Part 2: PK was linear with doses in the range of 1500–3000 mg. Administration of gepotidacin 3000 mg tablets in the fed state slightly reduced Cmax and slightly increased AUC at the 3000 mg dose level. The 1500 and 2250 mg doses were tolerated while the 3000 mg dose was better tolerated compared to the fastest state with fewer and short-lived GI AEs, mostly mild in intensity. After oral administration of 1500–3000 mg high urinary drug concentrations were described, remaining above the minimum inhibitory concentration of 4 μg/mL for up to 24 hours.

Conclusion. The PK of gepotidacin following administration of a single oral dose to Japanese subjects was linear from 1500–3000 mg and food decreased Cmax without impact on exposure. Administration of gepotidacin resulted in an improved GI tolerability profile at the higher dose tested in Japanese subjects.

Disclosures. Mohammad Hossain, PhD, GlaxoSmithKline plc. (Employee, Former employee of and past/current shareholder in GlaxoSmithKline plc.); Aline Barth, MSPH, GlaxoSmithKline plc. (Employer, Former employee of and past/current shareholder in GlaxoSmithKline plc.); Emily Shamir, PharmD, BCIDP (Consultant); Etienne F. Dumont, MD, GlaxoSmithKline plc. (Employee, Former employee of and shareholder in GlaxoSmithKline plc.)

1117. Tazobactam Pharmacokinetic/Pharmacodynamic Target Attainment in Healthy Volunteers and Critically-Ill Hospitalized Patients
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Session: P-62. PK/PD Studies
Background. Pharmacokinetic/pharmacodynamic (PK/PD) targets and attainment are well described for beta-lactams; however, are rarely considered for beta-lactamase inhibitors. Recent evidence suggests that tazobactam (TAZ) target exposures to restore piperacillin bacteriostatic and 1 log 10 bactericidal activity against Enterobacterales are fT> the piperacillin/tazobactam (TZP) MIC of 64% and 77%, respectively. The aim of this study was to evaluate TAZ probability of target attainment (PTA) of a 500 mg every 6-hour dose of tazobactam using population PK data in both healthy volunteers and hospitalized patients.

Methods. PK exposures in 1,000 patients with varying degrees of renal function were simulated using a previously described TAZ PK model developed with data from critically ill infected patients. An identical one-compartment structural model describing TAZ PK using mean population parameters observed in phase 1 PK studies was also used to simulate exposures in healthy volunteers. All simulated patients received 500 mg of TAZ as an intravenous infusion over 30 minutes or as a 3-hour extended-infusion.

Results. The table displays PTA results for patients with an estimated creatinine clearance of 60 mL/min. Based on healthy volunteer data, the highest TAZ MIC where >90% PTA was achieved for bacteriostasis was 1 mg/L and was 0.25 mg/L for bactericidal activity. These were only achieved with extended infusion administration of TAZ. In the cohort of hospitalized patients, >90% PTA of TAZ exposures associated with bacteriostasis and 1 log 10 bactericidal was achieved up to a MIC of 2 for intermittent infusion and up to 4 mg/L for extended infusion, due to decreased TAZ tration of TAZ. In the cohort of hospitalized patients, >90% PTA of TAZ exposures extended-infusion.

Conclusion. Tazobactam Pharmacokinetic/Pharmacodynamic Target Attainment in Healthy Volunteers and Critically-Ill Hospitalized Patients
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Session: P-62. PK/PD Studies
Background. Contezolid (CZD) is a novel oral oxazolidinone with comparable activity and potentially improved safety compared to current oxazolidinones. The intravenous (IV)-to-oral prodrug of contezolid acefosamil (CZDa) is converted via MRX-1352 to active CZD. CZDA paired with CZD holds promise as a safe and effective treatment for serious Gram-positive infections such as those caused by methicillin-resistant Staphylococcus aureus. Sequential therapy with CZDA IV followed by CZD oral (PO) offers flexible treatment options in hospital and outpatient settings for conditions such as diabetic foot infections. We aimed to design a CZD/CZDA dosage regimen leveraging population pharmacokinetic modeling (PopPK).

Methods. PopPK simultaneously fit data from 184 adult subjects. These were 1) plasma concentrations (by LC-MS/MS) of MRX-1352, CZD, and its metabolite CZDa from 66 healthy subjects receiving CZDa (150-2400 mg IV) for up to 10 days, 2) CZD and MRX-1352 concentrations from 44 healthy subjects receiving single CZD PO doses of 400, 800, or 1200 mg with and without food or multiple doses QID for up to 28 days, and 3) CZD concentrations from 74 Phase 2 patients receiving CZD 800 mg PO Q12h. PopPK and Monte Carlo simulations were used to optimize CZD exposures.

