SUPPLEMENTAL MATERIAL

Supplemental Table S1 Summary of animal infection model studies for evaluation of $T_{f>MIC}$

Infection model	Strain	MIC (μg/mL)	$T_{f>MIC}$		Reference
			Static effect	1 log reduction	
Murine thigh infection model[a]	*P. aeruginosa* SR27016[b]	0.25[c]	53.4%[d,e,f]	63.3%[d,e,f] 74.2% (2 log reduction)[d,e,f]	1
Murine lung infection model[g]	*P. aeruginosa* strains[h]	0.5 to 8[k]	43.5%[d,f,l]	68.5%[d,f,l]	2
	A. baumanni strains[i]	0.125 to 2[k]	68.6%[d,f,l]	76.2%[d,f,l]	
	K. pneumoniae strains[j]	0.063 to 16[k]	59.1%[d,f,l]	77.9%[d,f,l]	
Murine thigh infection model[a]	*P. aeruginosa* SR27001[m]	8[k]	41.7%[d,f,l]	54.2%[d,f,l]	3
	K. pneumoniae strains[n]	0.125 to 16[k]	71.0%[d,f,l]	80.0%[d,f,l]	
	E. coli strains[o]	0.125 to 2[k]	44.7%[d,f,l]	54.0%[d,f,l]	

[a] The male mice (5-week-old, Jcl: ICR mouse) were rendered neutropenic by intraperitoneal infection of cyclophosphamide with 150 and 100 mg/kg at 4 and 1 days before infection, respectively. Anesthetized mice were infected by intramuscular injection of bacterial suspension into thigh (n=3 to 5). Inoculation volume was 0.1 mL per site (10^5 to 10^6 CFU/mouse).

[b] A cephem susceptible strain. [c] MIC was measured using CAMHB supplemented with 20 μM of apo-transferrin, i.e., iron deficient medium.

[d] Single-dose serum PK studies were performed in the murine infection models. The dosing solution was subcutaneously administered to mice at 2 hours after infection. Plasma concentrations of cefiderocol were determined by LC/MS/MS.

[e] In the PD studies, the administration of cefiderocol was initiated at 2 hours after infection. The total daily dose of cefiderocol was given as one dose in 24 hours, two equally divided doses every 12 hours, four equally divided doses every 6 hours, and eight equally divided doses every 3 hours, respectively. The vehicle control groups were given 0.9% saline.

[f] In the PD studies, mice were dissected to take out tissue at 26 hours after infection. The samples were homogenized with MHB and the homogenates were serially diluted and incorporated into Drigalski improved medium. The plates were incubated at 37°C for 20 to 72 houurs and the number of colonies was counted.

[g] The male mice (5-week-old, Jcl: ICR mouse) were rendered neutropenic by intraperitoneal infection of cyclophosphamide with 150 and 100 mg/kg at 4

and 1 days before infection, respectively. Anesthetized mice were infected by intranasal instillation of bacterial suspension into thigh (n=3 to 5). Inoculation volume was 0.07 mL per site (10^5 to 10^6 CFU/mouse). For *A. baumannii* and carbapenem resistant *K. pneumoniae*, the inoculum was prepared with 5% gastric muchin to the desired concentration (bacteria:mucin=1:9).

[h] Four strains including multidrug-resistant (MDR) *P. aeruginosa* (MDRP). [i] Six strains including MDR *A. baumannii*.

[j] Three carbapenem resistant strains producing NDM-1, KPC-2 or OXA-48.

[k] MIC was measured using Chelex-treated Iso-sensitest broth (ISB), i.e., iron deficient medium. One hundred grams of Chelex was added to 1 L of autoclaved medium and stirred at 4 °C for over-night. The incubated medium was filtered with 0.2 μm filter, and pH was adjusted to 7.2 to 7.4. The filtered medium was supplemented with 20 to 25 mg/L $CaCl_2$, 10.0 to 12.5 mg/L $MgCl_2$ and 10 μM $ZnSO_4$.

[l] In the PD studies, the administration of cefiderocol was initiated at 2 hours after infection and repeated at regular intervals of every 3 hours subsutaneously.

[m] A strain of MDRP. [n] Nine strains producing NDM or KPC including ESBL producer and carbapenem resistant strains. [o] Two strains.

Supplemental Table S2 Summary of clinical study designs

Study	Dose regimen	Subjects	PK sampling
Single- and multiple-ascending dose study	Single dose: 100, 250, 500, 1000 and 2000 mg single infusion over 1 hour	8 subjects per dose group (active 6, placebo 2)	Plasma: pre-dose, 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours from the start of the infusion Urine: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 and 24-48 hours from the start of the infusion
	Multiple dose: 1000 and 2000 mg infusion over 1 hour for 10 days (consist of single dose on Day 1 and Day 10, and q8h from Day 2 to Day 9, total 26 times)	10 subjects per dose group (active 8, placebo 2)	Plasma: Day 1 (morning dose: first dose): pre-dose, 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 16 hours Days 2, 3, 5, 8 and 9 (each morning dose): pre-dose Day 10 (morning dose: last dose): pre-dose, 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours from the start of the infusion Urine: Day 1 (morning dose: first dose): 0-8 and 8-24 hours from the start of the first infusion Day 10 (morning dose: last dose): 0-8 and 8-24 hours from the start of the last infusion
Renal impairment study	1000 mg single infusion over 1 hour	Cohorts 1 to 5 (normal/mild/moderate/severe/ESRD requiring hemodialysis): 8 subjects per cohort (6 subjects in severe, 8 subjects in other 4 cohorts)	Plasma: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours from the start of the infusion Dialysate: 2-3, 3-4, 4-5, 5-6 from the start of the infusion (nominally, 4-hr hemodialysis started at 2 hours after the start of the infusion)

