Background. ME1100 (arbekacin inhalational solution) is an inhaled aminoglycoside being developed to treat patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP and VABP, respectively). PK-PD target attainment analyses were undertaken to evaluate ME1100 regimens for patients with HABP/VABP arising from Klebsiella pneumoniae (KP), Pseudomonas aeruginosa (PA) and Staphylococcus aureus (SA), including those with renal impairment.

Methods. Data used included a population pharmacokinetic (PPK) model developed using Phase 1 and post-marketing PK data, nonclinical PK-PD targets from one compartment in vitro and/or in vivo infection models, and MISC data. Using parameter estimates from the PPK model (four-compartment model with first-order elimination), total-drug epithelial lining fluid concentration-time profiles were generated for simulated patients with varying creatinine clearance (CLcr: mL/minute/1.73 m²) and by CLcr group. Twice daily (BID) ME1100 regimens ranging from 300 to 900 mg were assessed in simulated patients with CLcr >80 to ≤120 mL/minute/1.73 m². Percent probabilities of PK-PD target attainment by MIC were determined based on total-drug ELF AUC/MIC ratio targets associated with 1- and 2-log, CFU reductions from baseline for KP, PA and SA using Day 1 AUC. Regimens in simulated patients with renal impairment that best matched the BID regimen in the normal CLcr group with high percent probabilities of PK-PD target attainment and a low percent probability of Cmin > 2 mg/L were identified.

Results. ME1100 600 mg BID in simulated patients with CLcr >80 to ≤120 mL/minute/1.73 m², with 600 mg once daily, 450 mg BID and 600 mg BID in simulated patients with CLcr of 0 to ≤30, >30 to ≤50 and >50 to ≤80 mL/minute/1.73 m², respectively, achieved high percent probabilities of PK-PD target attainment based on PK-PD targets for a 1-log, CFU reduction from baseline at relevant MIC values for KP, PA and SA, and relatively lower Cmin values. In simulated patients with varying CLcr who received these regimens, high percent probabilities of PK-PD target attainment were achieved for KP, PA and SA at the upper margins of the MIC distributions (Figures 1-3).

Conclusion. The data provide support for ME1100 dose selection for patients with HABP/VAPB.

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1393. A Phase 1, Randomized, Open-Label, Crossover Study in Healthy Subjects Under Fasting Conditions of Orally Administered Sulopenem Etzadroxil Alone or with Probenecid to Determine the Pharmacokinetics of Sulopenem Michael Dunne, MD1; Steven Aronin, MD2; Elise Dunzo, Ph.D3 and Sailaja Puttagunta, MD4,1 Iterum Therapeutics, Old Saybrook, Connecticut, 2Parexel International, Baltimore, Maryland

Session: 145. PK/PD Studies Friday, October 5, 2018: 12:30-30 PM

Background. Antimicrobial resistance to available oral antibiotics is becoming progressively more common, precipitating the need for additional treatment options as step-down from initial intravenous (IV) therapy as well as for treatment of infections in the community. Sulopenem (CP-70,429) is a thiopenem antibiotic active against quinolone non-susceptible and ESBL-producing Enterobacteriaceae. As the key pharmacokinetic-pharmacodynamic variable correlating with efficacy for penem antibiotics is time above minimum inhibitory concentration (T > MIC), we examined the utility of probenecid, an OAT-1 inhibitor of β-lactam excretion, on the pharmacokinetic (PK) parameters for the oral prudrug of sulopenem, sulopenem etzadroxil.

Methods. Twelve healthy males and females received a single oral dose of 500 mg sulopenem etzadroxil as powder in bottle either alone or co-administered with a single oral dose of probenecid 500 mg in a crossover design with a washout period of 6 days. All doses were administered under fasting conditions. Blood samples for plasma PK analysis were collected and PK parameters for sulopenem, the parent compound of sulopenem etzadroxil, were determined.

Results. Treatment

| Treatment                  | N  | Cmax (mg/L) | AUC0-INF (hour mg/mL) | T > MIC (0.5 µg/mL) [hour] | T > MIC (0.5 µg/mL) [%] | 12 hour Interval |
|----------------------------|----|-------------|-----------------------|---------------------------|-------------------------|-----------------|
| 500 mg sulopenem etzadroxil| 10 | 1,928       | 3,871                 | 2.8                       | 23.3                    |                 |
| 500 mg sulopenem etzadroxil + 500 mg probenecid | 11 | 1,929       | 4,964                 | 3.6                       | 30.2                    |                 |

Conclusion. Probenecid increases the AUC of sulopenem by 28% in the fasted state and extends the mean time over MIC.

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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 KPC- 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 vitro and in vivo 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-fractonation 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-βL 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 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 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.

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1396. Predictions of Isavuconazonium Sulfate Dosage in Patients Aged 6 Months to <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 (AUCss) 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 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.