Results. CZDa was rapidly converted to MRX-1352, which was converted less rapidly to CZD. CZD was well absorbed and food enhanced its bioavailability. For CZD 400 mg PO with food, apparent total clearance of CZD was 13.1 L/h (22% coefficient of variation) in healthy subjects and 14.5 L/h (53% CV) in patients. The apparent volume of distribution at steady-state was 20.5 L. A loading dose of CZDa 2000 mg IV, then CZD 800 mg IV Q12h, and followed by CZD 800 mg PO Q12h achieved areas under the curve (AUC) between 75 and 100 mg*h/L (medians; Figure) on all study days. Compared to CZD AUCs, the MRX-1352 AUCs during IV dosing were higher. While the median MRX-1352 AUCs were lower (18 to 48 mg*h/L), some accumulation was predicted in ~5% of patients.

Conclusion. A loading dose of CZDa 2000 mg IV followed by either CZD 1000 mg IV or CZD 800 mg PO Q12h was predicted to reliably achieve efficacious CZD exposures on day 1 and maintain those exposures throughout therapy. This regimen will be evaluated in Phase 3 studies in complicated skin infections and diabetic foot infections.

Disclosures. Jürgen B. Bulitta, PhD, MicRx Pharmaceuticals, Inc. (Consultant); Barry HAFKIN, MD, MicRx Pharmaceuticals Inc. (Consultant)
respectively, 2.1 (IQ 1.4-2.8) mL/kg/min, 0.6 (IQ 0.5-0.7) L/kg and 3.2 (IQ 2.3-4.0) hours. After the initial dose regimen, 54% (42%) patients reached the therapeutic target.

Conclusion. Using the one-compartment model, we evaluate the pharmacokinetic parameters of vancomycin in pediatric patients after liver transplantation. Most of patients did not reach the therapeutic target with empirical regimen, so it is prudent to monitor the exposure to vancomycin directly by AUC/MIC ratio to maximize anti-microbial efficacy.

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1120. Absorption, Metabolism, and Excretion of [14C] Tebipenem Pivoxil Hydrobromide (TBP-PI-HBr) Following a Single Oral Dose in Healthy Male Subjects

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Session: P-62. PK/PD Studies

Background. Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is an oral prodrug that is converted to tebipenem (TBP), the active moiety, with activity against multidrug-resistant gram-negative pathogens, including extended-spectrum-β-lactamase (ESBL)-producing Enterobacteriales. TBP-PI-HBr is the first oral carbapenem intended for treating complicated urinary tract infections and acute pyelonephritis. This study evaluated the absorption, metabolism, and excretion (AME) of TBP-PI-HBr following a single oral dose of [14C] TBP-PI-HBr to healthy males and characterized metabolites in plasma, urine, and feces. For mass balance, total radioactivity derived from urine and feces collections were determined. PK parameters were calculated using noncompartmental methods.

Methods. This was a Phase 1, open-label, single-dose study in healthy subjects. Study drug was provided as radiolabeled and non-radiolabeled active pharmaceutical ingredients containing approximately 150 μCi of [14C] TBP-PI-HBr. On Day 1, each subject received a 600 mg dose of TBP-PI-HBr, administered with 240 mL of water and fasted overnight for at least 10 hours. Blood samples were collected to determine TBP concentrations (whole blood), total radioactivity (whole blood and plasma), and metabolite profiling and identification were determined from plasma, urine, and feces. For mass balance, total radioactivity derived from urine and feces collections were determined. PK parameters were calculated using noncompartmental methods.

Results. Total radioactivity in plasma and whole blood decreased rapidly with geometric mean t1/2 values of 6.0 hours and 3.5 hours, respectively and T1/2inf of 1 hour. The cumulative mean recovery of radioactivity was 38.7% in urine and 44.6% in feces. Most of the administered radioactivity was recovered in the first 144 hours post dose in urine and feces (80.0%). Six of 8 subjects achieved a mass balance recovery ranging from 80.1% to 85.0%. The TBP plasma to total radioactivity ratio of 0.536 indicated that other metabolites contribute to the total radioactivity AUC in plasma. Metabolite profiling and identification results indicated that TBP was the major component in plasma and urine. The inactive ring open metabolite of TBP (LJC 11,562) was also found in plasma (>10%), urine (5.27%), and feces (>10%) as a secondary metabolite.