The summary was based on the protocol for the clinical studies presented in the references (4, 5).

ESRD: end stage of renal disease.

Supplemental Table S3 Summary of PK parameters in clinical studies

(a) Single- and multiple-ascending dose study

PK parameter	Single dose group				
	100 mg (N=6)	250 mg (N=6)	500 mg (N=6)	1000 mg (N=6)	2000 mg (N=8)
C_{max} (μg/mL)	7.76 (7.8)	18.9 (4.9)	46.6 (10.7)	76.4 (4.6)	156 (7.9)
$AUC_{0\text{-}inf}$ (μg·hr/mL)	17.49 (8.5)	41.94 (6.3)	108.6 (22.7)	168.1 (7.0)	389.7 (9.0)
$t_{1/2}$ (hr)	2.00 (4.4)	1.98 (5.5)	2.12 (15.5)	2.26 (5.8)	2.74 (10.2)
CL (L/hr)	5.72 (8.5)	5.96 (6.3)	4.60 (22.7)	5.95 (7.0)	5.13 (9.0)
f_e (%)	68.4 (3.2)	64.0 (5.4)	65.8 (16.2)	68.3 (6.0)	61.5 (10.6)

PK parameter	Multiple dose group					
	1000 mg		1000 mg (2^{nd})		2000 mg	
N	8	8	8	7[a]	8	8
Day	1	10	1	10	1	10
C_{max} (μg/mL)	72.2 (12.0)	69.8 (13.3)	68.1 (16.2)	72.2 (11.5)	141 (22.7)	153 (12.9)
AUC[b] (μg·hr/mL)	177.4 (10.9)	160.5 (13.5)	172.0 (10.6)	168.6 (11.0)	338.5 (15.5)	366.5 (14.0)
$t_{1/2}$ (hr)	2.37 (11.4)	2.35 (18.5)	2.25 (8.8)	2.19 (4.3)	2.40 (13.2)	2.72 (21.6)
CL (L/hr)	5.64 (10.9)	6.23 (13.5)	5.81 (10.6)	5.93 (11.0)	5.91 (15.5)	5.46 (14.0)
f_e (%)	70.9 (6.7)	70.0 (6.1)	63.8 (12.3)	64.7 (12.8)	67.7 (4.7)	71.4 (5.3)

The summary was based on the results of clinical studies presented in the reference (4).

Geometric mean (CV% Geometric Mean).

C_{max}: maximum plasma concentration. $AUC_{0\text{-}inf}$: area under the plasma concentration-time curve from time zero to infinity. $t_{1/2}$: terminal half-life. CL: total clearance. f_e: fraction of dose excreted unchanged into urine.

[a] N=6 for f_e.

[b] $AUC_{0\text{-}inf}$ for Day1 and AUC over the dosing interval for Day 10.

Supplemental Table S3 (continued)

(b) Renal impairment study

PK parameter	Renal function group					
	Normal (N=8)	Mild (N=8)	Moderate (N=7)	Severe (N=6)	ESRD (w/o HD) (N=8)	ESRD (with HD) (N=8)
C_{max} (μg/mL)	81.0 (27.4)	73.4 (21.3)	78.0 (31.1)	80.1 (19.8)	93.0 (27.8)	75.4 (31.1)
$AUC_{0\text{-}inf}$ (μg·hr/mL)	213.4 (26.5)	218.7 (22.2)	312.3 (38.4)	543.2 (23.6)	880.7 (24.2)	318.1 (20.3)
$t_{1/2}$ (hr)	2.82 (16.5)	2.98 (8.4)	4.13 (12.6)	6.91 (30.6)	9.60 (33.4)	9.45 (32.8)
CL (L/hr)	4.69 (26.5)	4.57 (22.2)	3.20 (38.4)	1.84 (23.6)	1.14 (24.2)	3.14 (20.3)
V_{ss} (L)	13.5 (30.2)	14.8 (17.7)	15.4 (28.7)	16.4 (23.4)	14.2 (22.5)	26.6 (33.5)
Fu	0.420 (12.7)	0.372 (43.5)	0.353 (38.9)	0.360 (31.4)	0.424 (26.6)	0.466 (19.8)

The summary was based on the results of clinical studies presented in the reference (5).

Geometric mean (CV% Geometric Mean).

