Safety, Tolerability, and Pharmacokinetics of Single- and Multiple-dose Cefiderocol in Hospitalized Pediatric Patients: Results of the PEDI-CEFI Phase 2 Study

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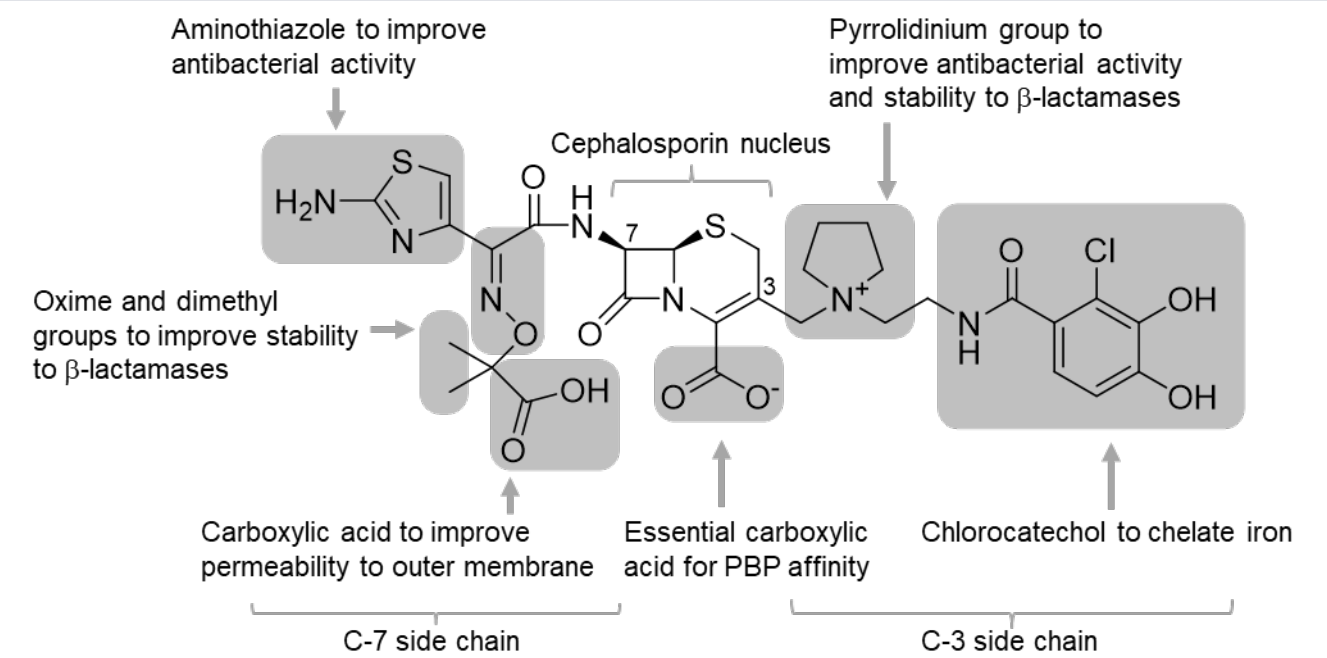
DISCLOSURES

- The study was funded by Shionogi.
- John Bradley has no personal financial interest in any company that develops, investigates, manufactures or sells antibiotics. His employer, the University of California, receives institutional funds to participate in antibiotic studies.

Cefiderocol

- Infections in pediatric patients caused by multidrug-resistant and carbapenem-resistant Gram-negative bacteria are becoming more prevalent.[1]



Sato T, Yamawaki K. *Clin Infect Dis* 2019; 69(Suppl 7): S538–S543.

- Cefiderocol is approved for the treatment of adult patients with complicated urinary tract infections, including pyelonephritis, hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia caused by susceptible Gram-negative microorganisms in the USA,[2] and for the treatment aerobic Gram-negative bacterial infections in adults with limited treatment options in Europe.[3] Cefiderocol is approved also in Japan for the treatment of Gram-negative bacterial infections.[4]

1. Caselli D, et al. *Infect Dis* 2016; 48: 152–155.
2. Fetroja (cefiderocol 1 g). Prescribing Information. Shionogi Inc., Florham Park, NJ, USA; 2021.
3. Fetcroja (cefiderocol 1 g). Summary of Product Characteristics. Shionogi BV, Amsterdam, The Netherlands; 2020.
4. https://www.shionogi.com/global/en/news/2023/11/20231130.html

STUDY DESIGN/OBJECTIVES: PEDI-CEFI

- Single-arm, open-label study to assess the safety, tolerability, and pharmacokinetics of single- or multiple-dose cefiderocol in hospitalized pediatric patients aged 3 months to <18 years with any suspected or confirmed aerobic Gram-negative bacterial infection, including but not limited to:
  - complicated urinary tract infection (cUTI)
  - complicated intra-abdominal infection (cIAI)
  - hospital-acquired and ventilator-associated pneumonia (HAP/VAP)
  - sepsis or bloodstream infection (BSI).

