Session: P-59. PK/PD studies

Background. Cefiderocol (CFDC), a novel siderophore cephalosporin, has demonstrated potent antibacterial activity against a wide range of Gram-negative bacteria including carbapenem-resistant strains. We aimed to evaluate relationships between drug exposure and outcomes in critically ill patients.

Methods. Sparse pharmacokinetic (PK) samples at steady state from critically ill patients with pneumonia, bloodstream infection/sepsis, or complicated urinary tract infection receiving CFDC in two Phase 3 studies were analyzed. Percent time of dosing interval of free drug concentration exceeding the minimum inhibitory concentration (MIC) in plasma and epithelial lining fluid (ELF) ($\%fT_{>MIC}$ and $\%fT_{>MIC,ELF}$, respectively) were determined for 60 (CREDIBLE-CR; NCT02714595) and 97 patients (APEKS-NP; NCT03032380), using a 3-compartment population PK model. The $\%fT_{>MIC,ELF}$ was calculated for 125 pneumonia patients based on an intrapulmonary PK model. Relationships between $\%fT_{>MIC}$, $\%fT_{>MIC,ELF}$ and clinical and microbiological outcomes at test of cure (TOC), or mortality at Day 28 were assessed.

Results. The median (90^{th} percentile) MICs of Gram-negative pathogens in the PK/pharmacodynamic (PD) analyses were 0.25 (4) µg/mL (CREDIBLE-CR) and 0.25 (2) µg/mL (APEKS-NP), respectively. Individual plasma $\%fT_{>MIC}$ was 100% in ≥95% of patients in each study, and estimated $\%fT_{>MIC,ELF}$ was 100% in 89.3% (25/28 pneumonia patients; CREDIBLE-CR) and 97.9% (95/97 pneumonia patients; APEKS-NP). Clinical cure rates and survival rates in patients with 100% $fT_{>MIC}$ or $\%fT_{>MIC,ELF}$ were similar between the two studies (Table). No PK/PD relationships between $\%fT_{>MIC}$, $\%fT_{>MIC,ELF}$ and clinical cure, microbiological eradication, or survival were identified in either study because high $\%fT_{>MIC}$ or $\%fT_{>MIC,ELF}$ was achieved in all patients.

Table. Clinical cure and survival rates in patients with 100% fT>MIC or %fT>MIC,ELF in CREDIBLE-CR and APEKS-NP studies

Table. Clinical cure and survival rates in patients with 100% $fT_{>MIC}$ or $\%fT_{>MIC,ELF}$ in CREDIBLE-CR and APEKS-NP studies

Study and outcome	$\%fT_{>MIC}$		$\%fT_{>MIC,ELF}$	
	<100%	100%	<100%	100%
CREDIBLE-CR, % (n/N)				
Clinical cure rate	0 (0/2)	62.1 (36/58)	0 (0/3)	64.0 (16/25)
Eradication rate	0 (0/2)	33.3 (25/75)	0 (0/3)	20.5 (8/39)
Survival rate	0 (0/2)	81.0 (47/58)	0 (0/3)	84.0 (21/25)
APEKS-NP, % (n/N)				
Clinical cure rate	100 (2/2)	65.3 (62/95)	100 (2/2)	65.3 (62/95)
Eradication rate	100 (2/2)	44.2 (53/120)	100 (2/2)	44.2 (53/120)
Survival rate	100 (2/2)	82.1 (78/95)	100 (2/2)	82.1 (78/95)

n=number achieving clinical cure, eradication, or survival; N=total number of patients for clinical outcome and mortality or total number of causative pathogens for microbiological outcome.

CREDIBLE-CR: n=60 (Median [Range] APACHE II score: 14 [2–29]). APEKS-NP: n=97 (Median [Range] APACHE II score: 15 [3–31])

Conclusion. PK/PD relationship was not identified between CFDC plasma or ELF exposure and clinical or microbiological outcomes, or mortality as high $\%fT_{>MIC}$ and $\%fT_{>MIC,ELF}$ were achieved, suggesting the recommended dosing regimen of 2 g q8h or renally adjusted dosage (including augmented renal clearance), infused over 3 hours, provides sufficient exposure to CFDC in critically ill patients.