ESRD: end stage renal disease. w/o HD: without hemodialysis (dosing post hemodialysis). with HD: dosing prior hemodialysis. C_{max}: maximum plasma concentration. $AUC_{0\text{-}inf}$: area under the plasma concentration-time curve from time zero to infinity. $t_{1/2}$: terminal half-life. CL: total clearance. V_{ss}: volume of distribution at steady state. Fu: fraction of drug unbound in plasma.

Supplemental Table S4 Model development process

Model No.	Model description	OBJ	-2l.l.d.	N_{parm}	Reference model
HV model					
1	3-comp model with urine output compartment, combination residual error, and IIV for CL, V1, Q2, V2, Q3, and V3	4688.084	---	17	---
2	2-comp model with urine output compartment, combination residual error, and IIV for CL, V1, Q, and V2	4768.308	80.224	13	1
3	Model #1 without IIV for Q3 and V3	4689.062	0.978	15	1
4	Model #3 with proportional residual error	4691.928	2.866	13	3
5	Model #4 without IIV for Q2 (HV model)	4691.928	0.000	12	4
Covariate model using MDRD-eGFR					
6	3-comp model without urine output compartment and with proportional residual error, and IIV for CL, V1, and V2	3873.678	---	10	---
7	Using linear model for effect of MDRD-eGFR on CL	3684.213	-189.465	11	6
8	Using piece-wise linear model for effect of MDRD-eGFR on CL	3668.895	-204.783	12	6
9	Using power model for effect of MDRD-eGFR on CL	3673.004	-200.674	11	6
10	Using piece-wise linear model with constant for MDRD-eGFR $\geq$ 100 mL/min/1.73 m^2	3669.007	-204.671	11	6
11	Using power model for effects of body weight on V1 and V2 (final MDRD-eGFR model)	3581.534	-87.473	13	10
Incorporation of CG-CrCL instead of MDRD-eGFR					
12	Using linear model for effect of CG-CrCL on CL	3628.224	-245.454	11	6
13	Using piece-wise linear model for effect of CG-CrCL on CL	3604.711	-268.967	12	6
14	Using power model for effect of CG-CrCL on CL	3621.543	-252.135	11	6
15	Using power model for effects of body weight on V1 and V2 (final CG-CrCL model)	3516.484	-88.227	14	13

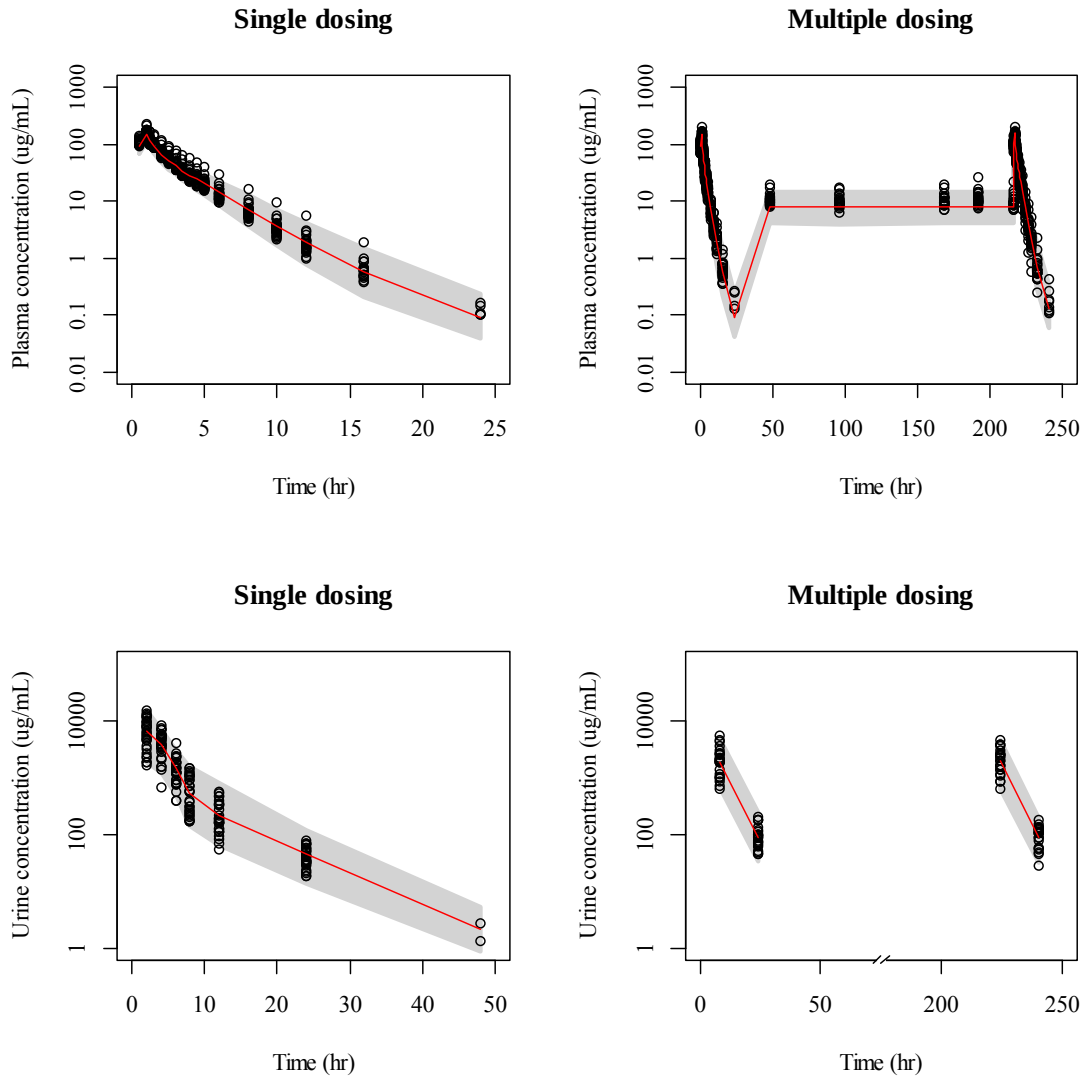
-2.l.l.d.: -2 log likelihood difference. N_{parm}: the number of estimable parameters.