STUDY DESIGN/OBJECTIVES: PEDI-CEFI

- Patients enrolled into either the single-dose phase or the multiple-dose phase.
- Screening of patients occurred within 4 days prior to administration of cefiderocol in the single-dose phase or prior to administration of the first dose of cefiderocol in the multiple-dose phase.
- Patients received standard-of-care (SOC) antibiotic treatment for the Gram-negative bacterial infection, with cefiderocol *in addition* to SOC.
- In the single-dose phase, cefiderocol was administered in addition to SOC *at any time* during the SOC treatment.
- In the multiple-dose phase, cefiderocol was administered (Day 1) in addition to SOC within 72 hours of the start of SOC treatment; patients received cefiderocol every 8 hours for 5–14 days to assess safety and pharmacokinetics of cefiderocol.

SOC, standard-of-care.

CEFIDEROCOL DOSING

Renal function	Dose		Infusion time*
	Body weight ≥34 kg	Body weight <34 kg	
Single-dose phase			
Normal renal function to mild renal impairment (eGFR 90 to <120 mL/min/1.73 m^2 or 60 to <90 mL/min/1.73 m^2)	2000 mg	60 mg/kg†	3 hours
Multiple-dose phase (every 8 hours)			
Normal renal function to mild renal impairment (eGFR 90 to <120 mL/min/1.73 m^2 or 60 to <90 mL/min/1.73 m^2)	2000 mg	60 mg/kg†	3 hours
Moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2)	1500 mg	45 mg/kg†	3 hours
Severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2)	1000 mg	30 mg/kg†	3 hours

*Shorter infusion time was allowed in the multiple-dose phase if agreed by the sponsor and in the best interest of the patient.

†No more than 2000 mg of cefiderocol could be administered.

eGFR, estimated glomerular filtration rate.

INCLUSION AND EXCLUSION CRITERIA

Key inclusion criteria:

- A suspected or confirmed Gram-negative bacterial infection that required hospitalization for treatment with intravenous antibiotics
- All patients or their legal guardian provided informed consent.

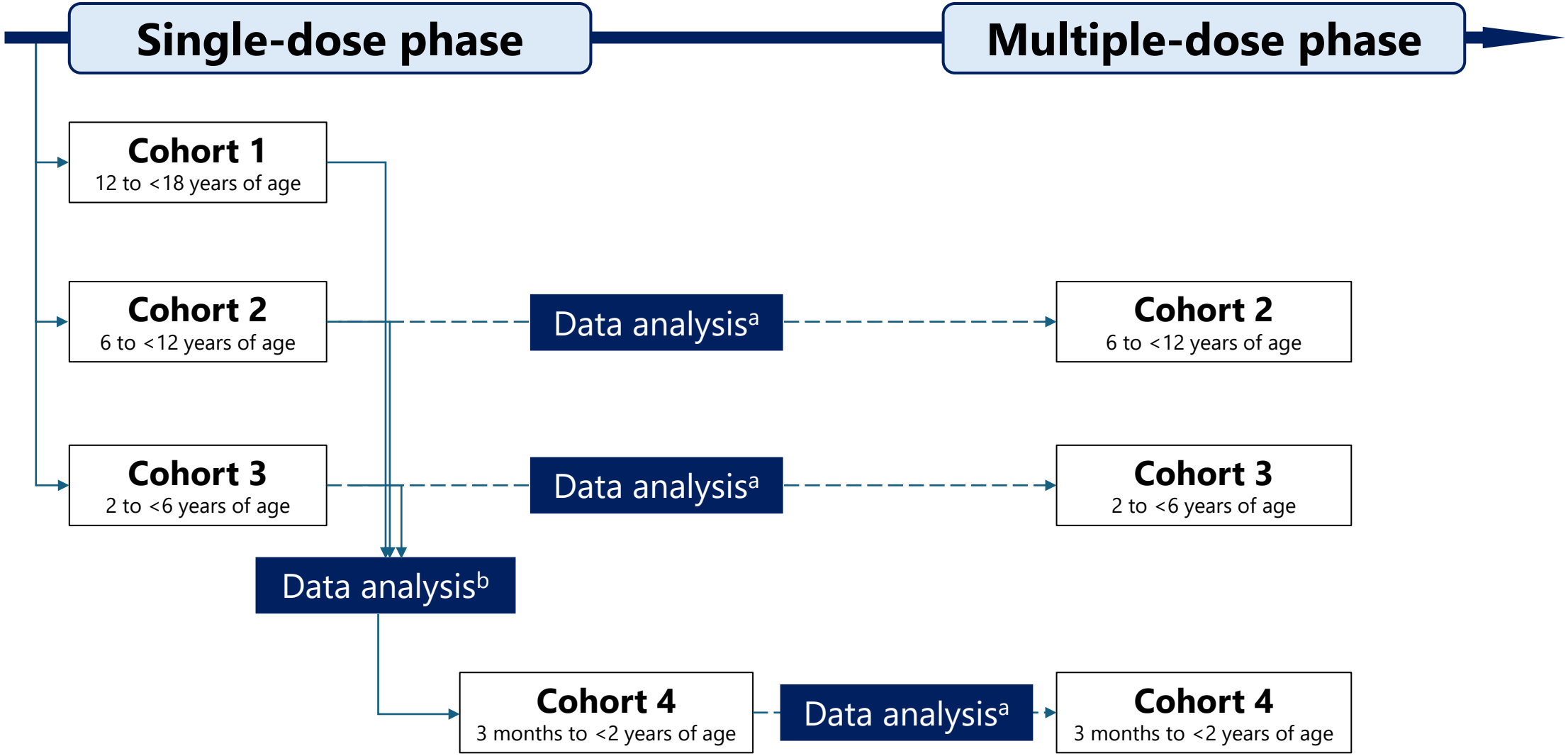
Exclusion criteria:

