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Pharmacokinetics, Safety and Tolerability of Single-dose or Multiple-dose Cefiderocol in Hospitalized Pediatric Patients Three Months to Less Than Eighteen Years Old With Infections Treated With Standard-of-care Antibiotics in the PEDI-CEFI Phase 2 Study

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Background: Multidrug-resistant Gram-negative bacterial infections are increasing globally in neonates, infants and children; antibiotic options are limited.

Methods: This international, multicenter, open-label phase 2 study, investigated the pharmacokinetics, safety and tolerability of single-dose and multiple-dose cefiderocol [as a 3-hour infusion (every 8 hours) dosed at 2000 mg for body weight ≥34 kg and at 60 mg/kg for body weight <34 kg], over a range of renal function, in hospitalized pediatric patients with aerobic Gram-negative bacterial infection; multiple-dose patients required standard-of-care systemic antibiotics for 5–14 days. Four cohorts of pediatric patients were enrolled (cohort 1: 12 to <18 years, cohort 2: 6 to <12 years, cohort 3: 2 to <6 years and cohort 4: 3 months to <2 years).

Results: A total of 53 patients (median age: 73.5 months) were enrolled. Plasma concentration profiles were similar with single-dose (n = 24) and multiple-dose (n = 29) cefiderocol, irrespective of age and body weight in those with normal renal function or mild renal impairment. Geometric mean concentrations at the end of infusion ranged between 72.7 and 97.1 μg/mL for single-dose cefiderocol and between 88.8 and 106.0 μg/mL after multiple doses. At 8 hours, corresponding trough concentrations ranged from 7.86 to 10.8 μg/mL with single-dose cefiderocol and from 9.64 to 18.1 μg/mL with multiple doses. There were no deaths, no cefiderocol-related serious adverse events, significant related laboratory abnormalities or discontinuations.

Conclusions: Multiple-dose cefiderocol, administered for 5–14 days and according to body weight, achieved steady-state plasma concentrations that remained above the susceptibility breakpoints of Gram-negative bacteria throughout the dosing period. Cefiderocol was well tolerated.

Key Words: cefiderocol, multidrug-resistant Gram-negative bacteria, pediatric, pharmacokinetics, safety

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There is a rising prevalence of multidrug-resistant (MDR) Gram-negative infections in infants and children, including neonates and preterm infants.[1–3] One of the latest surveillance studies in pediatric patients from Asia, Africa and Latin America showed that carbapenem-resistant (CR) and difficult-to-treat resistant Gram-negative bacteria phenotypes are increasing.[4] Among neonates with culture-positive sepsis, there is a high level of mortality and a considerable level of antibiotic resistance.[5] Several antibiotics have been approved for hospitalized adult patients with infections caused by MDR and/or CR Gram-negative bacteria,[6–9] but to date, the only approved agents for use in pediatric patients are ceftazidime-avibactam to treat CR Enterobacterales and ceftolozane–tazobactam to treat MDR *Pseudomonas aeruginosa*.[4,9–11]

Cefiderocol is a siderophore-conjugated cephalosporin with activity against a wide variety of aerobic Gram-negative pathogens, including MDR, CR and extensively drug-resistant organisms.[7,8,12–14] Cefiderocol is approved in Europe for the treatment of adult patients with Gram-negative bacterial infections caused by susceptible pathogens,[15] and in the United States for adult patients with complicated urinary tract infection (UTI) and hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia,[16] but does not yet have regulatory approval for use in children.

