OS117: 17:30-18:30 (20 April)
PK/PD-based antimicrobial dosing optimisation in children

【O0812】

Population pharmacokinetic/pharmacodynamic analyses of cefiderocol for paediatric patients

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ESCMID Global 2026, 17-21 April 2026, Munich, Germany

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Congress of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID Global) 2026

- Title　Population pharmacokinetic/pharmacodynamic analyses of cefiderocol for paediatric patients
- Affiliation　Shionogi & Co., Ltd.
- Presenters　Daichi Yamaguchi and Takayuki Katsube

Presenters are employees of Shionogi & Co., Ltd.

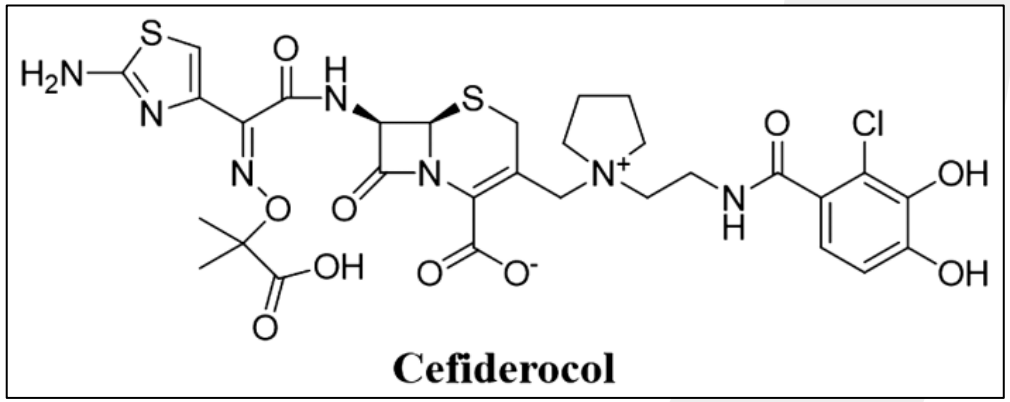
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Cefiderocol

Cefiderocol: parenteral cephalosporin

- Antibacterial activity against Gram-negative bacteria by inhibiting synthesis of bacterial cell walls
- Use for treatment of adult patients with serious Gram-negative bacterial infections
- Approved in the U.S., EU, Japan, and China

Structure of cefiderocol



Sato T, et al. Clin Infect Dis. 2019; 69: S538-S543.

＜ Indication ＞

	Complicated urinary tract infections (cUTI) including pyelonephritis, and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP)
	Infections due to aerobic Gram-negative organisms with limited treatment options
	Infections due to carbapenem-resistant Gram-negative bacteria susceptible to cefiderocol
	cUTI

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PK/PD Profiles of Cefiderocol for Adults

＜ PK profiles ＞

- ✓ Elimination Half-life of 2 to 3 hours (no PK accumulation)
- ✓ Excreted as unchanged cefiderocol through the kidneys
- ✓ 60% protein binding

＜ PD profiles ＞

- ✓ %$fT_{>MIC}$ of 75% required for 1-log bacterial reduction from *in vivo* study
- ✓ High PTA for 75%$fT_{>MIC}$ at the labeled dose regimens against up to MIC of 4 μg/mL

Labeled dose regimens for adult patients			
CLcr (mL/min)	**Dose**	**Dosing interval**	**Infusion time**
≧120	**2000 mg**	6 hours	3 hours
60 to < 120		8 hours	
30 to < 60	**1500 mg**		
15 to < 30	**1000 mg**		
< 15	**750 mg**	12 hours	

%$fT_{>MIC}$; percentages of time for which free drug concentration in plasma exceeds MIC over dosing interval, CLcr; creatinine clearance, PD; pharmacodynamic, PK; pharmacokinetic, MIC; minimum inhibitory concentration, PTA; probability of target attainment.