Supplemental Table S5 Summary of MIC to inhibit 50% and 90% of the strains for cefiderocol

Species	Number of strains	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Reference
A. baumannii	104	0.125	2	6
P. aeruginosa	104	≤0.063	1	6
β-lactamase-producing *A. baumannii*	29	0.5	8	6
β-lactamase-producing *P. aeruginosa*	33	0.5	4	6
Enterobacteriaceae	617	≤0.063	0.5	7

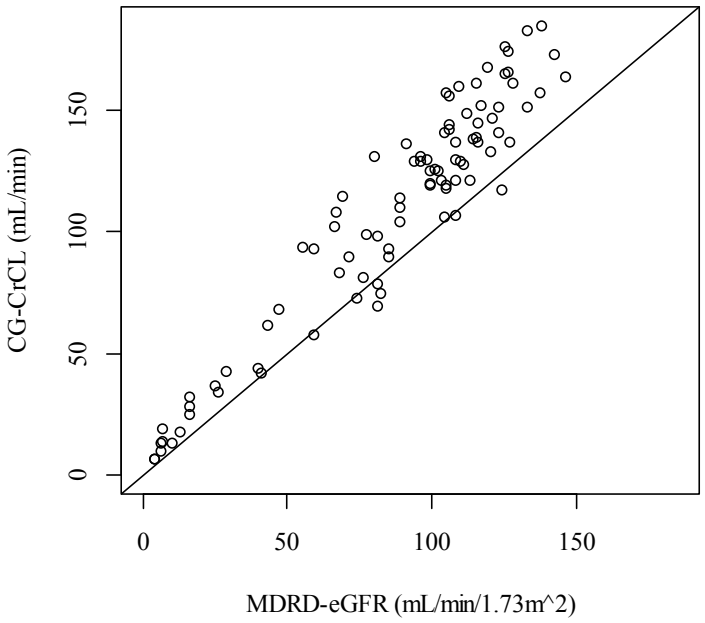
MIC_{50} and MIC_{90}: minimum inhibitory concentration to inhibit 50% and 90% of the strains, respectively.