- History of any hypersensitivity or allergic reaction to any β-lactam antibiotic
- Central nervous system infection, osteomyelitis
- Cystic fibrosis
- Moderate or severe renal impairment based on estimated glomerular filtration rate (eGFR) in the single-dose phase
- eGFR (based on modified bed-side Schwartz equation) of <15 mL/min/1.73 m^2 at screening in the multiple-dose phase
- End-stage renal disease, hemodialysis, or continuous venovenous hemofiltration in either phase
- Shock with acute kidney injury in the prior month or at the time of screening
- Severe neutropenia or severely immunocompromised; multiorgan failure; life expectancy of <30 days.

eGFR, estimated glomerular filtration rate.

STUDY SCHEMATIC

Planned enrollment:
Single-dose phase – 6 patients in each cohort
Multiple-dose phase – 10 patients in each cohort
Total – 54 patients



[a]Including safety and PK data from 6 subjects in the corresponding single-dose cohort.
[b]Including safety and PK data from at least 6 subjects from the single dose Cohorts 1, 2, and 3 (with a minimum of 3 subjects from Cohort 3).
Neonate study (https://www.clinicaltrials.gov/study/NCT06086626).

SUBJECT DISPOSITION FOR ALL ENROLLED (N=53)

C1: adolescents C2: school aged C3: pre-school C4: infants	Single-dose phase					Multiple-dose phase			
	C1 N=6 n (%)	C2 N=6 n (%)	C3 N=6 n (%)	C4 N=6 n (%)	Overall N=24 n (%)	C2 N=12 n (%)	C3 N=11 n (%)	C4 N=6 n (%)	Overall N=29 n (%)
Subjects received any study treatment	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)	12 (100)	11 (100)	6 (100)	29 (100)
Enrolled, not treated	0	0	0	0	0	0	0	0	0
Treatment completion status									
Completed study treatment	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)	11 (91.7)	9 (81.8)	6 (100)	26 (89.7)
Discontinued study treatment*	0	0	0	0	0	1 (8.3)	2 (18.2)	0	3 (10.3)
Other	0	0	0	0	0	1 (8.3)	2 (18.2)	0	3 (10.3)
Study completion status									
Completed the study	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)	12 (100)	10 (90.9)	6 (100)	28 (96.6)
Discontinued from the study#	0	0	0	0	0	0	1 (9.1)	0	1 (3.4)
Protocol deviation	0	0	0	0	0	0	1 (9.1)	0	1 (3.4)

**Discontinued the study treatment*

- 1 participant in Cohort 2 discontinued treatment (due to Gram-positive infection isolated).
- 2 participants in Cohort 3 discontinued treatment (discharged because of local challenges; HAP criteria were not met).

#Discontinued from the study

- 1 participant in Cohort 3 who had not met HAP criteria and was considered a protocol deviation.

C, cohort; HAP, hospital-acquired pneumonia.