Cefiderocol was developed for the treatment of serious CR Gram-negative bacterial infections.[17,18] It is largely stable against hydrolysis by many beta-lactamase enzymes frequently present in CR Gram-negative pathogens, including the nonfermenters *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia, Pseudomonas aeruginosa*, as well as Enterobacterales.[17,19] Cefiderocol is the only beta-lactam antibiotic with in-vitro activity that extends to both serine-carbapenemases and metallo-carbapenemases and other broad-spectrum serine-beta-lactamases, such as AmpC chromosomal class C enzymes.[14,19–21] Cefiderocol susceptibility rates in both Europe and the United States are >90% for a range of aerobic Gram-negative isolates collected from adult patients,[12,14,21,22] although activity may be lower in regions where certain metallo-beta-lactamases (eg, New Delhi metallo-beta-lactamase) are prevalent.[21,23–25] As expected, the in-vitro activity of cefiderocol against Gram-negative bacteria isolated from pediatric patients is comparable to that found in adult patients.[26]

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Early pharmacokinetic/pharmacodynamic (PK/PD) experiments, conducted in neutropenic murine lung-infection and thigh-infection models, have established that cefiderocol is a time-dependent antibiotic.[27] Thus, the fraction of time over minimum inhibitory concentration (%*f*T>MIC) that the free drug concentration is required to remain above the minimum inhibitory concentration (MIC) of the Gram-negative isolate was 64.4%–73.3% for Enterobacterales, 70.3%–77.2% for *P. aeruginosa*, 88.1% for *A. baumannii* and 53.9% for *S. maltophilia*.[27] Of note, this study also observed that the PD target is greater for CR isolates than for carbapenem-susceptible isolates among Gram-negative pathogens.[27]

In a phase 1 study in adult healthy subjects, single and multiple doses of cefiderocol, infused over 1 hour, showed linear PK and dose proportionality.[28] Cefiderocol is primarily excreted via the renal route and metabolism is minimal.[29] In adult subjects with moderate or severe renal impairment or end-stage renal disease, reduced clearance and increased half-life of cefiderocol were observed.[30]

Early PK modeling based on adult PK, but incorporating the maturation of renal function in infants given the primary renal elimination of cefiderocol, suggested that a dose of 60 mg/kg, infused over 3 hours every 8 hours, could provide comparable exposure in pediatric patients 3 months to <18 years old to that observed in adults, in whom it was demonstrated to be effective with a predictable safety profile.[31]

The efficacy of cefiderocol in adults has been demonstrated in phase 2 and phase 3 studies, which included serious CR Gram-negative bacterial infections.[32–34] Data from case reports show the utility of cefiderocol in pediatric patients with infections caused by *P. aeruginosa*, *Klebsiella pneumoniae* and *S. maltophilia*,[1,35,36] or by *Achromobacter xylosoxidans* in individuals with cystic fibrosis.[37,38] The safety profile of cefiderocol in adults has been observed to be similar to that of other beta-lactam antibiotics.[32–34]

In the current PEDI-CEFI study, the safety, tolerability and PK profile of cefiderocol was investigated in hospitalized pediatric patients 3 months to <18 years of age, to obtain the dosing required to match exposure needed to treat MDR/CR Gram-negative bacterial infections in adults, including exposures in bacterial pneumonia based on epithelial lining fluid penetration data in adults.[39]

MATERIALS AND METHODS

Study Design

The PEDI-CEFI study was an international, multicenter, single-arm, open-label phase 2 study to assess the PK, safety and tolerability of single and multiple doses of cefiderocol, in hospitalized children receiving systemic standard-of-care (SOC) antibiotics for suspected or confirmed aerobic Gram-negative bacterial infection; patients enrolled in the multiple-dose study were expected to receive 5–14 days of SOC treatment. The study enrolled patients between August 2020 and December 2022 (ClinicalTrials.gov identifier: NCT04335539; EudraCT identifier: 2019-002120-32).

Ethics

Written informed consent/assent was provided by the patient or the patient's parents/legally authorized representative, in accordance with local legal requirements. The study was conducted according to all applicable laws and regulations in the enrolling countries, the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines. The study design and all study-related documents received approval from local institutional review boards or ethics committees.

Inclusion/Exclusion Criteria

Hospitalized pediatric patients, 3 months to <18 years of age, with a suspected or confirmed aerobic Gram-negative pathogen, including complicated UTI, complicated intra-abdominal infection, hospital-acquired pneumonia/ventilator-associated pneumonia and sepsis or bloodstream infection were eligible for enrollment. Patients in the multiple-dose cohorts were expected to require inpatient intravenous antibiotic treatment for 5–14 days. Enrollment was planned at 24 sites in Belgium, Estonia, Latvia, Russia, Spain, Georgia, Hungary, Thailand and Ukraine.