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Objectives

01 **To develop population PK model using data from paediatric patients**

02 **To conduct PK/PD analyses to support the dose regimen**

3 months to < 18 years: Dose regimens adjusted based on **body weight** and **renal function**
Birth to < 3 months: Dose regimens adjusted based on **age** and **body weight**

Age	3 months to < 18 years				Birth to < 3 months			
Dose regimen	eGFR ($mL/min/1.73m^2$)	Dosing interval	WT		PNA (months)	Dosing interval	GA	
			≧ 34 kg	< 34 kg			≧ 32 weeks	< 32 weeks
	≧ 60	**8 hours**	**2000 mg**	**60 mg/kg**	0 to < 2	**8 hours**	**40 mg/kg**	**30 mg/kg**
	30 to < 60	**8 hours**	**1500 mg**	**45 mg/kg**	2 to < 3	**8 hours**	**60 mg/kg**	**40 mg/kg**
	15 to < 30	**8 hours**	**1000 mg**	**30 mg/kg**				
	< 15	**12 hours**	**750 mg**	**22.5 mg/kg**				

eGFR; body-surface-area-adjusted estimated glomerular filtration rate, GA; gestational age, PD; pharmacodynamic, PK; pharmacokinetic, PNA; postnatal age, WT; body weight.

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Clinical Studies for Paediatric Patients

Target	3 months to < 18 years			Birth to < 3 months		
Study	APEKS-PEDI study, PEDI-CEFI study			NEO-CEFI study		
Cohort	No	Age		No	PNA	GA
	1	12 o < 18 years		1	28 days to < 3 months	≧ 37 weeks
	2	6 to < 12 years		2	0 to < 28 days	≧ 7 weeks
	3	2 to < 6 years		3	≧ 14 days	32 to < 37 weeks
	4	3 months to < 2 years		4	0 to < 14 days	32 to < 37 weeks
				5	≧ 14 days	26 to < 32 weeks
				6	0 to < 14 days	26 to < 32 weeks
Infusion-length	3 hours			1 or 3 hours		
Sampling points	Cohorts 1/2: 1, 3, 3.5, 5, 8 hours Cohorts 3/4: 3, 5, 8 hours			End of infusion (1 hour or 3 hours) End of dosing period (8 hours)		
Dose	eGFR (mL/min/1.73m^2)	WT ≧ 34 kg	WT < 34 kg	PNA	GA ≧ 32 weeks	GA < 32 weeks
	≧ 60	2000 mg	60 mg/kg	0 to < 2 months	40 mg/kg	30 mg/kg
	30 to < 60	1500 mg	45 mg/kg	2 to < 3 months	60 mg/kg	40 mg/kg
	15 to < 30	1000 mg	30 mg/kg			

eGFR; body-surface-area-adjusted estimated glomerular filtration rate, GA; gestational age, PNA; postnatal age, WT; body weight.