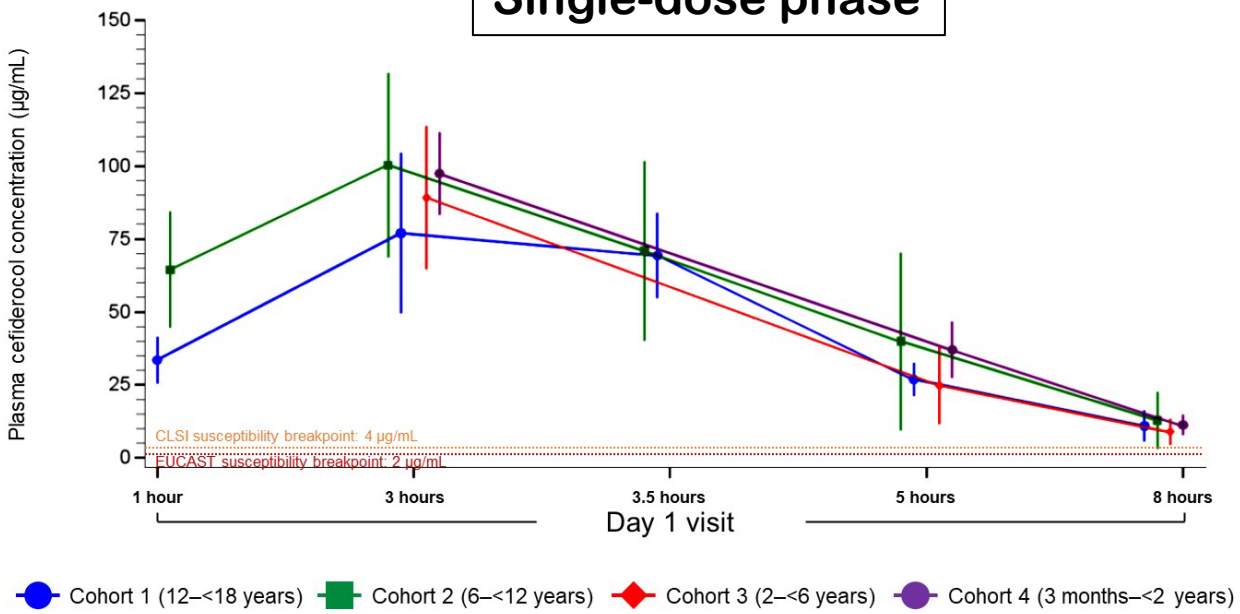
BASELINE CHARACTERISTICS

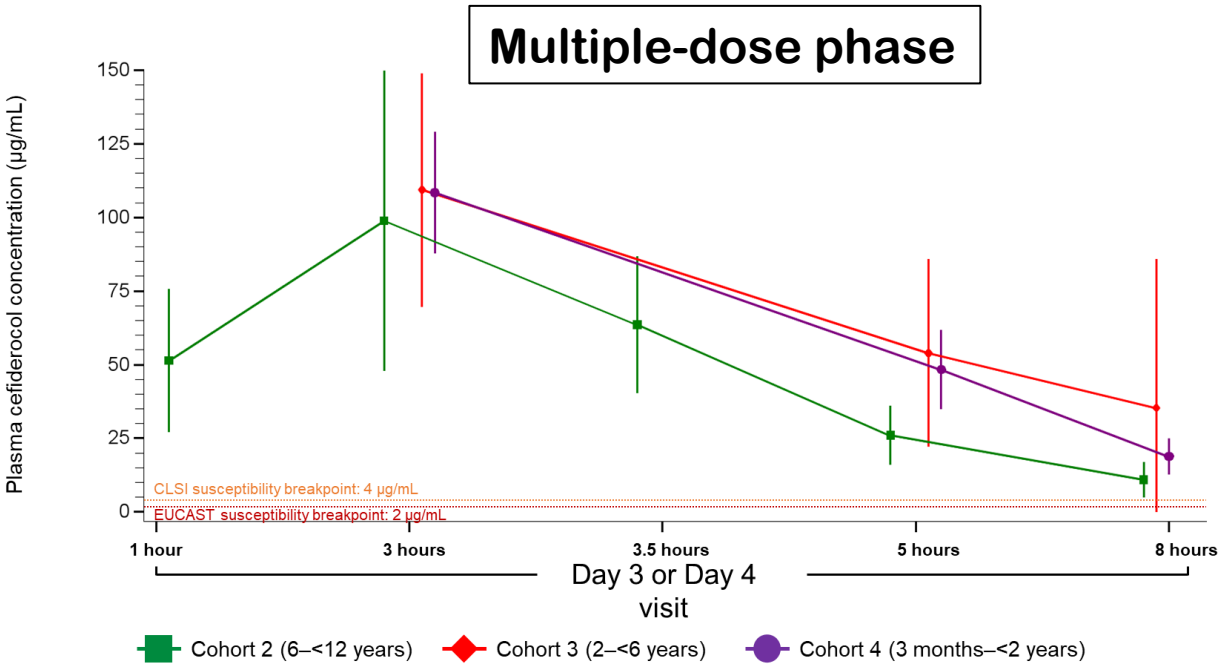
C1: adolescents C2: school aged C3: pre-school C4: infants	Single-dose phase				Multiple-dose phase		
	C1 N=6	C2 N=6	C3 N=6	C4 N=6	C2 N=12	C3 N=11	C4 N=6
Age, months							
Mean ± SD	171.2 ± 16.1	109.2 ± 20.4	34.3 ± 15.6	12.2 ± 6.3	104.3 ± 22.7	52.4 ± 14.3	8.8 ± 5.0
Age, years							
Mean ± SD	14.27 ± 1.34	9.10 ± 1.68	2.87 ± 1.30	1.05 ± 0.53	8.72 ± 1.88	4.35 ± 1.20	0.73 ± 0.42
Sex, n (%)							
Male	2 (33.3)	2 (33.3)	3 (50.0)	3 (50.0)	3 (25.0)	2 (18.2)	4 (66.7)
Female	4 (66.7)	4 (66.7)	3 (50.0)	3 (50.0)	9 (75.0)	9 (81.8)	2 (33.3)
Body weight, kg							
Mean ± SD	60.17 ± 10.19	30.32 ± 8.43	14.25 ± 4.03	8.62 ± 2.13	27.37 ± 3.85	16.95 ± 3.97	6.82 ± 0.84
eGFR grading group, n (%)							
≥120 mL/min/1.73 m^2	2 (33.3)	1 (16.7)	2 (33.3)	4 (66.7)	3 (25.0)	1 (9.1)	4 (66.7)
90 to <120 mL/min/1.73 m^2	4 (66.7)	4 (66.7)	4 (66.7)	0	7 (58.3)	5 (45.5)	2 (33.3)
60 to <90 mL/min/1.73 m^2	0	1 (16.7)	0	2 (33.3)	2 (16.7)	5 (45.5)	0
Infection type, n (%)							
cUTI	0	2 (33.3)	2 (33.3)	1 (16.7)	3 (25.0)	4 (36.4)	3 (50.0)
cIAI	6 (100)	3 (50.0)	1 (16.7)	0	9 (75.0)	4 (36.4)	1 (16.7)
HAP/VAP	0	0	1 (16.7)	0	0	2 (18.2)	0
BSI	0	0	0	3 (50.0)	0	0	1 (16.7)
Sepsis	0	0	1 (16.7)	0	0	0	1 (16.7)
Other*	0	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (9.1)	0

