after being dosed. 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 C_{max} 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 fasted state with fewer and short-lived GI AEs, mostly mild in intensity. After oral administration of 1500–3000 mg, high urine drug concentrations were achieved, 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 C_{max} without impact on exposure (AUC). Administration of gepotidacin with food resulted in an improved GI tolerability profile at the higher dose tested in Japanese subjects.

Disclosures. **Mohammad Hossain, PhD**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) **Courtney Tiffany, BSc**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) **Aline Barth, MSC;PHD**, **GlaxoSmithKline plc.** (Employee, Shareholder, Employee of and shareholder in GlaxoSmithKline plc.) **Aparna Raychaudhuri, Ph.D.**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) **Etienne F. Dumont, MD**, **GlaxoSmithKline plc.** (Employee, Shareholder, 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 TZP 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 both bacteriostasis and 1 log kill were achieved up to a MIC of 2 for intermittent infusion and up to 4 mg/L for extended infusion, due to decreased TAZ clearance in hospitalized patients. These values are significantly lower than the CLSI TZP susceptibility breakpoint of 16 mg/L, and PTA rates were lower at increased creatinine clearances.

Table: Percent Target Attainment of Tazobactam exposures associated with restoring bacteriostasis (fT> MIC of 64%) and bactericidal activity (fT> MIC of 77%) of piperacillin in simulated patients receiving 500 mg every six hours of tazobactam with a creatinine clearance of 60 mL/min

TZP MIC	Healthy Volunteer		Critically-Ill Hospitalized Patients	
fT>MIC of 64%	30-min infusion	3-hour infusion	30-min infusion	3-hour infusion
0.25	82	98	100	100
0.5	78	96	99	100
1	71	93	98	100
2	60	87	94	99
4	41	72	84	96
8	14	37	51	79
16	1	6	<1	6
fT>MIC of 77%				
0.25	77	92	99	100
0.5	71	89	97	100
1	63	83	95	99
2	50	73	90	97
4	30	51	77	90
8	8	21	41	62
16	0.5	3	0	0

Conclusion. fT>TZP MIC target attainment is poor with maximal package insert tazobactam doses given with piperacillin, even when administered as an extended infusion. These findings have serious implications for the role of TZP in beta-lactamase producing Enterobacterales, including ESBLs, and suggest the current susceptibility breakpoints are 4-32 fold higher than those supported by PK/PD data.

Disclosures. **Jason M Pogue, PharmD, BCPS, BCIDP**, **Merck** (Consultant)**QPex** (Consultant)**Shionogi** (Consultant)**Utility Therapeutics** (Consultant)**VenatoRX** (Consultant) **Emily Heil, PharmD, MS, BCIDP**, Nothing to disclose

1118. Population Pharmacokinetics of Contezolid Acefosamil and Contezolid – Rationale for a Safe and Effective Loading Dose Regimen

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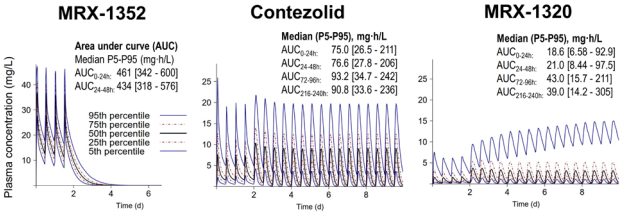
Session: P-62. PK/PD Studies

Background. Contezolid (CZD) is a novel oral oxazolidnone with comparable activity and potentially improved safety compared to current oxazolidinones. The intravenous (IV) double prodrug 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 CZDa/CZD 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 MRX-1320 from 66 healthy subjects receiving CZDa (150-2400 mg IV) for up to 10 days, 2) CZD and MRX-1320 concentrations from 44 healthy subjects receiving single CZD PO doses of 400, 800, or 1200 mg with and without food or multiple doses Q12h 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 800 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 CZDa 1000 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-1320 AUCs were lower (18 to 48 mg*h/L), some accumulation was predicted in ~5% of subjects.

Figure: Monte Carlo simulation of contezolid acefosamil 2000 mg IV at 0 h, then 1000 mg IV at 12, 24 & 36 h, followed by 800 mg oral contezolid Q12h



Conclusion. A loading dose of CZDa 2000 mg IV followed by either CZDa 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**, **MicuRx Pharmaceuticals, Inc.** (Consultant) **Barry HAFKIN, MD**, **MicuRx Pharmaceuticals Inc.** (Consultant)

1119. Assessment of Vancomycin Pharmacokinetic Parameters in Pediatric Patients After Liver Transplantation

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Session: P-62. PK/PD Studies

Background. Vancomycin is largely prescribed to treat gram-positive bacterial infections in pediatric patients after liver transplantation with the same empirical doses prescribed in other critical conditions due to the absence of pharmacokinetic studies in this population. The objective of this investigation was to describe the vancomycin pharmacokinetic parameters and to assess the vancomycin percentage of target attainment with empirical regimen.

Methods. Prospective and longitudinal study with pediatric post-liver transplantation patients who received at least 48 hours of vancomycin between January 2020 and May 2021. Patients with acute or chronic renal failure or receiving renal replacement therapy were excluded. Vancomycin therapy started with 40-60mg/kg daily, one-hour infusion. The pharmacokinetic parameters were determined by one-compartment model with first-order kinetics using near steady-state postdistributional peak and trough within the same dosing interval. Therapeutic target was defined as vancomycin 24-hour area under the curve/minimum inhibitory concentration (AUC^{ss}_{0-24}/MIC) ≥ 400 and < 600. The study protocol was approved by the local ethics committee.