Exclusion criteria: meningitis, osteomyelitis, cystic fibrosis; moderate or severe renal impairment based on estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 in the single-dose cohorts; eGFR <15 mL/min/1.73 m^2 in the multiple-dose cohorts; end-stage renal disease; hemodialysis or receipt of continuous venovenous hemofiltration; vasopressor therapy; shock in the prior month or at screening; severe neutropenia or immunocompromised; multiorgan failure; life expectancy <30 days due to a concurrent illness and pregnancy.

Screening occurred on or within 4 days before day 1 of cefiderocol treatment.

Age Cohorts

Patients were stratified into 4 separate age cohorts: cohort 1, 12 to <18 years; cohort 2, 6 to <12 years; cohort 3, 2 to <6 years and cohort 4, 3 months to <2 years. The single-dose phase of the study involved cohorts 1–4, and the multiple-dose phase involved cohorts 2–4. Cohort 1 (12 to <18 years old) was not included in the multiple-dose phase following a decision by the European Medicines Agency that extrapolation from adults was reasonable for this age group. The minimum planned enrollment was 6 patients in each cohort in the single-dose phase and 10 in each cohort in the multiple-dose phase, for a total of 54 patients. Patients were included in only one dosing phase of the study.

In cohorts 1–3, the safety, tolerability and plasma concentrations of cefiderocol in the single-dose phase were assessed in all 6 patients/cohort before opening enrollment of patients into the multiple-dose phase of the same age cohort. The single-dose phase of cohort 4 (ie, 3 months to <2 years) was initiated only when safety, tolerability and PK data had been evaluated in at least 6 patients from single-dose cohorts 1–3, and following enrollment of a minimum of 3 patients in cohort 3.

Cefiderocol Dosing and Treatment Duration

The dosing of cefiderocol (Shionogi & Co. Ltd, Osaka, Japan) was based on body weight and renal function (Table, Supplemental Digital Content 1, http://links.lww.com/INF/F685). In the single-dose phase, patients were required to have normal renal function (eGFR ≥90 mL/min/1.73 m^2) or only mild renal impairment (eGFR 60 to <90 mL/min/1.73 m^2). On day 1, cefiderocol was administered as an intravenous infusion over 3 hours (maximum dose 2000 mg for body weight ≥34 kg and at 60 mg/kg for body weight <34 kg) at any time during SOC treatment (Table, Supplemental Digital Content 1, http://links.lww.com/INF/F685). In the multiple-dose phase, patients may have had normal renal function (eGFR ≥90 mL/min/1.73 m^2), or mild (eGFR 60 to <90 mL/min/1.73 m^2), moderate (eGFR 30 to <60 mL/min/1.73 m^2) or severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/F685). Cefiderocol, each dose infused over 3 hours, was administered within 72 hours of the start of SOC antibiotic treatment (day 1) and then every 8 hours, with an expected duration of 5–14 days. A minimum of 6 doses was permissible to be considered evaluable. However, if considered by the investigator to be

TABLE 1. Patient Disposition

	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)
Patient disposition, n (%)									
Received treatment	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)	12 (100)	11 (100)	6 (100)	29 (100)
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)*†
Completed study‡	6 (100)	6 (100)	6 (100)	6 (100)	24 (100)	12 (100)	10 (90.9)	6 (100)	28 (96.6)
Discontinued from study	0	0	0	0	0	0	1 (9.1)§	0	1 (3.4)§

Percentages were based on the number of enrolled patients in each cohort.
*Reason for discontinuing treatment was "Other" (due to Gram-positive infection isolated).
†Patient discharged due to outbreak of hostilities.
‡Patient was marked as "Completed" in completion/discontinuation case report form.
§Protocol deviation (hospital-acquired pneumonia criterion not met).
C indicates cohort.
Cohort 1 = 12 to <18 years, cohort 2 = 6 to <12 years, cohort 3 = 2 to <6 years and cohort 4 = 3 months to <2 years.

in the patient's best interest, extended treatment duration beyond 14 days could be considered following the review and approval of individual cases by study personnel. SOC antibiotics were selected, and modified as required, by the investigator in accordance with local standards.