Analysis Population

Background characteristics	3 months to < 18 years (N = 121)		Birth to < 3 months (N =29)	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)
Body weight (kg)	23.8 (17.6)	18.6 (4.9 - 83.4)	2.1 (1.0)	1.9 (1.0 - 4.5)
BSA (m^2)	0.84 (0.43)	0.75 (0.27 - 2.00)	0.16 (0.05)	0.15 (0.10 - 0.26)
Age (years)	6.5 (5.1)	6 (0 - 18)	0.0 (0.0)	0 (0 - 0)
Age (months)	77.5 (61.0)	66.0 (3.0 - 212.0)	0.5 (0.5)	0.3 (0.1 - 2.0)
GA (weeks)	-	-	33.7 (4.8)	32 (26 - 41)
eGFR (mL/min/1.73 m^2)	111.0 (54.0)	98.2 (27.3 - 469.3)	36.7 (22.2)	29.6 (11.1 - 121.5)
Albumin (g/dL)	3.9 (0.6)	3.9 (2.5 - 5.8)	3.2 (0.5)	3.3 (2.4 - 4.2)
Aspartate aminotransferase (U/L)	30.1 (22.4)	25.0 (9.0 - 150.0)	42.0 (28.0)	32.4 (12.0 - 119.6)
Alanine aminotransferase (U/L)	24.9 (28.1)	16.0 (2.4 - 183.0)	30.1 (67.2)	11.0 (1.6 - 366.1)
Total bilirubin (mg/dL)	30.74 (123.52)	0.46 (0.14 - 836.26)	5.74 (4.98)	4.48 (0.18 - 16.56)
Sex (male : female)[a]	46 (38.0%) : 75 (62.0%)		15 (51.7%) : 14 (48.3%)	
Race (White : non-White)[a]	109 (90.1%) : 12 (9.9%)		2 (6.9%) : 27 (93.1%)	
(Asian : White : Black or African American : native American or Alaska native : others)[a]	8 (6.6%) : 109 (90.1%) : 3 (2.5%) : 0 (0.0%) : 1 (0.8%)		7 (24.1%) : 2 (6.9%) : 17 (58.6%) : 0 (0.0%) : 3 (10.3%)	
Disease status (no infection : cUTI/AUP : HAP/VAP/HCAP : BSI/Sepsis : cIAI : others)[a]	0 (0.0%) : 76 (62.8%) : 8 (6.6%) : 7 (5.8%) : 25 (20.7%) : 5 (4.1%)		0 (0.0%) : 0 (0.0%) : 6 (20.7%) : 6 (20.7%) : 4 (13.8%) : 13 (44.8%)	

a Number of subjects (percentage of all subjects).

AUP; acute uncomplicated pyelonephritis, BSA; body surface area, BSI; bloodstream infection, cIAI; complicated intra-abdominal infections, cUTI; complicated urinary tract infection, eGFR; body-surface-area-adjusted estimated glomerular filtration rate, GA; gestational age, HAP/VAP/HCAP; hospitalacquired pneumonia/ventilator-associated pneumonia/healthcare-associated pneumonia.

Methods

＜ Analysis workflow ＞

1. Population PK analysis

- ✓ Population PK model of cefiderocol was updated including paediatric patients based on **the model for adults**
- ✓ The impacts of patients' backgrounds on PK were assessed

Kawaguchi N, et al. *AAC*. 2021; 65: e01437-20.

2. PK/PD analysis

- ✓ Paediatric plasma cefiderocol profiles were estimated using individual post-hoc PK parameters
- ✓ %$fT_{>MIC}$ in each paediatric patients were calculated

3. Monte-Carlo simulations

- ✓ PTA for 75%$fT_{>MIC}$ at steady state in 5000 virtual paediatric patients for each scenario was calculated
- ✓ Various renal function (eGFR: 5 to 200 mL/min/1.73m^2) and various age group were simulated

＜ Data ＞

666 subjects, 3961 concentration data

＜ Software ＞

NONMEM ver.7.4.4.

Category	N (subjects)	N (plasma concentration)
Adult subjects	516	3427
3 months to < 18 years	121	474
Birth to < 3 months	29	60
Overall	666	3961

eGFR; body-surface-area-adjusted estimated glomerular filtration rate, MIC; minimum inhibitory concentration, PD; pharmacodynamic, PK; pharmacokinetic, PTA; probability of target attainment.

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Population PK Model including Paediatric Patients