**2 participants with community-associated pneumonia, 1 participant with cutaneous infection, and 1 participant with lingering bronchitis in the single-dose phase, and 1 participant with community-associated pneumonia in the multiple-dose phase.*

BSI, bloodstream infection; C, cohort; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; eGFR, estimated glomerular filtration rate; HAP/VAP, hospital-acquired and ventilator-associated pneumonia; SD, standard deviation.

PK OF CEFIDEROCOL





Geometric mean values (µg/mL), Day 1, after start of infusion at:	Single-dose phase			
	C1 N=6	C2 N=6	C3 N=6	C4 N=6
1 h, n	6	6	0	0
	32.7	61.8	NA	NA
3 h, n	5	6	6	4
	72.7	97.1	86.6	96.5
3.5 h, n	5	6	0	0
	68.1	66.2	NA	NA
5 h, n	6	6	6	6
	26.3	30.8	19.9	36.0
8 h, n	6	6	6	6
	9.89	10.0	7.86	10.8

Geometric mean values (µg/mL), Day 3 or 4, after start of infusion at:	Multiple-dose phase		
	C2 N=12	C3 N=10	C4 N=6
1 h, n	12	0	0
	43.0	NA	NA
3 h, n	10	5	4
	88.8	103.0	106.0
3.5 h, n	12	0	0
	60.1	NA	NA
5 h, n	12	10	6
	24.0	45.0	46.8
8 h, n	11	10	5
	9.64	17.9	18.1

C, cohort; CLSI, Clinical & Laboratory Standards Institute; CV, coefficient of variance; EUCAST, European Committee on Antimicrobial Susceptibility Testing; NA, not applicable.

TREATMENT-EMERGENT ADVERSE EVENTS (SAFETY POPULATION)

C1: adolescents
C2: school aged
C3: pre-school
C4: infants

	Single-dose phase										Multiple-dose phase							
	C1 N=6		C2 N=6		C3 N=6		C4 N=6		Overall N=24		C2 N=12		C3 N=11		C4 N=6		Overall N=29	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Any TEAEs	0	0	1 (16.7)	1	3 (50.0)	7	1 (16.7)	4	**5 (20.8)**	**12**	2 (16.7)	2	1 (9.1)	1	4 (66.7)	7	**7 (24.1)**	**10**
Drug-related TEAEs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Treatment-emergent SAEs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (16.7)	2	**1 (3.4)**	**2**
Drug-related SAEs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Drug withdrawn due to drug-related TEAEs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

C, cohort; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

SAFETY SUMMARY

- No abnormal findings in vital signs or physical examination were reported in study subjects.
- No clinically significant changes in laboratory parameters were recorded with cefiderocol treatment.
- There was no drug discontinuation due to adverse events.
- Adverse events occurred in 5 of 24 patients in the single-dose phase and 7 of 29 patients in the multiple-dose phase of the study; all adverse events were mild or moderate, not related to cefiderocol as assessed by investigators and DSMB.