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1317. Pharmacokinetics (PK) of Ampicillin-Sulbactam (SAM) during Orthotopic Liver Transplantation (OLT)

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Session: P-59. PK/PD studies

Background. SAM is used as surgical prophylaxis during OLT due to its broad spectrum activity against Gram-positive,-negative and anaerobic pathogens. SAM resistance among Gram-negatives is rising, making dosage selection paramount to preventing surgical site infections. Current guidelines recommend a 3g dose, consisting of 2g ampicillin (AMP) and 1g sulbactam (SUL), every 2h. There are no data; however, describing SAM PK during OLT to support an optimized dosing regimen.

Methods. This was a single-center PK study of OLT patients receiving SAM for surgical prophylaxis at a dose selected by the anesthesiologist. Patients were excluded if they were undergoing simultaneous liver and kidney transplantation and had a CrCL < 30 mL/min at start of surgery. Up to 24 blood samples, along with times of pertinent events, were collected throughout the OLT. AMP and SUL plasma concentrations were determined. Population PK analyses were conducted in Pmetrics using R. Akaike information criterion (AIC) and visual inspection determined best model fit. Individual PK parameters were simulated to describe free AMP time above the MIC_{90} ($fT>MIC_{90}$) of 32 mg/L.

Results. Five patients were enrolled. Participants had a mean ± SD age of 64 ± 7 years, body weight 82 ± 8 kg, CrCL of 75 ± 35 mL/min, and received various SAM doses (1.5-3g q2-3h). A 2 compartment model fitted the data better than a 1 compartment model for both AMP (AIC: 396 vs. 423) and SUL (AIC: 334 vs. 347). Final models included fractional clearance (CL_f) terms on typical total body clearance (CL_θ) to account for the placement of the portal vein clamp. AMP PK parameters (AIC: 372) were: CL_θ, 9.7 ± 2.6 L/h; CL_f, 0.73 ± 0.49; volume of central compartment (Vc), 7.2 ± 1.4 L; intercompartment constants (k12 and k21), 4.08 ± 3.28 and 2.63 ± 2.9 h^{-1}, respectively. Final SUL PK parameters (AIC: 314) were: CL_θ, 8.3 ± 2.5 L/h; CL_f, 0.92 ± 0.55; Vc, 7.3 ± 1.6 L; k12, 4.60 ± 4.41 h^{-1}, and k21, 4.07 ± 3.31 h^{-1}. Exposures ranged from 58-96% with only 3g q2h providing nearly 100% $fT>MIC_{90}$.

Conclusion. This is the first study to describe intra-operative SAM PK in OLT recipients and the effect of portal vein clamp on AMP and SUL clearance. These data will help guide optimized SAM dosing regimens for OLT surgery based on local MIC distributions for targeted pathogens.

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1318. Pharmacokinetics and Safety of Cefepime-Taniborbactam (formerly Cefepime/VNRX-5133) in Subjects with Renal Impairment

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Session: P-59. PK/PD studies

Background. Taniborbactam is a novel, non-ß-lactam, ß-lactamase inhibitor with activity against serine (Class A, C, D) and metallo (Class B) ß-lactamases including epidemiologically important carbapenemases. Both cefepime and taniborbactam are predominantly renally excreted and are likely to require dose adjustment in patients with renal impairment and end-stage renal disease (ESRD). The current study was designed to evaluate the pharmacokinetics and safety in patients with renal impairment and ESRD.

Methods. This was a Phase 1, open-label study in subjects with normal renal function (eCL_{CR} ≥ 90 mL/min) matched to subjects with mild, moderate, and severe renal impairment (eGFR 60-89, 30-59, and < 30 mL/min/1.73m^2, respectively), and patients with ESRD on hemodialysis. Subjects received a single dose of cefepime 2 g and taniborbactam 500 mg; subjects with ESRD received a single dose before HD and after a 9 day washout period, following HD. PK parameters including $AUC_{0\text{-}inf}$ and total body clearance (CL) were evaluated. Safety assessments included adverse events (AEs), vital signs, clinical laboratory evaluations, electrocardiograms, and physical examinations.

Results. Thirty-three subjects were enrolled; 67% male, 58% white and 39% black/African Americans. Median age and BMI were 55.0 years and 29.5 kg/m^2, respectively. For both cefepime and taniborbactam, exposures increased, and CL decreased with increasing renal impairment (see Table). The hemodialysis extraction ratio was 49.7% and 47.4% for taniborbactam and cefepime respectively. No safety signals were observed and there were no serious adverse events.