Objective

The primary objective was to assess the PK, safety and tolerability of single-dose and multiple-dose cefiderocol in hospitalized pediatric patients with suspected or confirmed Gram-negative bacterial infections.

Assessments

Safety assessments included adverse event (AE) monitoring, physical examinations, vital sign measurements and clinical laboratory tests performed before, during and after cefiderocol administration. AEs were monitored from the time of written consent up to 28 (+7) days after the last administered dose of cefiderocol in both the single-dose phase and multiple-dose phase. Ongoing AEs were monitored until resolution or stabilization.

Pharmacokinetic Assessments

PK sampling (0.18–0.4 mL of blood per patient) was performed at prespecified time points (ie, 1, 3, 3.5, 5 and 8 hours for cohorts 1 and 2 and 3, 5 and 8 hours for cohorts 3 and 4), with flexibility in the PK sampling schedule allowed for cohorts 1 and 2 (Table, Supplemental Digital Content 2, http://links.lww.com/INF/F686). In the multiple-dose phase of the study, blood samples were taken between the 6th and 12th doses of cefiderocol. Individual plasma concentrations are summarized for each cohort in both dosing phases using descriptive statistics, including geometric mean and geometric coefficient of variation. The unbound concentrations were calculated based on the unbound fraction of 0.422 derived from previous studies.[40]

Statistics

Continuous variables are summarized by using the number of nonmissing observations (N), arithmetic mean (mean), standard deviation, median and range (minimum–maximum) values. Categorical variables are summarized by using the frequency count and the percentage of patients in each category. Analysis populations are shown in Text, Supplemental Digital Content 3 (http://links.lww.com/INF/F687).

RESULTS

Patient Disposition

Of 55 patients screened with appropriate assent or consent in Belgium, Estonia, Latvia, Spain, Georgia, Thailand and Ukraine, 2 withdrew. Of the 53 patients enrolled, 24 received a single dose of cefiderocol and 29 patients received multiple doses (Tables 1 and 2). Slow recruitment into the multiple-dose phase resulted in only 6 patients being enrolled in cohort 4. All patients in the single-dose phase and 89.7% and 96.6% of those in the multiple-dose phase completed treatment and the study, respectively (Table 1, Table, Supplemental Digital Content 4, http://links.lww.com/INF/F688). All patients received cefiderocol in combination with SOC (Table, Supplemental Digital Content 5, http://links.lww.com/INF/F689).

Patient Characteristics

The median (range) age of patients was 73.5 (3–190) months [6.2 (0.3–15.8) years] in the single-dose phase and 64.0 (5–143) months [5.3 (0.4–11.9) years] in the multiple-dose phase (Table 2, Table, Supplemental Digital Content 6, http://links.lww.com/INF/F690). Nine patients (37.5%) in the single-dose phase across cohorts 1–4 and 8 patients (27.6%) in the multiple-dose phase across cohorts 2–4 had eGFR of ≥120 mL/min/1.73 m^2. Most commonly, patients had complicated UTI and complicated intra-abdominal infections in both the single-dose phase and multiple-dose phase (Table 2).

Cefiderocol Exposure in Multiple-dose Phase

The median extent of cefiderocol exposure was 8.0 (range: 2–15) days, 86.2% of patients received 5–14 days of treatment: the median (range) number of cefiderocol doses received was 21.0 (12–42) in cohort 2, 27.0 (6–42) in cohort 3 and 15 (7–18) in cohort 4. All patients received 3-hour infusions of cefiderocol in the multiple-dose phase.