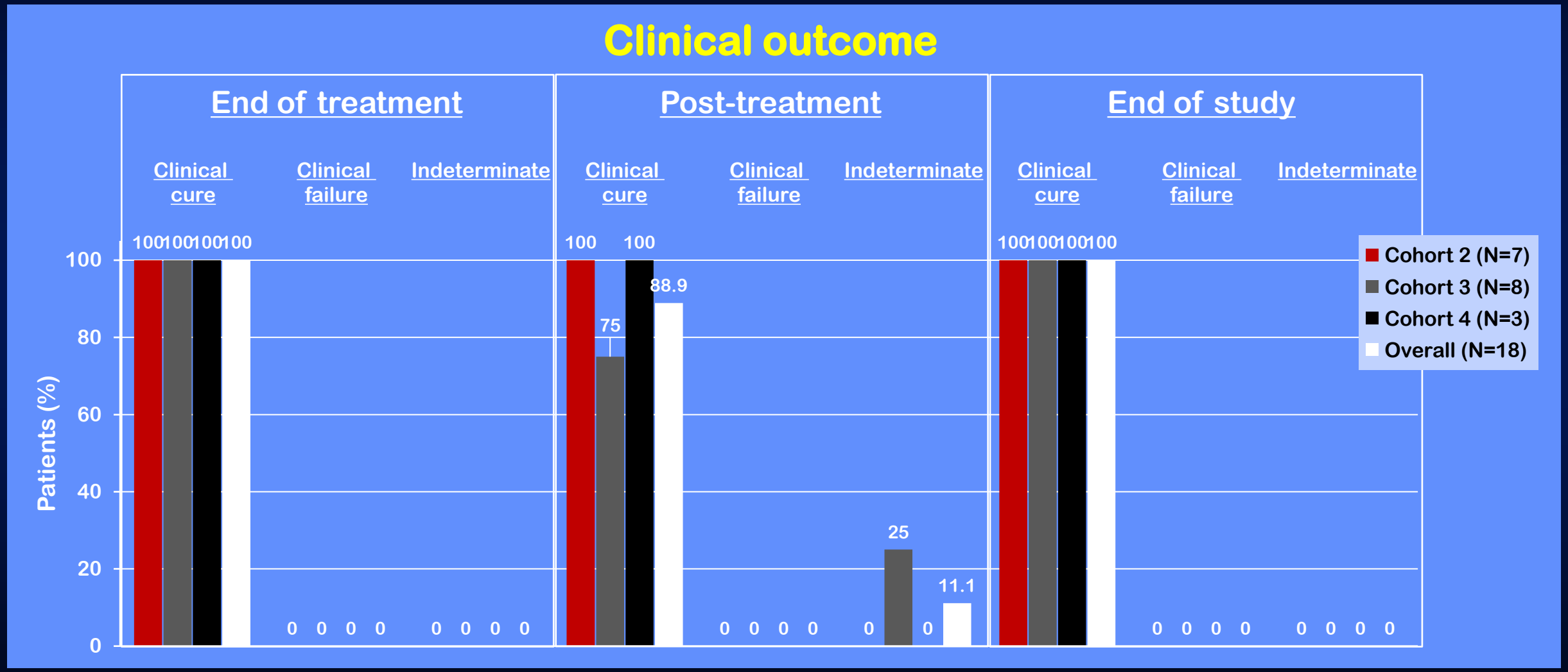
AE, adverse event; DSMB, data safety monitoring board; TEAE, treatment-emergent adverse event.

GRAM-NEGATIVE PATHOGENS (MITT POPULATION)

Baseline infection site	Baseline pathogen	Cefiderocol susceptibility by EUCAST		Multiple-dose phase			
		Susceptible	Resistant	C2 N=7	C3 N=8	C4 N=3	Overall N=18
cIAI	*Escherichia coli* (n=7)	100%	0%	5 (71.4)	2 (25.0)	0	7 (38.9)
cUTI	*Escherichia coli* (n=6)	100%	0%	2 (28.6)	4 (50.0)	0	6 (33.3)
	Enterobacter cloacae complex (n=1)	0% (MIC= 4 µg/mL)	100%	0	0	1 (33.3)	1 (5.6)
HAP/VAP	*Klebsiella pneumoniae* (n=2)	100%	0%	0	2 (25.0)	0	2 (11.1)
BSI	*Neisseria meningitidis* (n=1)	NA		0	0	1 (33.3)	1 (5.6)
Sepsis	*Salmonella* spp. (n=1)	NA		0	0	1 (33.3)	1 (5.6)