Supplemental Figure S1 VPC for the PK model developed for healthy subjects



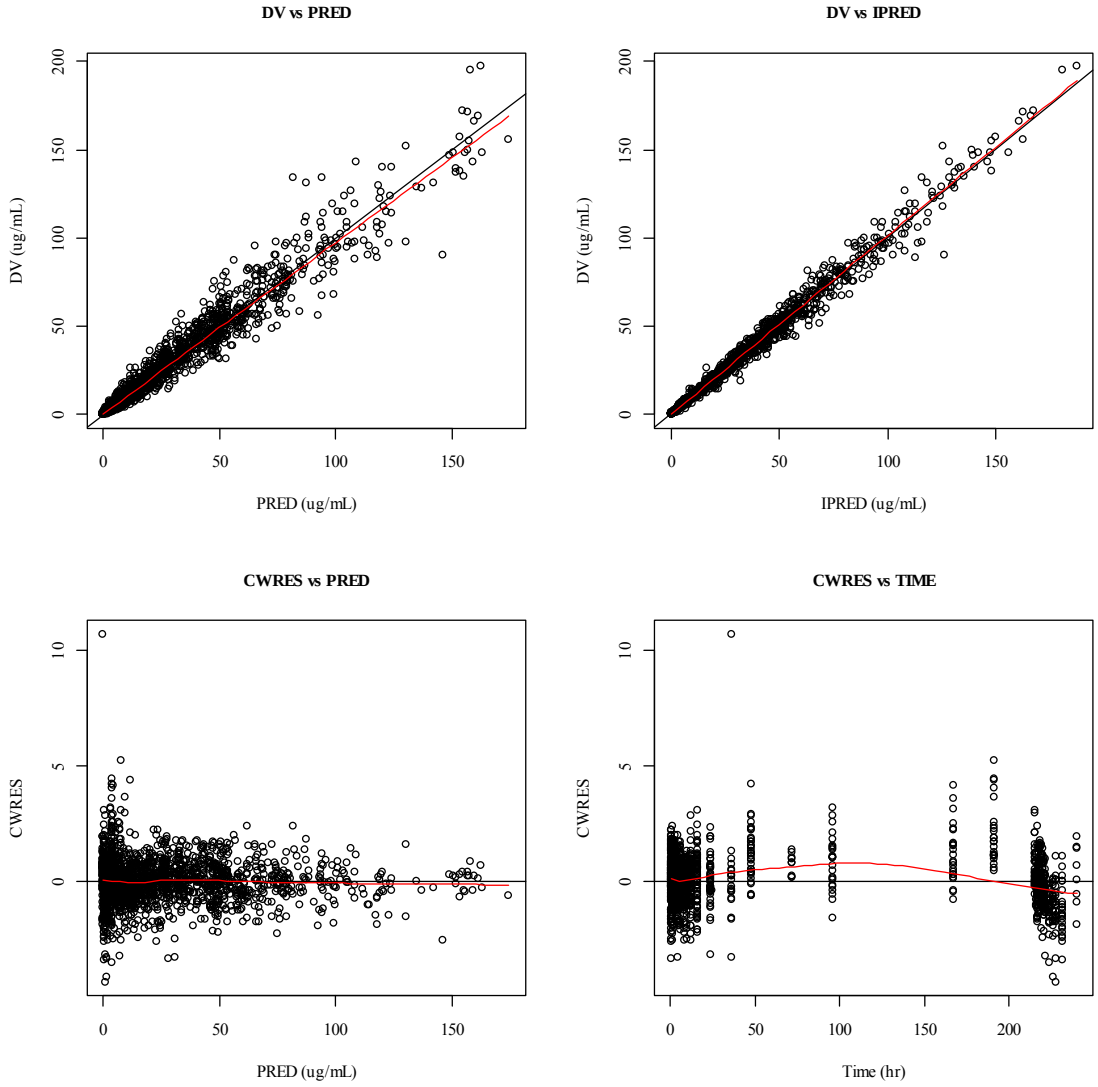
Semi-logarithmic y-axis. Upper figures: plasma data. Lower figures: urine data.

Supplemental Figure S2 Relationships between MDRD-eGFR and CG-CrCL



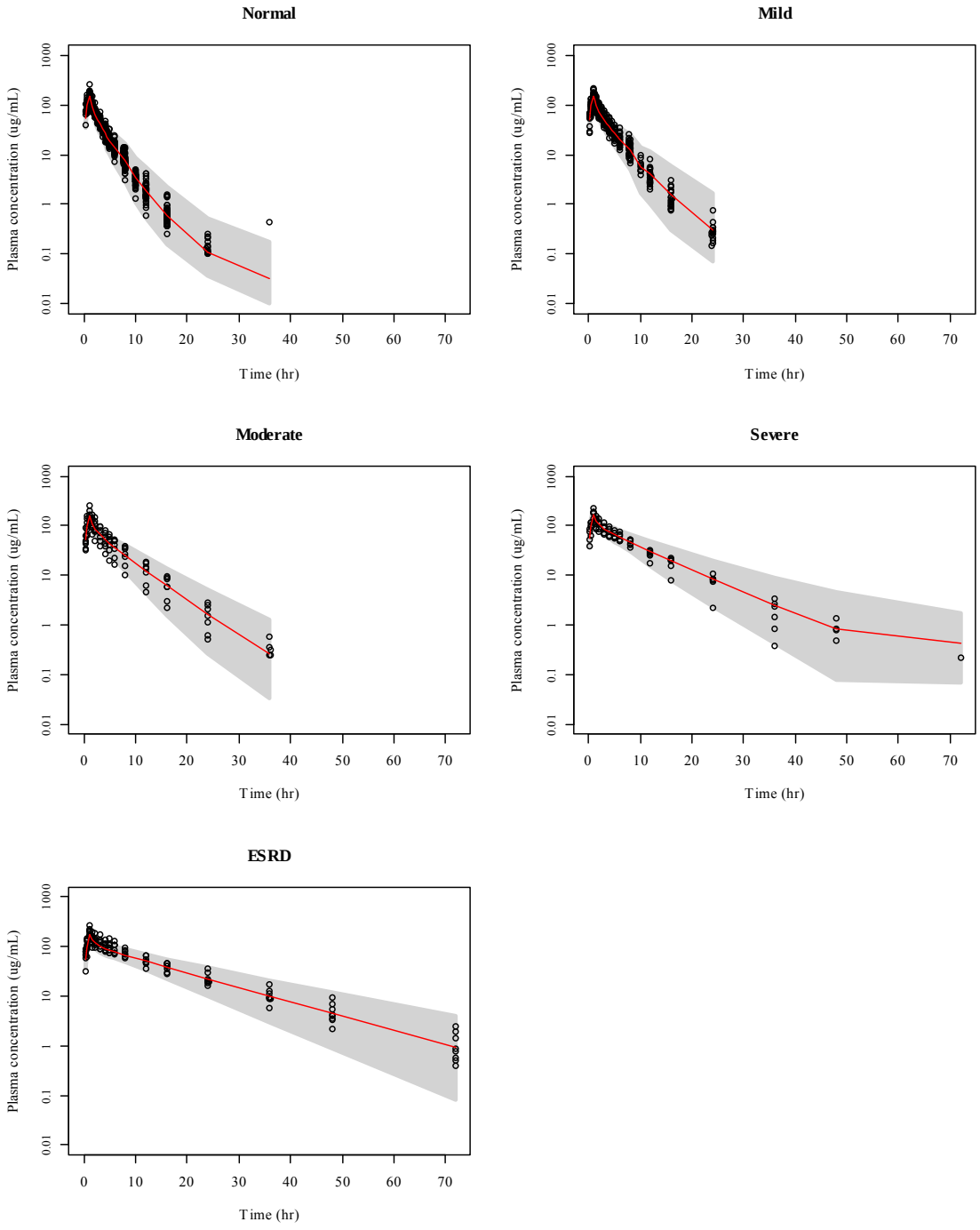
Solid line: y = x.