Pharmacokinetics

The plasma cefiderocol concentration profiles after the single and multiple doses were similar in all age cohorts (Fig. 1A and B). The geometric mean concentrations at 3 hours after the start of infusion (the end of infusion, considered peak concentrations) ranged between 72.7 and 97.1 μg/mL in the single-dose cohorts and between 88.8 and 106.0 μg/mL in the multiple-dose cohorts (Table, Supplemental Digital Content 7, http://links.lww.com/INF/F691). The geometric mean concentrations at 8 hours after the start of infusion (considered trough concentrations, before the next infusion in the multiple-dose cohort) ranged between 7.86 and 10.8 μg/mL

TABLE 2. Demographics and Baseline Characteristics of Pediatric Patients Receiving Single-dose or Multiple-dose Cefiderocol (Safety Population)

	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)
Age (yr)									
Mean	14.27	9.10	2.87	1.05	6.82	8.72	4.35	0.73	5.41
SD	1.34	1.68	1.30	0.53	5.48	1.88	1.20	0.42	3.43
Median	14.65	9.25	2.40	1.15	6.15	8.90	5.00	0.55	5.30
Range	12.5–15.8	6.8–10.9	2.1–5.5	0.3–1.8	0.3–15.8	6.3–11.9	2.3–5.7	0.4–1.4	0.4–11.9
Sex, n (%)									
Male	2 (33.3)	2 (33.3)	3 (50.0)	3 (50.0)	10 (41.7)	3 (25.0)	2 (18.2)	4 (66.7)	9 (31.0)
Female	4 (66.7)	4 (66.7)	3 (50.0)	3 (50.0)	14 (58.3)	9 (75.0)	9 (81.8)	2 (33.3)	20 (69.0)
BMI (kg/m^2)									
Mean	23.42	17.02	16.38	15.95	18.19	16.14	14.62	14.81	15.29
SD	2.08	2.30	3.41	3.50	4.12	2.34	2.05	1.65	2.16
Median	24.02	16.78	15.06	17.00	17.84	15.49	14.57	14.45	15.26
Range	20.3–25.3	14.4–20.7	13.3–22.4	9.2–18.5	9.2–25.3	13.5–20.6	11.0–18.0	13.3–17.2	11.0–20.6
Body weight (kg)									
Mean	60.17	30.32	14.25	8.62	28.34	27.37	16.95	6.82	19.16
SD	10.19	8.43	4.03	2.13	21.47	3.85	3.97	0.84	8.66
Median	63.50	29.15	13.90	8.80	19.85	26.50	16.00	6.85	19.00
Range	43.0–69.0	20.0–44.6	9.8–19.7	4.9–11.4	4.9–69.0	20.0–35.5	11.0–25.0	5.7–7.9	5.7–35.5
eGFR grading group, n (%)*									
≥120 (mL/min/1.73 m^2)	2 (33.3)	1 (16.7)	2 (33.3)	4 (66.7)	9 (37.5)	3 (25.0)	1 (9.1)	4 (66.7)	8 (27.6)
90 to <120 (mL/min/1.73 m^2)	4 (66.7)	4 (66.7)	4 (66.7)	0	12 (50.0)	7 (58.3)	5 (45.5)	2 (33.3)	14 (48.3)
60 to <90 (mL/min/1.73 m^2)	0	1 (16.7)	0	2 (33.3)	3 (12.5)	2 (16.7)	5 (45.5)	0	7 (24.1)
eGFR (mL/min/1.73 m^2)									
Mean	110.57	110.80	119.95	128.48	117.45	103.66	85.33	139.02	104.02
SD	16.35	36.61	39.26	54.25	37.17	28.72	24.50	37.04	34.40
Median	109.40	103.80	109.05	131.10	109.40	95.00	90.70	126.55	95.90
Range	92.3–136.6	66.0–177.0	91.5–195.0	60.1–216.1	60.1–216.1	60.9–162.8	61.1–129.5	101.7–192.0	60.9–192.0

Percentages were calculated using the number of patients in the column heading as the denominator.