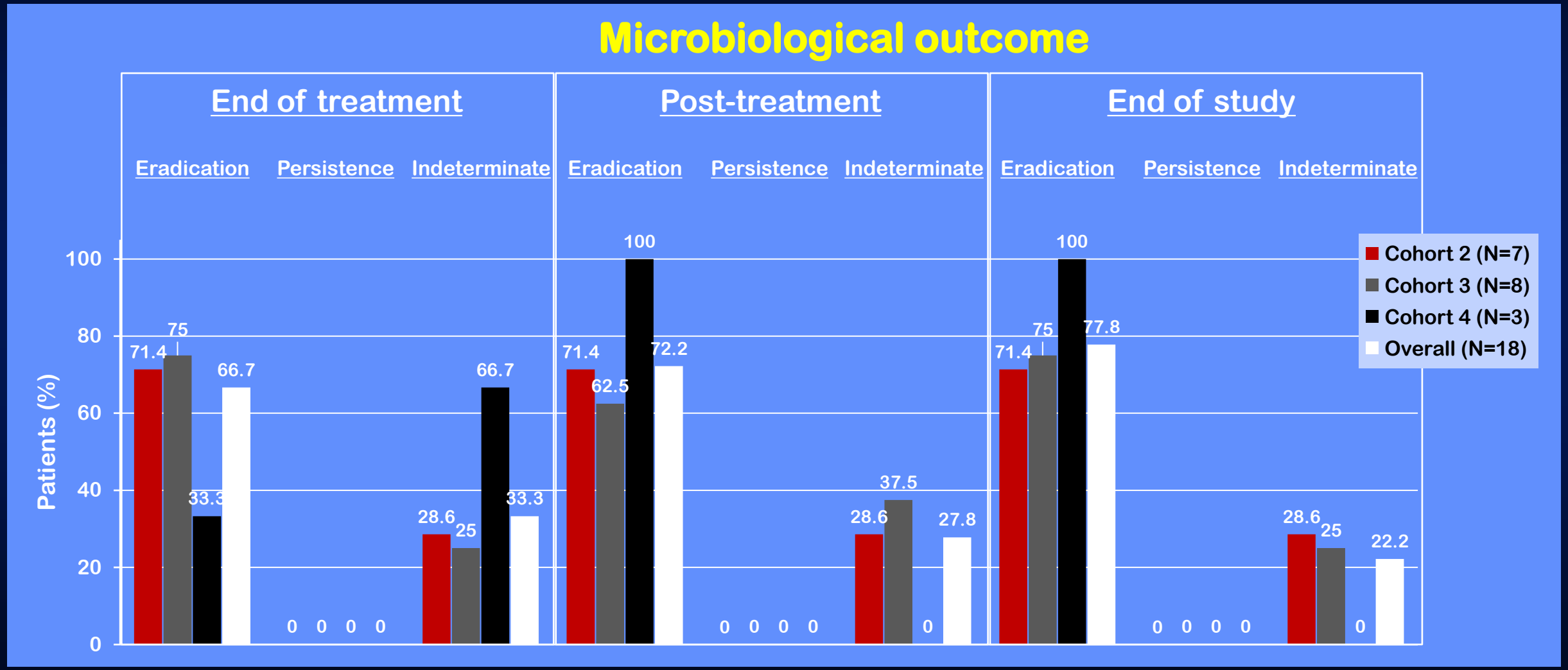
The microbiological intent-to-treat (MITT) population included all cefiderocol-treated patients, who had a baseline Gram-negative pathogen from any specimen from the baseline infection site.
BSI, bloodstream infection; C, cohort; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HAP/VAP, hospital-acquired and ventilator-associated pneumonia; MIC, minimum inhibitory concentration; MITT, microbiological intent-to-treat; NA, not applicable.

SECONDARY OUTCOMES ASSESSED: CLINICAL AND MICROBIOLOGICAL (MITT POPULATION)



All indeterminate outcomes were missing assessments; end of treatment: assessment occurred within 24 hours after last day of study treatment; post treatment: assessment occurred 7 days after EOT ± 4 days; end of study: assessment occurred 28 days after the last dose of cefiderocol + 7 days. MITT, microbiological intent-to-treat. MITT, microbiological intent-to-treat.

SECONDARY OUTCOMES ASSESSED: CLINICAL AND MICROBIOLOGICAL (MITT POPULATION)



Indeterminate: missing/not applicable sample or out of time window; end of treatment: assessment occurred within 24 hours after last day of study treatment; post treatment: assessment occurred 7 days after EOT ± 4 days; end of study: assessment occurred 28 days after the last dose of cefiderocol + 7 days. MITT, microbiological intent-to-treat.

CONCLUSIONS

- Cefiderocol was well tolerated by hospitalized children receiving cefiderocol *in addition to standard-of-care antibiotics* for a documented or presumed underlying Gram-negative bacterial infection.
- Cefiderocol was administered every 8 hours *in 3-hour infusions* at a dose of 60 mg/kg up to a maximum dose of 2000 mg/dose for body weight ≥34 kg, *to maximize the pharmacodynamic metric, %T>MIC*.
- The total plasma cefiderocol concentration profiles after single and multiple doses were similar among the four cohorts.
- Trough concentrations <u>remained above the susceptibility breakpoints for all patients</u>.

CONCLUSIONS

- All patients received standard-of-care antibiotics; thus, clinical and microbiological outcomes cannot be attributed to cefiderocol; all subjects had good outcomes.
- Cefiderocol could be an effective antibiotic treatment option, with a similar safety profile to other beta-lactams, for pediatric patients with multidrug-resistant Gram-negative infections: phase 3 studies in children and neonates are underway.