Supplemental Figure S3 Goodness-of-fit plots for the covariate model with MDRD-eGFR.



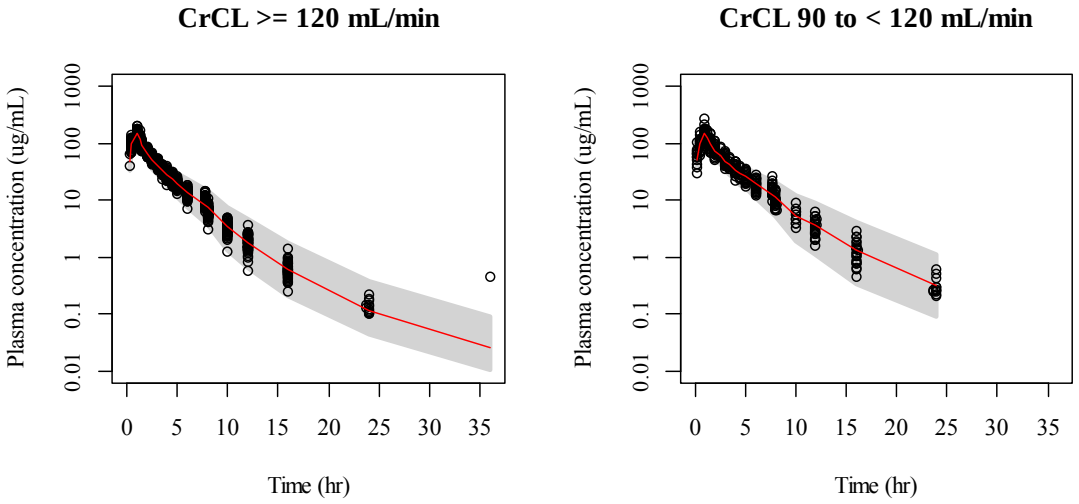
Black solid line: y = x in upper figures and y = 0 in lower figures. Red solid line: LOESS smoother line. DV: Observed data. PRED: Population-predicted data. IPRED: Individual-predicted data. CWRES: Conditional weighted residuals.

Supplemental Figure S4 Visual predictive check for the covariate model with MDRD-eGFR by renal function group.