*For ages ≥3 months to <1 year, eGFR = 0.45 × (height/SCr); for ages ≥1 to <18 years, eGFR = 0.413 × (height/SCr), where height is expressed in centimeters and SCr is expressed in mg/dL.

BMI indicates body mass index; C, cohort; eGFR, estimated glomerular filtration rate; SCr, standardized serum creatinine; SD, standard deviation.

Cohort 1 = 12 to <18 years, cohort 2 = 6 to <12 years, cohort 3 = 2 to <6 years and cohort 4 = 3 months to <2 years.

in the single-dose cohorts and between 9.64 and 18.1 μg/mL in the multiple-dose cohorts (Table, Supplemental Digital Content 7, http://links.lww.com/INF/F691). In the multiple-dose phase of the study in each age cohort, the free drug trough concentrations ranged between 4.07 and 7.67 μg/mL (Table, Supplemental Digital Content 8, http://links.lww.com/INF/F692). In this patient population, no correlation was found between total trough concentrations and eGFR (Figure, Supplemental Digital Content 9, http://links.lww.com/INF/F693).

Safety

Five patients experienced 12 treatment-emergent adverse events (TEAEs) in the single-dose phase (1 event in cohort 2, 7 in cohort 3 and 4 in cohort 4) and 7 patients experienced 10 TEAEs in the multiple-dose phase (2 events in cohort 2, 1 in cohort 3 and 7 in cohort 4). There were no deaths or treatment-related serious adverse events (SAEs) and no discontinuations due to treatment-related AEs. TEAEs are shown by System Organ Class and Preferred Term in Table 3. All TEAEs were mild or moderate in severity. Only 1 patient, in cohort 4 of the multiple-dose phase, had 2 treatment-emergent SAEs reported by the investigator [UTI (resolved on day 37) and staphylococcal bacteremia (resolved on day 44)], both of which were of moderate severity and considered by the investigator to be unrelated to cefiderocol.

Throughout the study, several patients had laboratory test results outside the normal range (Table, Supplemental Digital Content 10, http://links.lww.com/INF/F694). There was no evidence of liver toxicity with cefiderocol. No clinically significant changes in laboratory results from baseline were recorded. No abnormal findings in vital signs (blood pressure, pulse rate, respiratory rate and body temperature) were observed in either the single-dose or multiple-dose phase.

Gram-negative Bacterial Isolates

A total of 18 Gram-negative bacterial isolates were collected from patients in the microbiologic intent-to-treat population, including 13 *Escherichia coli*, 2 *Klebsiella pneumoniae*, 1 *Enterobacter cloacae*, 1 *Neisseria meningitidis* and 1 *Salmonella* spp. (Table, Supplemental Digital Content 11, http://links.lww.com/INF/F695). All but one isolate was susceptible to cefiderocol by EUCAST breakpoints. One *E. cloacae* isolate had cefiderocol MIC of 4 μg/mL. None of the Gram-negative isolates were CR or MDR.

DISCUSSION

The PEDI-CEFI study aimed to investigate the safety, tolerability and PK profile of cefiderocol in pediatric patients between 3 months and <18 years old in 4 age cohorts receiving weight-adjusted doses, who were hospitalized due to a suspected or confirmed Gram-negative bacterial infection.

Based on previous simulations,[31] the initial dose selected for testing in pediatric patients was 2000 mg for patients with body weight ≥34 kg and 60 mg/kg for those <34 kg and normal renal function, with no subject receiving >2000 mg. In the multiple-dose phase of the study, while an eGFR <60 mL/min/1.73 m^2 was

