mg doses. From this adult model, a virtual pediatric population (n = 4,600) from 6 months to <18 years was created. Simulations with the pediatric model assessed optimal doses of isavuconazonium sulfate based on age and weight to achieve at least a median steady-state daily area under the curve (AUC_{ss}) of 100 mg hour/L, and the majority below 230 mg hour/L. These targets were derived from efficacy and safety data in clinical trials with adults.

Results. As shown in the figure, an isavuconazonium sulfate dose of 10 mg/kg is expected to result in AUC_{ss} within the target range for the majority of patients >1 year old, in agreement with that predicted by allometry for patients aged 2–17 years. For patients aged 6 months to 1 year, a dose of 6 mg/kg predicts comparable exposures.

Conclusion. A proposed isavuconazonium sulfate dose of 10 mg/kg administered every 8 hours for the first 2 days and once daily thereafter is predicted to result in safe and efficacious steady state exposures in patients aged 1–17 years, similar to predictions from allometric scaling for patients aged 2–17 years. For subjects aged 6 months to 1 year, a dose of 6 mg/kg is predicted to achieve similar exposures. These doses should be tested in clinical trials to confirm.