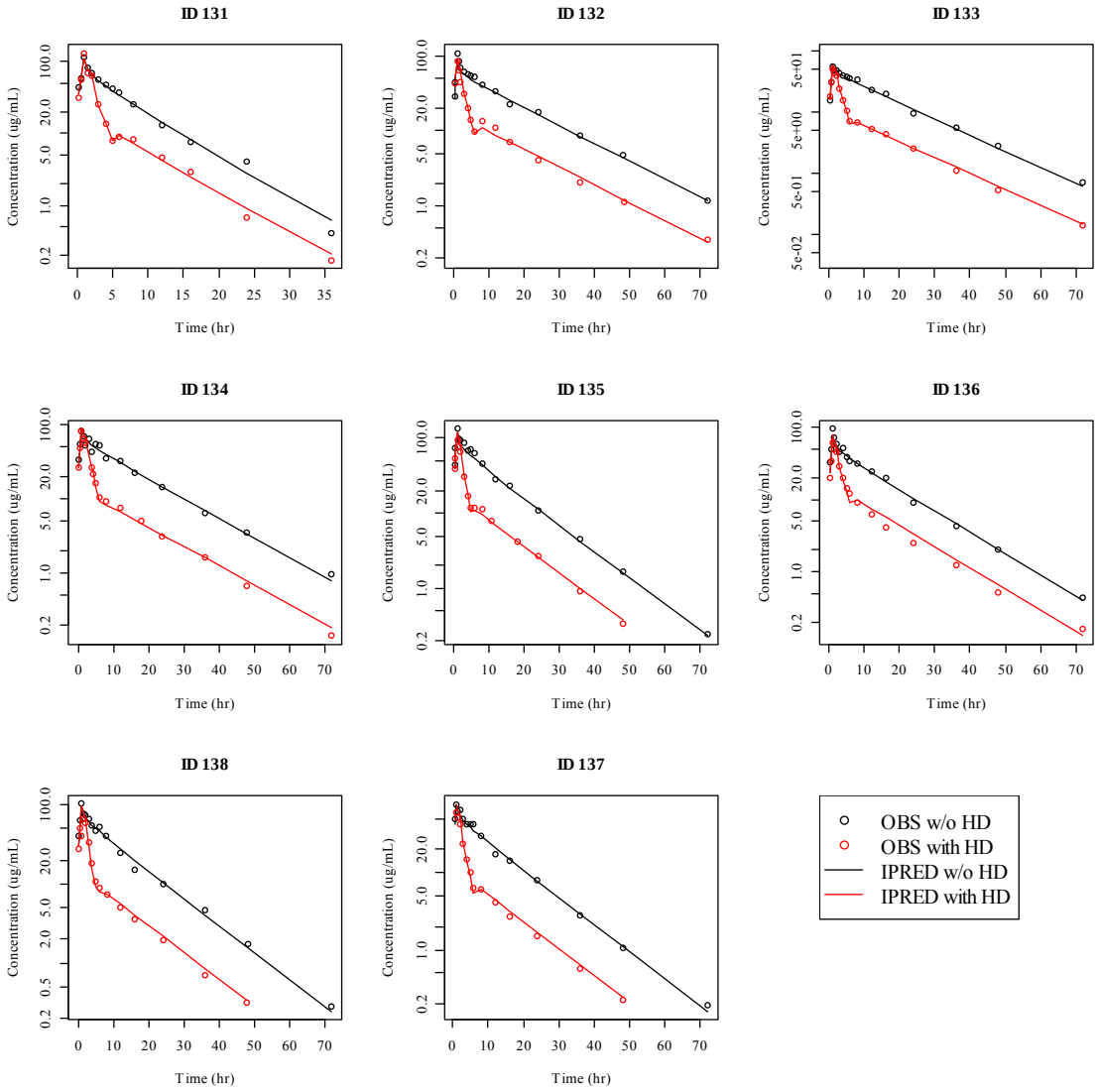
Red line: predicted median. Shaded area: 90% prediction interval. Time: time after the previous dose. Plasma concentration: 2-g dose-adjusted plasma concentration. Normal: MDRD-eGFR ≥90 mL/min/1.73 m^2. Mild: MDRD-eGFR 60 to <90 mL/min/1.73 m^2. Moderate: MDRD-eGFR 30 to <60 mL/min/1.73 m^2. Severe: MDRD-eGFR 15 to <60 mL/min/1.73 m^2. ESRD: MDRD-eGFR <15 mL/min/1.73 m^2.

Supplemental Figure S5 Visual predictive check for the covariate model with CG-CrCL in the range of high CG-CrCL



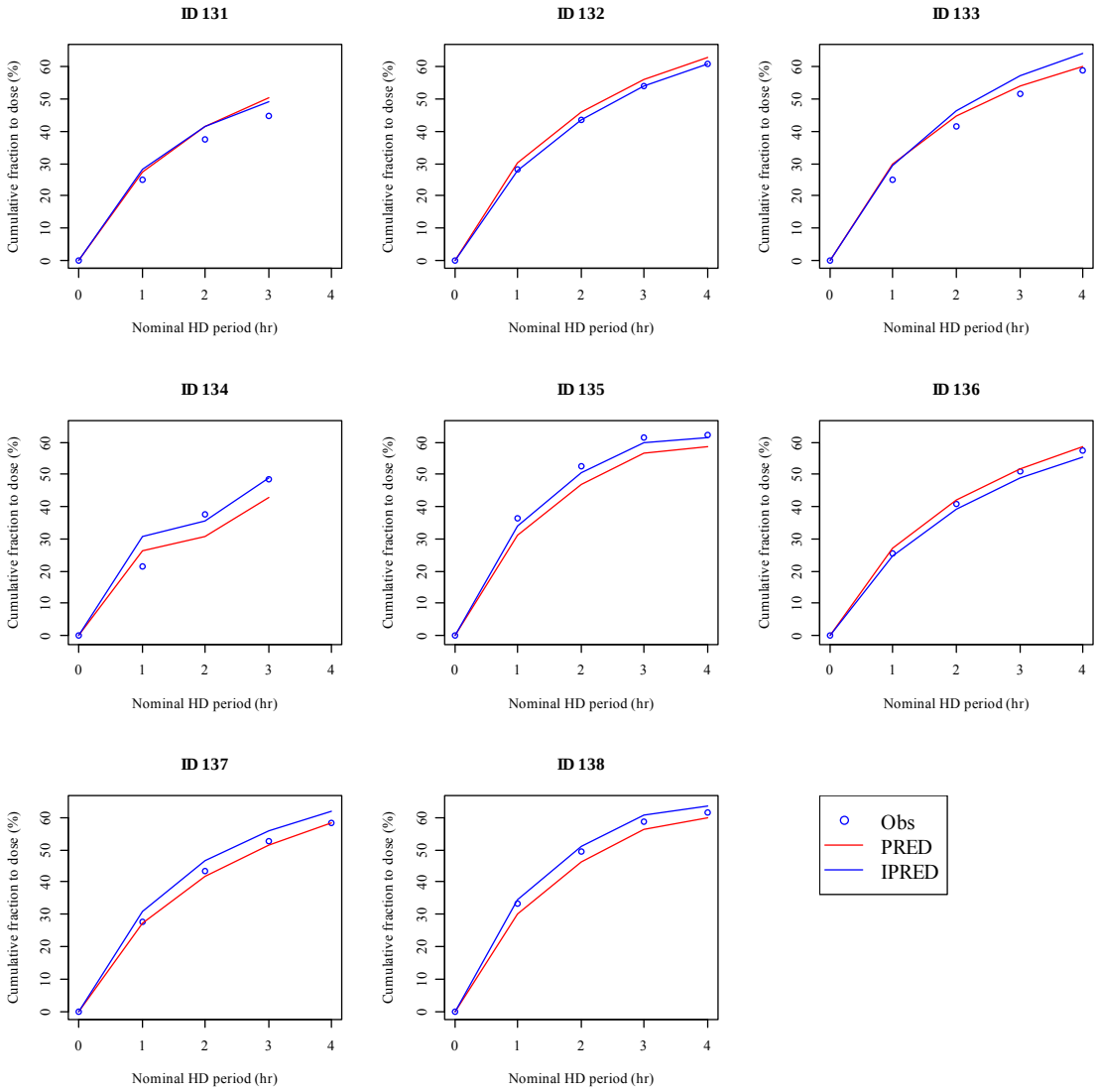
Red line: predicted median. Shaded area: 90% prediction interval. Time: time after the previous dose. Plasma concentration: 2-g dose-adjusted plasma concentration.