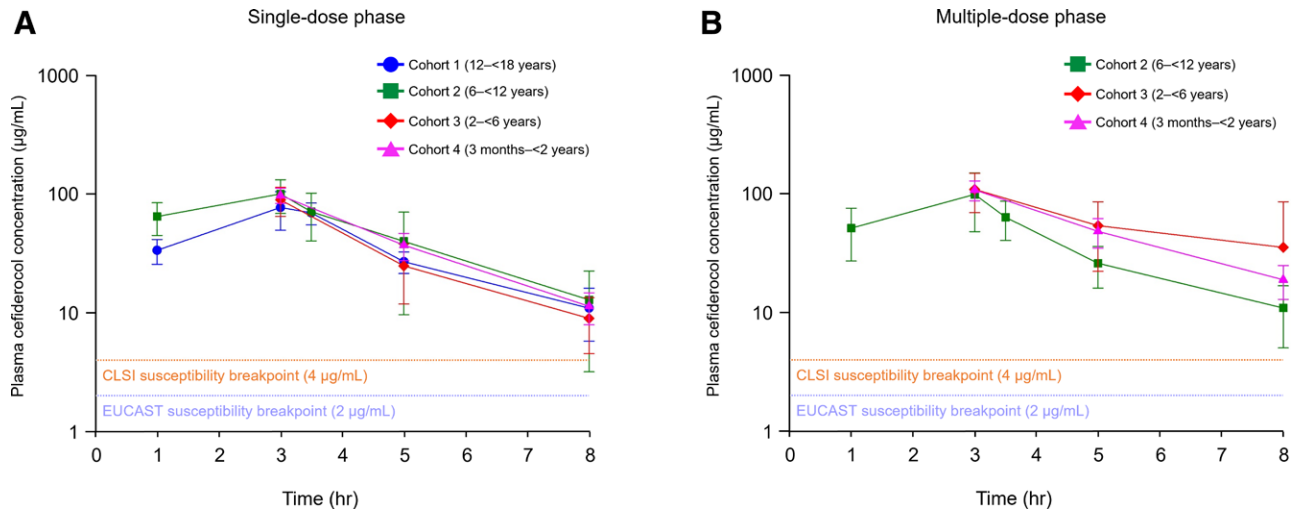

FIGURE 1. Mean (SD) plasma cefiderocol concentration over time for pediatric patients in the single-dose phase (A) and multiple-dose phase (B) by age cohort (PKCS population). Cohort 1 = 12 to <18 years, cohort 2 = 6 to <12 years, cohort 3 = 2 to <6 years and cohort 4 = 3 months to <2 years. By study design, multiple-dose cefiderocol was not administered to subjects in age cohort 1 (ie, 12–<18 years). Mean and SD of plasma cefiderocol concentration presented at ≥0 µg/mL in these plots even though the lower range for SD could be <0 µg/mL. PKCS indicates pharmacokinetic concentration summary (n = 28; 1 patient did not have blood sample for pharmacokinetic analysis); CLSI indicates Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; SD, standard deviation.

permitted in the eligibility criteria, no enrolled patient had this level of renal function. Seventeen patients had an eGFR ≥120 mL/min/1.73 m^2. While study enrollment was relatively slow for the youngest cohort in the multiple-dose phase of the study and only 6 patients were enrolled before a decision by the sponsor and regulators was made to close the study, PK data from this age cohort provide some useful data.

The mean PK concentration–time profile curves in the multiple-dose phase of the study suggest that the weight-adjusted doses applied in the study across the 4 age cohorts resulted in similar maximum and trough concentrations in pediatric patients, and this was applicable regardless of their age, and renal function over the ranges present in the enrolled subjects (both eGFR 60–120 and ≥120 mL/min/1.73 m^2). Of note, collectively, dosing every 8 hours for pediatric patients with eGFR ≥120 mL/min/1.73 m^2 provided sufficient exposures compared with patients with eGFR 60–120 mL/min/1.73 m^2, but the number of patients were limited per age cohort. Studies in adults reported that cefiderocol demonstrates effective lung epithelial lining fluid penetration in parallel with plasma concentrations following a single intravenous dose (2000 mg) in healthy subjects,[41] and achieves lung epithelial lining fluid concentrations sufficient to treat Gram-negative pulmonary bacterial infections with a relatively high MIC of ≤4 µg/mL in patients with pneumonia undergoing mechanical ventilation and receiving multiple cefiderocol doses (2 g every 8 hours).[39] The PD driver of cefiderocol efficacy is the proportion of the dosing interval spent above the MIC by the unbound antibiotic at the site of infection (%*f*T>MIC).[40,42] In the current study, cefiderocol total trough concentrations in plasma in pediatric patients (9.64–18.1 µg/mL on average in all age groups and 4.07–7.64 µg/mL of free drug concentrations (using unbound fraction of 0.422) remained above the approved European Committee on Antimicrobial Susceptibility Testing (EUCAST)[43] and Clinical and Laboratory Standards Institute[44] susceptibility breakpoints for the various Gram-negative pathogens, thereby providing uniform attainment of a stringent PD target of 100% T>MIC. According to MIC distribution curves, most Gram-negative isolates have low cefiderocol MIC values[12,22,26]; thus, exposure, as linked to the MIC and achieved with these weight-adjusted doses, is likely to exceed those necessary for cure.