Results. We included 18 sets of peak/trough serum concentrations obtained from 12 patients. The patients had median age of 11 (interquartile range [IQ] 8-16) months. The found vancomycin clearance, volume of distribution and half-life values were,

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, 5 (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 antimicrobial efficacy.

Disclosures. **All Authors**: No reported disclosures

1120. Absorption, Metabolism, and Excretion of [^{14}C]-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 Enterobacterales. 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 [^{14}C]-TBP-PI-HBr to healthy males and characterized metabolites in plasma, urine, and feces.

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 ingredient 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 $t_{½}$ values of 6.0 hours and 3.5 hours, respectively and T_{max} 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** (Employee, Shareholder) **Gary Maier, PhD**, **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. Bioequivalence of Two Formulations of Oral Tebipenem-Pivoxil Hydrobromide in Healthy Subjects

Vipul K. Gupta, Ph.D.[1]; Gina Patel, PhD[2]; Leanne Gasink, MD[1]; Floni Bajraktari, MSc[1]; Yang Lei, PhD[1]; Akash Jain, PhD[3]; Praveen Srivastava, MS, BS[1]; Angela Talley, MD[1]; [1]Spero Therapeutics, Inc., Cambridge, Massachusetts; [2]Patel Kwan Consultancy LLC, Madison, Wisconsin; [3]Spero Therapeutics, Cambridge, Massachusetts

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. There was by 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 AUC_{0-t}, AUC_{0-inf}, and C_{max} 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 AUC_{0-t} and AUC_{0-inf} was comparable under fed and fasted conditions (**Figure 2**). Five (14%) subjects reported adverse events of mild severity. No deaths, serious AEs or discontinuations due to AEs were reported, and no clinically relevant ECGs, vital signs or safety laboratory findings were observed.

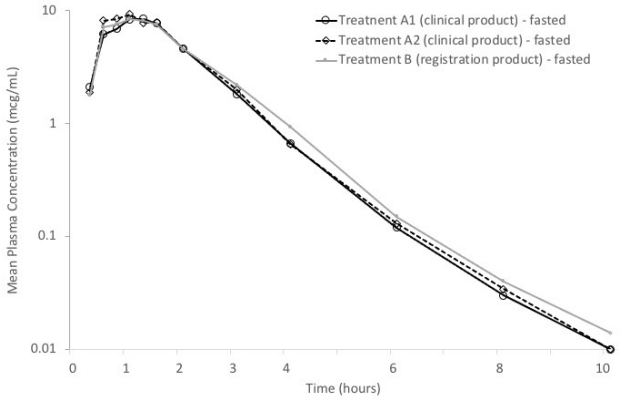

Figure 1. Arithmetic mean plasma TBP concentrations following a 600 mg dose of clinical study drug product (A1 and A2) and registrational drug product (B) – PK population.

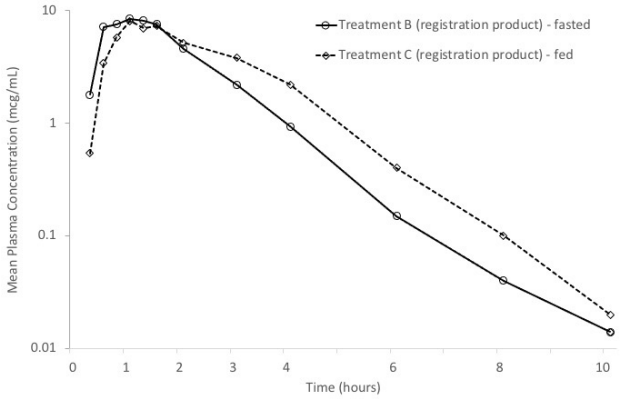

Figure 2. Arithmetic mean plasma TBP concentrations following a 600 mg dose of registrational drug product (B) under fasted and fed conditions – PK population.

Conclusion. The TBP-PI-HBr registration product was bioequivalent to the clinical study product under fasted conditions, and no meaningful effect of a high fat meal on TBP PK was observed.

Disclosures. **Vipul K. Gupta, Ph.D.**, **Spero Therapeutics** (Employee, Shareholder) **Gina Patel, PhD**, **Spero Therapeutics, Inc.** (Consultant) **Leanne Gasink, MD**, **Spero Therapeutics, Inc.** (Consultant) **Floni Bajraktari, MSc**, **Spero Therapeutics, Inc.** (Employee) **Yang Lei, PhD**, **Spero Therapeutics, Inc.** (Employee) **Akash Jain, PhD**, **Spero Therapeutics, Inc.** (Employee) **Praveen Srivastava, MS, BS**, **Spero Therapeutics, Inc.** (Employee) **Angela Talley, MD**, **Spero Therapeutics, Inc.** (Employee)

1122. Effect of Aluminum Hydroxide/Magnesium Hydroxide/Simethicone and Omeprazole on the Pharmacokinetics of Tebipenem Pivoxil Hydrobromide (TBP-PI-HBr) in Healthy Adult 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 being developed for treating complication urinary tract infections. Antacids and proton pump inhibitors are known to change gastric pH after administration, which could affect the absorption of oral medications. 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