Support)**Hoffmann-La Roche** (Grant/Research Support)**Horizon Orphan LLC** (Grant/Research Support)**ICPD Biosciences, LLC** (Grant/Research Support, Other Financial or Material Support, member/owner)**Indalo Therapeutics** (Grant/Research Support)**Insmed Inc.** (Grant/Research Support)**Institute for Clinical Pharmacodynamics** (Employee)**Iterum** (Grant/Research Support)**KBP Biosciences USA** (Grant/Research Support)**Kyoto Biopharma, Inc.** (Grant/Research Support)**Matinas** (Grant/Research Support)**Meiji Seika Pharma Co., Ltd.** (Grant/Research Support)**Melinta Therapeutics** (Grant/Research Support)**Menarini Ricerche S.p.A.** (Grant/Research Support)**Merck & Co., Inc** (Grant/Research Support)**Mutabilis** (Grant/Research Support)**Nabriva Therapeutics AG** (Grant/Research Support)**Naeja-RGM Pharmaceuticals** (Grant/Research Support)**Nosopharm SAS** (Grant/Research Support)**Novartis Pharmaceuticals Corp.** (Grant/Research Support)**NuCana Biomed** (Grant/Research Support)**Paratek Pharmaceuticals, Inc.** (Grant/Research Support)**Polyphor, Ltd.** (Grant/Research Support)**Prothena Corporation** (Grant/Research Support)**PTC Therapeutics** (Grant/Research Support)**Rempex Pharmaceuticals** (Grant/Research Support)**Roche TCRC** (Grant/Research Support)**Sagimet** (Grant/Research Support)**scPharmaceuticals Inc.** (Grant/Research Support)**Scynexis** (Grant/Research Support)**Spero Therapeutics** (Grant/Research Support)**TauRx Therapeutics** (Grant/Research Support)**Tetraphase Pharmaceuticals** (Grant/Research Support)**Theravance Biopharma Pharmaceutica** (Grant/Research Support)**USCAST** (Grant/Research Support)**VenatoRx** (Grant/Research Support)**Vical Incorporated** (Grant/Research Support)**Wockhardt Bio AG** (Grant/Research Support)**Zavante Therapeutics** (Grant/Research Support)**Zogenix International** (Grant/Research Support)

1106. Evaluation of Penetration of Cefiderocol into Cerebrospinal Fluid Using a Rat Meningitis Model

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Session: P-62. PK/PD Studies

Background. Central nervous system (CNS) infections caused by Gram-negative bacteria (GNB) are sometimes hard to treat due to antibiotic resistance and difficulty with penetration into cerebrospinal fluid (CSF). Cefiderocol (CFDC) which was approved by the FDA and the EMA in 2019 to 2020 is a siderophore cephalosporin with potent activity against various GNB including carbapenem-resistant strains. In this study, we evaluated the penetration of CFDC into CSF using a rat meningitis model.

Methods. To induce meningitis, the anesthetized immunocompetent rats were infected by intracisternal inoculation of a bacterial suspension of 8.7×10^1 CFU of *E. coli* SR200138. 200 mg/kg or 50 mg/kg of CFDC was administered via tail vein bolus injection to uninfected rats (n=4/sampling point) and rats with meningitis (n=4/sampling point) 24 hours after infection. CSF was collected by cisternal puncture and blood was collected from heart. The samplings were performed 0.25, 0.5, 1, 3, and 5 hours after dosing. The concentrations of CFDC in plasma and CSF for individuals were determined by LC/MS/MS. PK parameters for the average values in plasma and CSF were calculated.

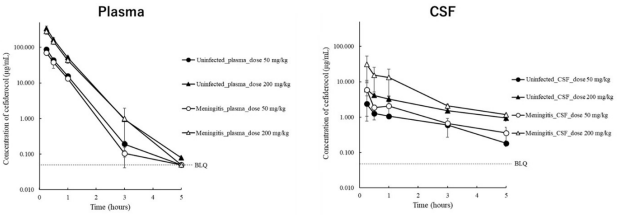
Results. CFDC concentration and the PK parameters are shown in Figure and Table, respectively. The penetration of CFDC from plasma to CSF was observed in both uninfected and meningitis groups, and the penetration rates increased in the rats withs meningitis (AUC_{CSF}/AUC_{plasma}: 0.149-0.183) compared with the uninfected rats (AUC_{CSF}/AUC_{plasma}: 0.0508-0.0588). The penetration rates of CFDC in the meningitis were comparable to those of piperacillin, cefepime, and meropenem in human (0.32, 0.103, and 0.39 in strongly inflamed meninges, respectively) [1]. In both groups, elimination of CFDC from CSF was slower compared with that from plasma as seen with other β-lactam antibiotics such as meropenem, suggesting that $T_{>MIC}$, an indicator that correlates with the efficacy of β-lactams, may be higher in CSF [2].