Table

	Taniborbactam		Cefepime	
Renal Function Group (eGFR range [mL/min])	**$AUC_{0\text{-}inf}$ (h*µg/mL) Mean (SD)**	**CL (L/h) Mean (SD)**	**$AUC_{0\text{-}inf}$ (h*µg/mL) Mean (SD)**	**CL (L/h) Mean (SD)**
Normal (≥ 90)	**84.1 (9.7)**	**5.83 (0.66)**	**345.8 (45.9)**	**5.69 (0.75)**
Mild (60-89)	**97.9 (11.1)**	**4.99 (0.70)**	**419.5 (37.7)**	**4.64 (0.54)**
Moderate (30-59)	**229.8 (50.2)**	**2.17 (0.55)**	**927.9 (182.1)**	**2.13 (0.48)**
Severe (<30)	**557.5 (462.6)**	**1.30 (0.73)**	**1,891.4 (1330.1)**	**1.41 (0.74)**

Conclusion: Cefepime and taniborbactam CL is similarly reduced with varying degrees of renal impairment. Dialysis removes a high fraction of both drugs. Dose adjustments recommended for cefepime are appropriate for taniborbactam.

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1319. Pharmacokinetics of Ceftolozane/Tazobactam in Patients with Burns

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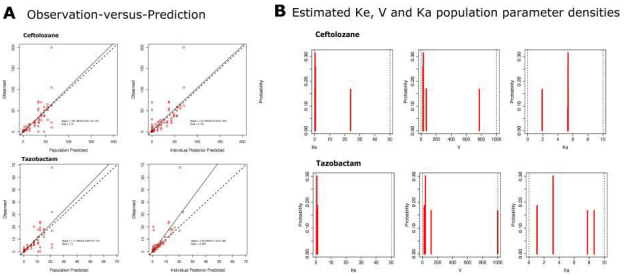
Session: P-59. PK/PD studies

Background. Antimicrobial dosing in moderate/severe burns patients is complicated due to the potential unpredictable hyperdynamic pathophysiologic states including 1) hypoproteinemia, 2) acute kidney injury and 3) onset of septicemia. Therefore, distribution assumptions about the population pharmacokinetic (PopPK) profiles of either endogenous or xenobiotic pharmacophores in this patient population can lead to biased parameter estimates. In order to prevent potential bias an agnostic nonparametric adaptive grid approach to describe ceftolozane/tazobactam (C/T) PopPK profiles in patients with partial- and full-thickness burns was employed.

Methods. A human clinical PK study in burn patients was conducted using the standard approved dose of C/T (2 grams/1 gram). A single intravenous dose was administered over 60 minutes. Whole blood was obtained pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours following the start of infusion. LC-MS/MS bioanalytical methods were developed, validated and employed to determine C/T concentrations in human plasma. PopPK were modeled using Pmetrics package for R. One-, two- and three-compartment models were examined and compared. The influence of several parameters, including %body surface area burns, creatinine clearance (CrCL), weight, albumin and age were tested.

Results. The bioanalytical method for determination of C/T in human plasma met all recommended criteria of the LC-MS/MS. Five males and one female (ages 24 to 66 years), contributed 148 plasma PK samples. The female had 35% partial-thickness burns. The males had full-thickness burns ranging from 27 to 66%. The median CrCL was 104 mL/min (range 73-148 mL/min). Two-compartment model with absorption (Ka) from compartment 1 to 2 and elimination from compartment 2 (Ke), with nonlinear interactions between C/T elimination and CrCL best described the data. Figure A show that bias was minimal. Importantly, both drugs exhibited marked variability for both volume and elimination (Table), since volume was bimodally distributed (Figure B).

A) Observation-versus-Prediction; B) Estimated Ke, V and Ka population parameter densities



Summary of pharmacokinetic parameters

Parameter	Mean	SD	%CV	Median	%Shrinkage
Ceftolozane					
Ke	4.232	8.760	206.994	0.375	0.001
V	157.610	275.586	174.853	28.956	0.006
Ka	4.785	1.283	26.807	5.355	0.003
Tazobactam					
Ke	0.649	0.253	38.939	0.567	6.022
V	206.158	356.305	172.831	38.555	0.007
Ka	20.459	15.279	74.681	15.973	1.531

Conclusion: C/T exhibited high variability surpassing that observed with severe infections, suggesting that dose adjustment and/or may be therapeutic drug monitoring may be needed to balance target attainment from dose-related toxicities.