There were no safety concerns with cefiderocol in pediatric patients and safety results were within expectations of the beta-lactams class from adult studies. No deaths or treatment-related SAEs and no discontinuations due to treatment-related AEs were reported. The 2 treatment-emergent SAEs that were experienced by one patient were considered not to be related to cefiderocol. There were no clinically significant abnormal findings in laboratory tests, including hematology or chemistry, or in vital signs.

As all patients in the study also received SOC antibiotics; thus, no formal assessment of clinical or microbiologic efficacy attributable to cefiderocol can be made. The clinically relevant species isolates causing pneumonia, UTI, and/or bloodstream infection were limited to *E. coli*, *E. cloacae* and *K. pneumoniae* isolates, all but one of which had cefiderocol susceptibility, according to current EUCAST breakpoints for concentrations in plasma (ie, 2 µg/mL for Enterobacterales).[43] The exception was one *E. cloacae* urinary tract isolate with a cefiderocol MIC of 4 µg/mL. However, the plasma trough concentrations indicated that adequate cefiderocol exposure required for clinical and microbiologic activity was achieved for this pathogen. A phase 1 study conducted in healthy adult subjects confirmed that >60% of cefiderocol in the plasma is excreted into the urine in an unchanged form, and cefiderocol urine concentrations remain very high at 8 hours following administration.[28] It should also be noted that investigators reported no clinical failures or microbiologic persistence in this setting (data not shown).

The limitations of this study include the low number of patients in the individual cohorts and renal function subgroups. Furthermore, patients with moderate or severe renal impairment were not enrolled, thus, extrapolation of the data to these subgroups is not possible, and require additional studies. Further data are required to confirm that the current doses are appropriate for pediatric patients and that high probability of target attainment can

TABLE 3. Safety in Pediatric Patients Receiving Single-dose or Multiple-dose Cefiderocol (Safety Population)

System Organ Class Preferred Term, n (%)	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 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 spp. 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)

Percentages were based on number of patients within each column header.

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

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

Cohort 1 = 12 to <18 years, cohort 2 = 6 to <12 years, cohort 3 = 2 to <6 years and cohort 4 = 3 months to <2 years.

Adverse events are coded using Medical Dictionary for Regulatory Activities version 23.0. A patient is counted only once for multiple events within Preferred Term/System Organ Class. The same patient may appear in different categories. TEAEs are defined as adverse events reported after the initial dose of study drug and were assessed and reported by the investigators.

be achieved in pediatric patients with different age, sex, ethnicity, race and clinical characteristics. To better understand the safety and PK of cefiderocol in pediatric patients, one clinical study is recruiting patients 3 months to <18 years of age (ClinicalTrials.gov NCT04215991; expected completion in 2024) and another study is recruiting neonates and infants (ClinicalTrials.gov NCT06086626; expected completion in 2024).

In conclusion, this study demonstrated that a 3-hour infusion of cefiderocol was adequate for providing activity against clinically relevant Gram-negative species in a variety of infection types. Cefiderocol was well tolerated in both the single-dose and multiple-dose phases of the study, with infrequent AEs, none of which were related to cefiderocol. Thus, cefiderocol could be a valuable treatment option for pediatric patients with MDR and CR Gram-negative bacterial infections.

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