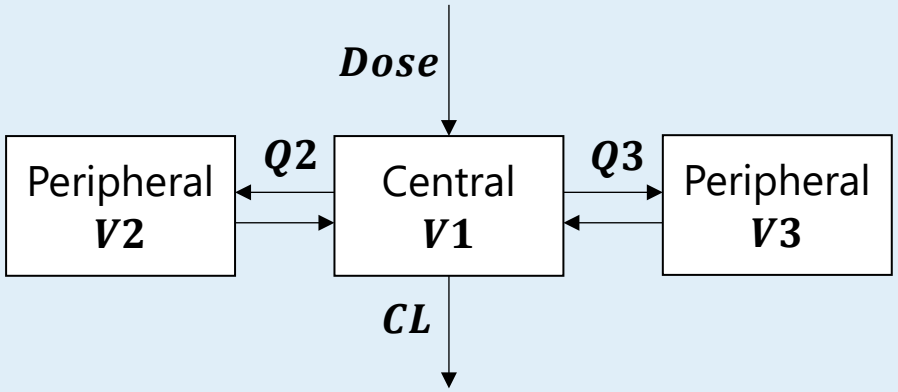
$$CL_{(L/hr)} = 4.44 \times \left(\frac{\boldsymbol{eGFR}}{79.0}\right)^{0.611} \times \left(\frac{\boldsymbol{WT}}{68.0}\right)^{0.713} \times 1.20^{cUTI} \times 0.853^{HAP/VAP/HCAP} \times 0.903^{BSI/sepsis} \times 1.32^{cIAI}$$

If eGFR > 150 mL/min/1.73m^2, eGFR was fixed as 150 mL/min/1.73m^2.

$$V1_{(L)} = 7.28 \times \left(\frac{\boldsymbol{WT}}{68.0}\right)^{0.795} \times 1.48^{infection}$$

$$Q2_{(L/hr)} = 5.91 \qquad Q3_{(L/hr)} = 0.103$$

$$V2_{(L)} = 5.58 \times \left(\frac{\boldsymbol{WT}}{68.0}\right)^{0.795} \qquad V3_{(L)} = 0.712$$



- ✓ Cefiderocol plasma concentrations were described by 3-compartmental model
- ✓ eGFR and body weight were influential factors on cefiderocol PK, as expected