APEKS-PEDI: https://www.clinicaltrials.gov/study/NCT04215991
Neonate study: https://www.clinicaltrials.gov/study/NCT06086626

Thank you!

Questions??

BACKUP SLIDES

TREATMENT-EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS (SAFETY POPULATION)

System organ class	Single-dose phase					Multiple-dose phase			
Preferred term, n (%)	C1 N=6	C2 N=6	C3 N=6	C4 N=6	Overall N=24	C2 N=12	C3 N=11	C4 N=6	Overall N=29
Patients with any TEAEs	0	1 (16.7)	3 (50.0)	1 (16.7)	5 (20.8)	2 (16.7)	1 (9.1)	4 (66.7)	7 (24.1)
Blood and lymphatic system disorders	0	0	1 (16.7)	0	1 (4.2)	0	0	1 (16.7)	1 (3.4)
Anemia	0	0	1 (16.7)	0	1 (4.2)	0	0	0	0
Neutropenia	0	0	0	0	0	0	0	1 (16.7)	1 (3.4)
Cardiac disorders	0	0	1 (16.7)	0	1 (4.2)	0	0	0	0
Bradycardia	0	0	1 (16.7)	0	1 (4.2)	0	0	0	0
Congenital, familial, and genetic disorders	0	0	0	1 (16.7)	1 (4.2)	0	0	0	0
Laryngomalacia	0	0	0	1 (16.7)	1 (4.2)	0	0	0	0
Gastrointestinal disorders	0	1 (16.7)	2 (33.3)	1 (16.7)	4 (16.7)	0	0	0	0
Abdominal pain	0	1 (16.7)	1 (16.7)	0	2 (8.3)	0	0	0	0
Gastroesophageal reflux disease	0	0	0	1 (16.7)	1 (4.2)	0	0	0	0
Hematochezia	0	0	1 (16.7)	0	1 (4.2)	0	0	0	0
General disorders and administration site conditions	0	0	1 (16.7)	0	1 (4.2)	0	0	0	0
Pyrexia	0	0	1 (16.7)	0	1 (4.2)	0	0	0	0
Infections and infestations	0	0	0	1 (16.7)	1 (4.2)	1 (8.3)	0	3 (50.0)	4 (13.8)
Candida infection	0	0	0	1 (16.7)	1 (4.2)	0	0	0	0
Pneumocystis jirovecii infection	0	0	0	1 (16.7)	1 (4.2)	0	0	0	0
Urinary tract infection	0	0	0	0	0	0	0	2 (33.3)^	2 (6.9)
Purulent discharge	0	0	0	0	0	1 (8.3)	0	0	1 (3.4)
Respiratory syncytial virus infection	0	0	0	0	0	0	0	1 (16.7)	1 (3.4)
Staphylococcal bacteremia	0	0	0	0	0	0	0	1 (16.7)^	1 (3.4)
Investigations	0	0	1 (16.7)	0	1 (4.2)	0	0	1 (16.7)	1 (3.4)
C-reactive protein increased	0	0	1 (16.7)	0	1 (4.2)	0	0	0	0
Alanine aminotransferase increased	0	0	0	0	0	0	0	1 (16.7)*	1 (3.4)
Product issues	0	0	1 (16.7)	0	1 (4.2)	0	0	0	0
Device connection issue	0	0	1 (16.7)	0	1 (4.2)	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	0	1 (9.1)	1 (16.7)	2 (6.9)
Renal impairment	0	0	0	0	0	0	1 (9.1)	1 (16.7)	2 (6.9)
Respiratory, thoracic, and mediastinal disorders	0	0	0	0	0	1 (8.3)	0	0	1 (3.4)
Epistaxis	0	0	0	0	0	1 (8.3)	0	0	1 (3.4)

C, cohort; TEAE, treatment-emergent adverse event.

All TEAEs were mild or moderate in intensity.

^1 patient in Cohort 4 experienced a UTI and a staphylococcal bacteremia as serious adverse events; both events were moderate in intensity, unrelated to cefiderocol, and both events resolved within 3 and 6 days, respectively.

*1 patient in Cohort 4 of the multiple-dose phase experienced a temporary alanine aminotransferase elevation unrelated to cefiderocol treatment following end of treatment.

ENROLLING COUNTRIES AND PATIENTS

	No. of sites activated	Planned no. of patients	Actual screened	Actual enrolled	Evaluable subjects
Georgia	3	7	21	21	20*
Ukraine	4	9	14	14	14
Thailand	4	8	8	8	8
Belgium	2	7	6	6	5**
Estonia	2	5	4	4	4
Latvia	2	4	1	1	1
Hungary	3	6	0	0	0
Russia	2	4	0	0	0
Spain	2	4	0	0	0
Total	24	54	54	54	52

*1 patient in Georgia was not evaluable as patient was not eligible and no PK samples were taken.
**1 patient in Belgium was not evaluable as patient was not dosed.