Disclosures. Ronald G. Hall, II, PharmD, MSCS, Medical Titan Group (Grant/Research Support)Merck (Research Grant or Support)

1320. Pharmacokinetics of Isavuconazole Administered as Isavuconazonium Sulfate Intravenous Solution via Nasogastric Tube or Orally in Healthy Volunteers

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Session: P-59. PK/PD studies

Background. Nasogastric (NG) tube feeding is most common in the intensive care unit and is also used for cancer patients who are unable to eat (e.g. patients with mucositis) or do not want to eat due to severe nausea[1]. For such critically ill patients with invasive fungal infections, administration of isavuconazonium sulfate (ISAVUSULF) via NG tube can be an alternate route of drug administration.

Methods. This was a randomized, open-label, 2-period, 2-sequence single dose crossover study in healthy male and female subjects. Each subject participated in 2 treatment periods separated by a washout of at least 30 days between investigational product administrations in each period. Subjects were administered a single dose of 372 mg ISAVUSULF intravenous (IV) solution via NG tube (test formulation) or 372 mg ISAVUSULF capsules for oral (PO) administration (i.e., PO capsules administered to subjects without NG tube) (reference formulation) under fasting conditions on day 1 of each period. Pharmacokinetic (PK) samples were collected predose on day 1 of each period and at multiple time points postdose through day 21. Standard safety and tolerability assessments were conducted in each period.

Results. Eighteen subjects were randomized in this study and 13 provided concentrations in both sequences that were PK evaluable. The analysis of variance estimate (Table 1) of the study population suggests that the isavuconazole IV NG tube administration geometric least-square (LS) mean values of the observed maximum concentration (C_{max}), area under the plasma concentration-time curve (AUC) to the last measurable concentration (AUC_{last}), AUC to time infinity (AUC_{inf}), and AUC from start of dosing to 72 hours (AUC_{72}) were 105.3%, 97.6%, 99.3% and 97.8%, respectively, of the corresponding oral administration values. The geometric LS mean ratio and 90% Confidence Intervals for the C_{max}, AUC_{last}, AUC_{inf}, and AUC_{72} are completely contained within the prespecified limits of 80% to 125%. There were no deaths or serious adverse events that led to withdrawal of treatment during the conduct of the study.

Table 1

Table 1: Statistical Assessment of Bioequivalence of Isavuconazonium Sulfate IV Solution via NG Tube (Test Formulation) Compared to Isavuconazonium Sulfate Oral Capsules (Reference Formulation)

Parameter	Isavuconazonium Sulfate IV Solution via NG Tube (Test Formulation)		Isavuconazonium Sulfate PO Capsules (Reference)		Geometric LS Mean Ratio (%)†	90% CI of Ratio†
	n	Geometric LS Means	n	Geometric LS Means		
AUC_{inf} (mg*hr/L)	12	90.30	12	91.00	99.3	(92.70, 106.29)
AUC_{last} (mg*hr/L)	13	81.40	13	83.40	97.6	(92.37, 103.13)
AUC_{72} (mg*hr/L)	13	34.00	13	34.70	97.8	(92.67, 103.24)
C_{max} (ng/mL)	13	2230	13	2120	105.3	(89.25, 124.33)

†Ratios and confidence limits are transformed back to raw scale and values are expressed as percentages.

Conclusion. The study met its primary endpoint of bioequivalence between the two routes of administration in this population. Both routes of administration are well tolerated.

Reference 1

References:

1. Pille, S., and D. Bohmer. 1998. Options for artificial nutrition of cancer patients. Strahlenther. Onkol. 174:52-55

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1321. Population Pharmacokinetic (PK) and Pharmacokinetic/Pharmacodynamic (PK/PD) Target Attainment Analyses for Dalbavancin in Pediatric Patients

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Session: P-59. PK/PD studies

Background. Dalbavancin is a lipoglycopeptide approved for treating adults with acute bacterial skin and skin structure infections (ABSSSI). It has a terminal half-life of >14 days, which allows for administration as a single-dose regimen. Pediatric studies for dalbavancin include three phase 1 studies and a phase 3 study in patients from birth to 17 years with ABSSSI or neonatal sepsis.

Methods. A population PK model was developed using 1124 concentrations from 211 pediatric patients. Allometric scaling of clearance, and volume parameters was included with exponents fixed at 0.75 and 1, respectively. Based on exploratory analysis and prior knowledge, serum albumin was included as a covariate on all PK parameters, and creatinine clearance or estimated glomerular filtration rate (eGFR) was included as a covariate on clearance. eGFR for patients < 2 years accounted for renal maturation. Additional covariates were assessed by stepwise covariate modeling (SCM). The final model was qualified by visual predictive checks (VPCs) and bootstrapping and