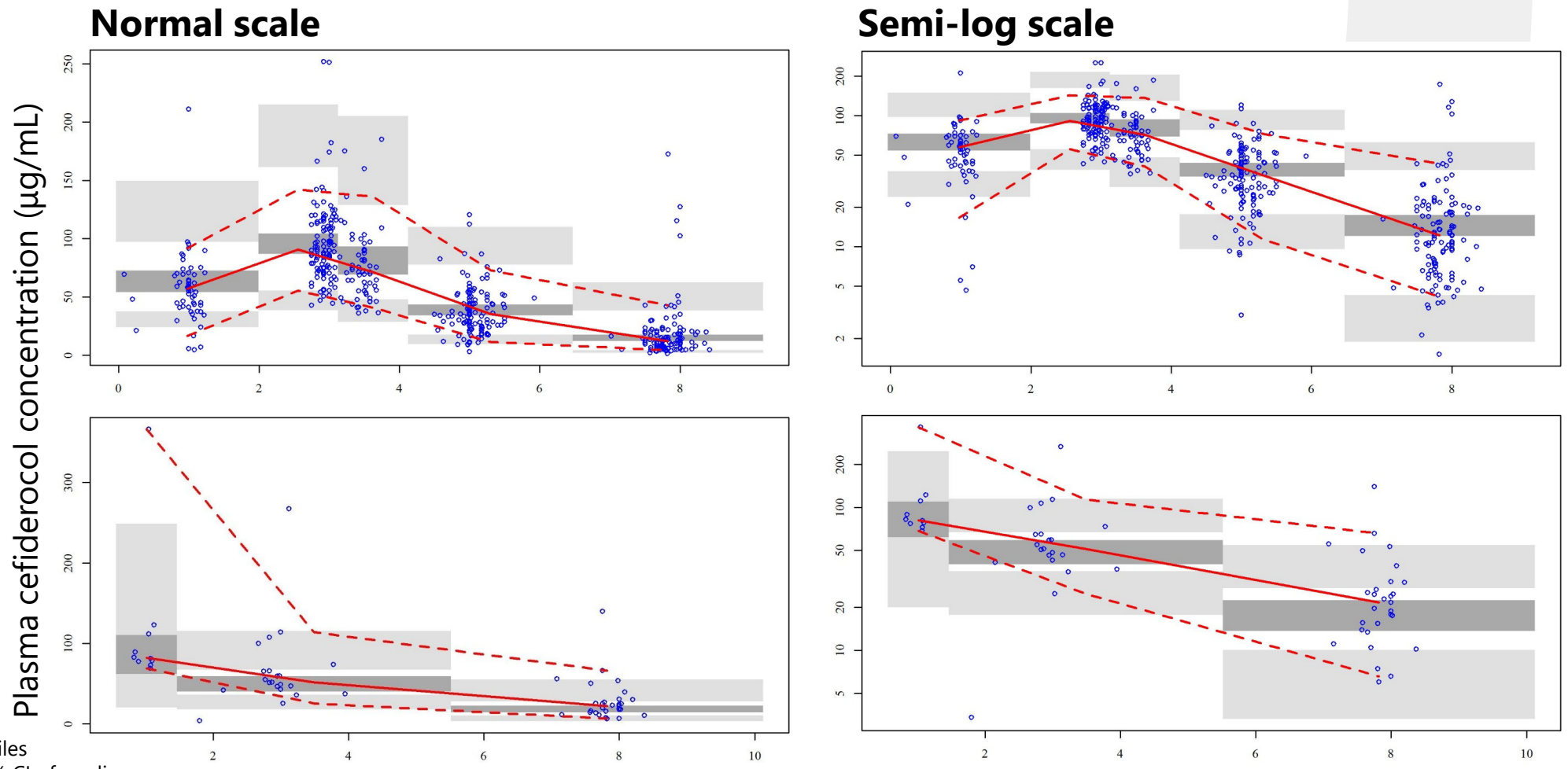
BSI/sepsis; patients with bloodstream infection or sepsis, cIAI; complicated intra-abdominal infections, CL; clearance, cUTI; complicated urinary tract infections, eGFR; body-surface-area-adjusted estimated glomerular filtration rate, HAP/VAP/HCAP; hospitalacquired pneumonia/ventilator-associated pneumonia/healthcare-associated pneumonia, PK; pharmacokinetic, Q2/Q3; intercompartmental clearance, V1/V2/V3; volume of distribution in the central or peripheral compartments, WT; body weight.

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Prediction-corrected Visual Predictive Check