Supplemental Figure S6 Individual predicted and observed plots of plasma cefiderocol concentration data with or without 3- to 4-hour HD for the HD model



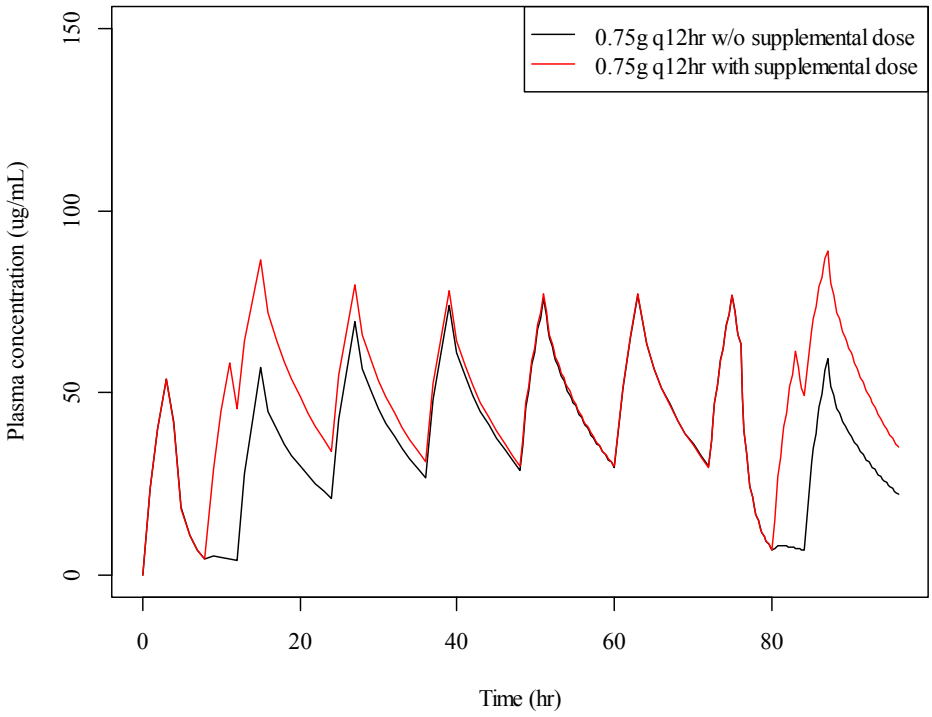
OBS: Observed data. IPRED: Individual-predicted data. W/o HD: Cefiderocol PK without non-dialysis period. With HD: Cefiderocol PK with dialysis period.

Supplemental Figure S7 Individual predicted and observed plots of excretion ratios of cefiderocol in dialysate relative to dose for the HD model.



OBS: Observed data. PRED: Population-predicted data. IPRED: Individual-predicted data.

Supplemental Figure S8 Simulated typical plasma cefiderocol concentration profiles in patients requiring intermittent HD following 0.75 g q12hr dose with or without a supplemental dose of 0.75 g.



The 4-hr HD initiating at 1 hour after the end of 1st regular infusion was simulated on Days 1 and 4 assuming a three-times-a-week HD regimen.
The infusion time was 3 hours.

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