Conclusion. This study adequately characterized the AME of TBP-PI-HBr in humans.

Disclosures. Vipul K. Gupta, Ph.D., Spero Therapeutics, Inc., Employee; Shareholder Gary Maier, Ph.D., Spero Therapeutics, Inc., Consultant; Leanne Gasink, MD, Spero Therapeutics, Inc., Consultant; Amanda Ek, MS, Spero Therapeutics, Inc., Employee; Mary Fudeman, BA, MBA, Spero Therapeutics, Inc., Employee; Praveen Srivastava, MS, BS, Spero Therapeutics, Inc., Employee; Angela Talley, MD, Spero Therapeutics, Inc., Employee.

1121. Binequivalence of Two Formulations of Oral Tebipenem-Pivoxil Hydrobromide in Healthy Subjects

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Session: P-62. PK/PD Studies

Background. Tebipenem-pivoxil-hydrobromide (TBP-PI-HBr) is a novel oral carbapenem being developed to treat serious bacterial infections including complicated urinary tract infection. The objectives of this study were to assess the bioequivalence (BE) of two tablet formulations of TBP-PI-HBr in healthy adult subjects under fasted conditions and to evaluate the food-drug interactions of the registration drug product.

Methods. This was an open-label, randomized, single-dose, semi- replicate, 3-sequence, 4-period crossover, BE, and food effect study. Subjects were randomized to one of three sequences where they received a single 600 mg oral dose of TBP-PI-HBr as either the reference clinical study drug product (Treatment A) or the registration drug product (Treatment B) under fasted conditions. Subsequently, all subjects received a single 600 mg oral dose of TBP-PI-HBr as the registration drug product under fed conditions. This was a 7-day washout between each period. Whole blood sampling to determine TBP pharmacokinetics (PK) was conducted predose and up to 24 hours post dose in each period. Safety and tolerability were monitored throughout the study.

Results. Thirty-six healthy, adult male and female subjects were enrolled and completed the study. The TBP-PI-HBr registration product was bioequivalent to the clinical study product (Figure 1). For TBP, 90% confidence intervals (CIs) for AUC0-inf, Cmax, and T1/2 were within the 80% to 125% BE limits when administered under fasted conditions. A standard high-fat/high-calorie meal had no meaningful effect on the total plasma exposure of TBP after administration of the registration product, thus, overall exposure based on AUC0-inf and Cmax was comparable under fed and fasted conditions (Figure 2). Five (14%) subjects reported adverse events of mild severity. No QT interval prolongation or discontinuations due to AEs were reported, and no clinically relevant ECGs, vital signs or safety laboratory findings were observed.

Disclosures. Vipul K. Gupta, Ph.D., Spero Therapeutics, Inc., Employee; Shareholder Gina Patel, Ph.D., Spero Therapeutics, Inc., Consultant; Leanne Gasink, MD, Spero Therapeutics, Inc., Consultant; Flolini Bajraktar, MSc, Spero Therapeutics, Inc., Consultant; Praveen Srivastava, MS, BS, Spero Therapeutics, Inc., Consultant; Angela Talley, MD, Spero Therapeutics, Inc., Consultant.

1122. Effect of Aluminum Hydroxide/Magnesium Hydroxide/Simethicone and Omeprazole on the Pharmacokinetics of Tebipenem Pivoxil Hydrobromide (TBP-PI-HBr) in Healthy Adult Subjects

Vipul K. Gupta, Ph.D.;1 Gina Patel, Ph.D.;2 Leanne Gasink, MD;1 Flolini Bajraktar, MSc;1 Yang Lei, PhD;1 Akash Jain, PhD;2 Praveen Srivastava, MS, BS;1 Angela Talley, MD;1 Spero Therapeutics, Inc., Cambridge, Massachusetts;2 Patel Kwan Consultancy LLC, Madison, Wisconsin; Spero Therapeutics, Cambridge, Massachusetts

Session: P-62. PK/PD Studies

Background. Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is an oral prodrug that is converted to tebipenem (TBP), the active moiety being developed for treating complicated urinary tract infections. Antacids and proton pump inhibitors are known to change gastric pH after administration, which could affect the absorption of oral antibiotics. This study evaluated the effect of a single dose of aluminum hydroxide/magnesium hydroxide/simethicone and the effect of multiple doses of omeprazole on the PK of TBP following a single dose of TBP-PI-HBr.

Methods. This was an open-label, 3-period, fixed sequence drug-drug interaction study. On Day 1, Period 1, subjects received a single oral dose of TBP-PI-HBr