3 months to < 18 years

Birth to < 3 months

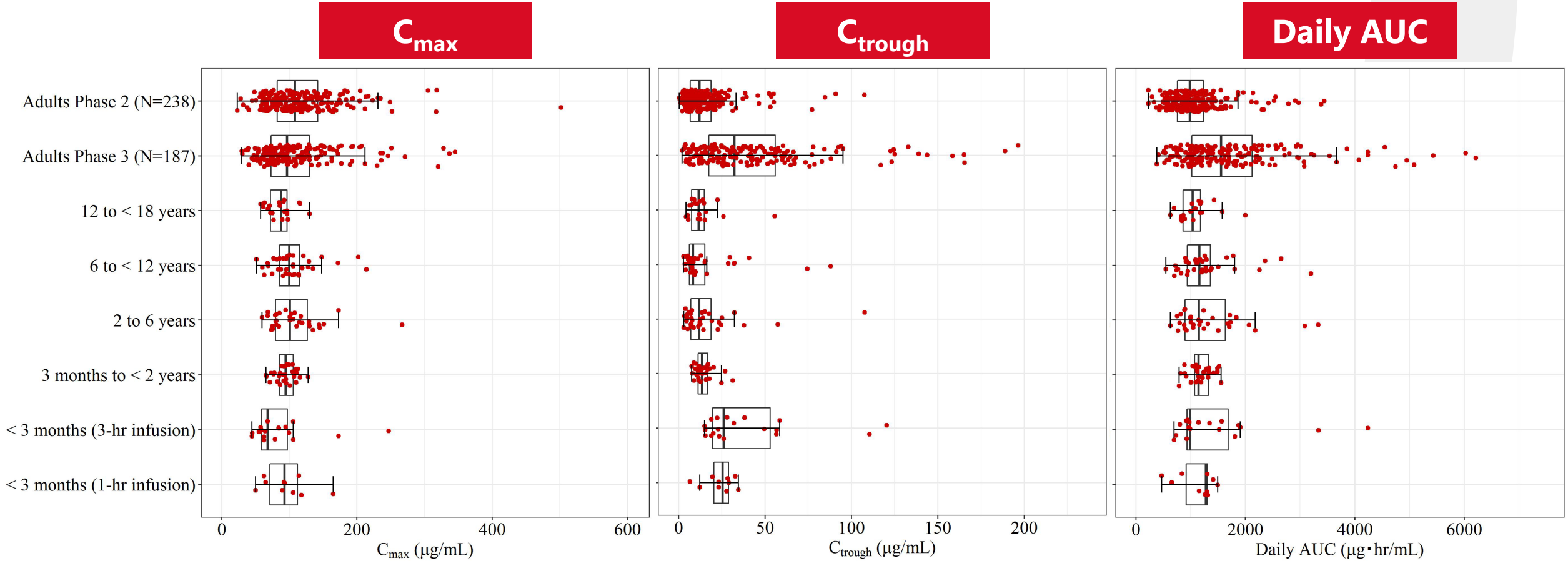


Solid line: observed median
dashed line: observed 5/95th percentiles
Dark grey shaded area: predicted 95% CI of median
Grey shaded area: predicted 95% CIs of 5/95th percentiles

✓ Population PK model adequately described the observed plasma concentration data in paediatric patients

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Post-hoc Individual Exposures at Steady State (q8h)



- ✓ C_{max}, C_{trough}, and daily AUC at steady state in paediatric patients were similar among the age groups
- ✓ Exposures (C_{max}, C_{trough}, and daily AUC) in paediatric patients overlapped those in adult patients

AUC; area under the concentration-time curve, C_{max}; maximum concentration, C_{trough}; concentration at trough (8 hours).

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%$fT_{>MIC}$ and PTA in Enrolled Paediatric Patients

%$fT_{>MIC}$ (MIC = 4 µg/mL)			PTA
Age range	**N**	**Median (range)**	**75%$fT_{>4}$**
12 to < 18 years	20	100 (75.8 - 100)	100
6 to < 12 years	36	95.4 (69.6 - 100)	97.2
2 to < 6 years	34	100 (71.4 - 100)	94.1
3 months to < 2 years	31	100 (91.3 - 100)	100
< 3 months (3-hr infusion)	19	100 (100 - 100)	100
< 3 months (1-hr infusion)	10	100 (73.9 - 100)	90.0