Table. PK Parameters of Cefiderocol after Intravenous Bolus Administration in Uninfected Rats and Rats with Meningitis

Pharmacokinetic parameters	Sample	Uninfected		Meningitis	
		50 mg/kg[a]	200 mg/kg[a]	50 mg/kg[a]	200 mg/kg[a]
C_{max} (μg/mL)	Plasma	88.0	339	70.3	280
$t_{1/2,z}$ (hr)		0.317	0.427	0.292	0.353
$AUC_{0\text{-}inf}$ (hr·μg/mL)		80.4	301	64.9	248
C_{max} (μg/mL)	CSF	2.36	6.09	5.97	31.2
$t_{1/2,z}$ (hr)		1.57	2.24	1.58	1.14
$AUC_{0\text{-}inf}$ (hr·μg/mL)		4.73	15.3	9.66	45.4
AUC ratio		0.0588	0.0508	0.149	0.183

Animal: Crl:CD(SD) rat, male; n = 3 or 4 for each sampling point in each treatment group
Infection: intracisternal inoculation (challenge dose: 8.7×10^1 CFU/rat)
Dose: bolus administration into tail vein; 24 hours after infection for meningitis group
Sampling point after dosing: 0.25, 0.5, 1, 3, and 5 hours
a: Dose of cefiderocol as free base

Figure. Concentrations of Cefiderocol after Intravenous Bolus Administration in Uninfected Rats and Rats with Meningitis



Animal: Crl:CD(SD) rat, male; n = 3 or 4 for each sampling point in each treatment group
Infection: intracisternal inoculation (challenge dose: 8.7×10^1 CFU/rat)
Dose: bolus administration into tail vein; 24 hours after infection for meningitis group
Sampling point after dosing: 0.25, 0.5, 1, 3, and 5 hours
Concentrations of cefiderocol were represented as mean ± standard deviation concentrations
BLQ means below the lower limit of quantification

Conclusion. It was confirmed that CFDC penetrates into CSF from plasma in a rat model and the penetration rate was increased 3-fold in meningitis.

References.

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1107. Vancomycin AUC Dosing: Is One Concentration in the Hand Worth Two in the Bush?

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Session: P-62. PK/PD Studies

Background. Recent guidelines recommend a transition from trough-based to area-under the curve-based (AUC) monitoring for vancomycin for serious invasive methicillin-resistant *Staphylococcus aureus* infections. Due to the challenges of performing AUC monitoring in clinical practice, this study sought to compare the accuracy of an AUC calculated from two points using trapezoidal calculations and from a single steady-state trough combined with population assumptions.

Methods. This prospective cohort analysis included hospitalized patients with stable renal function from 10.2020 to 12.2020 with two vancomycin concentrations obtained at steady-state during a single dosing interval. For each patient, AUC was calculated via trapezoidal equations utilizing peak and trough concentrations (P/T) and using the trough concentration (T) combined with population volume of distribution. Appropriate concentrations were defined as a peak at least 2 hours after the end of the infusion and a trough within one hour of the next dose. The percent and actual differences were calculated between the P/T and T AUC assessments for each patient. A patient level review was independently conducted by two clinical pharmacists to evaluate if a change in dosing would have been made according to AUC estimation methodology.

Results. Thirty-one patients had appropriate steady-state P/T obtained. Baseline demographics are shown in Table 1 with the majority of patients being overweight with normal renal function. The mean calculated AUC for both groups was similar, P/T 544.8 and T 549.8. The mean and median percent differences were 1.85% and 0.65%, with a standard deviation of 7.3% and an apparent normal distribution (Figure 1, p = 0.94 by Shapiro's test). The median absolute difference in AUC was 25.82 mg*h/L between methodologies. Both methods would have resulted in the same modification to the vancomycin regimen based on patient level chart review.

Table 1. Vancomycin AUC Demographics

Parameter (n=31)	Value
Age, median	59 years
Scr, median (IQR)	1 mg/dL (1.75 to 1.07)
CrCl, median (IQR)	83 mL/min (69.5 to 120)
BMI, median (IQR)	28.16 kg/m² (25.3 to 34.5)
Mean % difference in AUC* (SD)	1.85% (7.3)
Median % difference in AUC*(IQR)	0.65% (-3.8 to 8.2)
Mean absolute difference in AUC* (SD)	30.85 mg*h/L (24.4)
Median absolute difference in AUC* (IQR)	25.82 mg*h/L (16.7 to 42.2)
Trough values, mean (SD)	14.3 mg/L (5.9)

* Trough-only vs. two level
AUC: area under the curve, BMI: body mass index, CrCl: creatinine clearance, IQR: interquartile range, Scr: serum creatinine, SD: standard deviation