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 (90th 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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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/1.73m², 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-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/m², 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

Renal Function Group (eGFR range [mL/min])	Taniborbactam		Cefepime	
	AUC(0-inf) (h*μg/mL) Mean (SD)	CL (L/h) Mean (SD)	AUC(0-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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