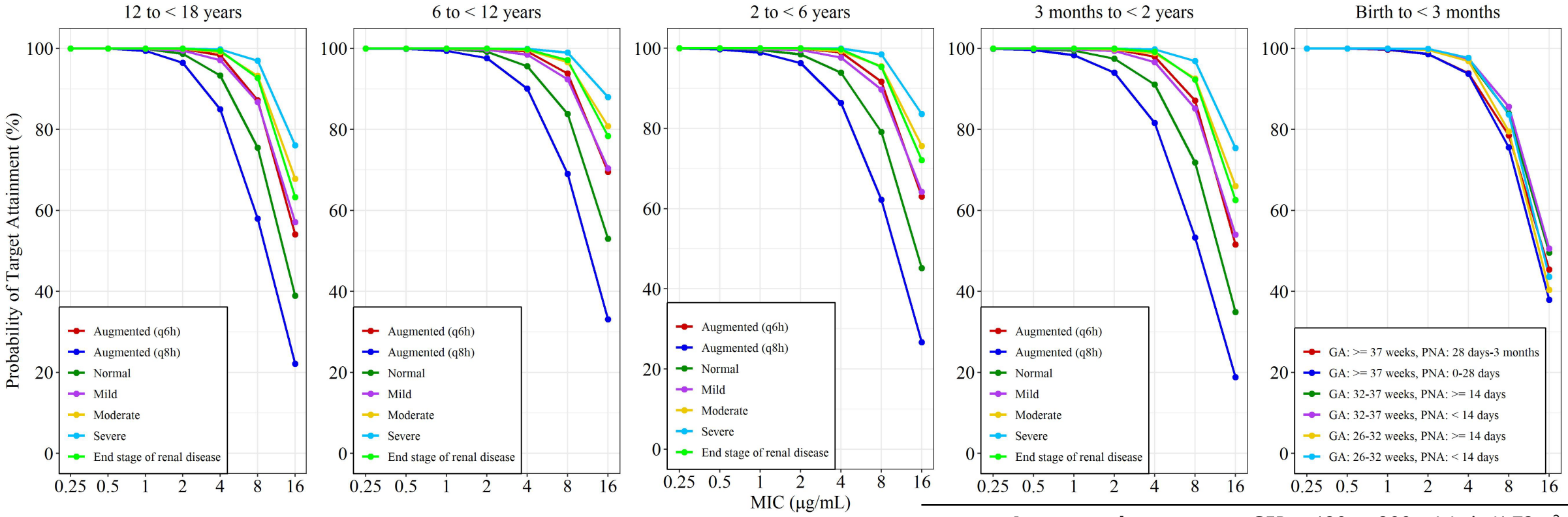
✓ Median %$fT_{>4}$ was 95.4% or 100% in the age groups

✓ The PTA for 75%$fT_{>MIC}$ was >90% against a MIC of 4 µg/mL in enrolled paediatric patients

%$fT_{>MIC}$; percentages of time for which free drug concentration in plasma exceeds MIC over dosing interval, MIC; minimum inhibitory concentration, PTA; probability of target attainment.

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PTA for 75%$fT_{>MIC}$ in Simulated Paediatric patients



Augmented	eGFR = 120 to 200 mL/min/1.73m^2
Normal	eGFR = 90 to < 120 mL/min/1.73m^2
Mild	eGFR = 60 to < 90 mL/min/1.73m^2
Moderate	eGFR = 30 to < 60 mL/min/1.73m^2
Severe	eGFR = 15 to < 30 mL/min/1.73m^2
End stage of renal disease	eGFR = 5 to < 15 mL/min/1.73m^2

✓ The PTA for 75%$fT_{>MIC}$ was ≧ 82% in all age groups and renal function groups against a MIC of 4 μg/mL

%$fT_{>MIC}$; percentages of time for which free drug concentration in plasma exceeds MIC over dosing interval, MIC; minimum inhibitory concentration, PTA; probability of target attainment.

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Conclusion

- Cefiderocol plasma concentrations were described by 3-compartmental model
  - ✓ eGFR and body weight were influential factors on cefiderocol PK, as expected
  - ✓ C_{max}, C_{trough}, and daily AUC at steady state were similar among paediatric and adult patients
- The PTA for 75%$fT_{>MIC}$ was high against MICs ≦4 μg/mL in enrolled or simulated paediatric patients
- The population PK and PK/PD analyses supports the dose regimens

Age	**3 months to < 18 years**				**Birth to < 3 months**			
Dose regimen	eGFR (mL/min/1.73m^2)	Dosing interval	WT		PNA (months)	Dosing interval	GA	
			≧ 34 kg	< 34 kg			≧ 32 weeks	< 32 weeks
	≧ 60	**8 hours**	**2000 mg**	**60 mg/kg**	0 to < 2	**8 hours**	**40 mg/kg**	**30 mg/kg**
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	15 to < 30	**8 hours**	**1000 mg**	**30 mg/kg**				
	< 15	**12 hours**	**750 mg**	**22.5 mg/kg**				

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End of Slides

Thank you for your attention!

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