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Pharmacokinetics, Safety and Tolerability of Cefiderocol in Paediatric Patients Aged 3 Months to <18 Years with Suspected or Confirmed Gram-Negative Bacterial Infections: Results of the Phase 1b–2 APEKS-PEDI Study

Emmanuel Roilides[1], John S. Bradley[2], Oluwaseun Makinde[3], Mari Ariyasu[4], Takamichi Baba[4], Takayuki Katsube[4], Brigitte Johnson[3], Maria Paabol Larsen[3], Simon Portsmouth[3]

[1]Aristotle University of Thessaloniki, and Hippokration General Hospital, Thessaloniki, Greece, [2]University of California San Diego School of Medicine, and Rady Children's Hospital, San Diego, California, USA, [3]Shionogi Inc., Florham Park, New Jersey, USA, [4]Shionogi & Co., Ltd, Osaka, Japan

Contact: Emmanuel Roilides
Email: roilides@auth.gr

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INTRODUCTION

Cefiderocol, a siderophore cephalosporin, is approved in the USA for the treatment of adult patients with complicated urinary tract infections (cUTI), including acute pyelonephritis, hospital-acquired bacterial pneumonia (HABP), and ventilator-associated bacterial pneumonia (VABP) [1]. In Europe, it is approved for the treatment of adults with Gram-negative bacterial infections with limited treatment options [2]. New antibiotics are urgently needed to treat paediatric multidrug-resistant Gram-negative bacterial infections [3].

OBJECTIVES

The safety, tolerability, and pharmacokinetic (PK) profile of cefiderocol were investigated in the APEKS-PEDI (*Acinetobacter*, *Pseudomonas*, *Escherichia coli*, *Klebsiella*, *Stenotrophomonas* - paediatric) study in hospitalised children aged 3 months to <18 years with suspected or confirmed Gram-negative bacterial infections, who were also receiving standard-of-care (SOC) antibiotic treatment for 5–14 days (ClinicalTrials.gov: NCT04215991). Prolonged administration (i.e., over 3 hours) was used to maximise the time antibiotic concentrations in plasma were above the minimum inhibitory concentration (MIC) of potential pathogens.

METHODS

- **Study design:** multicentre, open-label, phase 1b–2 clinical study.
- **Age cohorts: 1**: 12–<18 years; **2**: 6–<12 years; **3**: 2–<6 years; **4**: 3 months–<2 years.
- **Non-randomised single-dose (SD) phase (Cohorts 2–4):** one dose of cefiderocol was infused over 3 hours while patients received SOC antibiotics. Patients with suspected or documented Gram-negative infections were enrolled. Patients had normal renal function or mild renal impairment and received cefiderocol 2000 mg (for body weight ≥34 kg) or 60 mg/kg (for body weight <34 kg).
- **Randomised (4:1) multiple-dose (MD) phase (Cohorts 1–4):** cefiderocol (infused over 3 hours) was administered every 8 hours for 5–14 days in addition to SOC vs. SOC alone. Cefiderocol monotherapy was permitted if SOC antibiotics had not been initiated by the time infection was confirmed as Gram-negative only. Only patients with cUTI, HABP, or VABP were enrolled. Patients had normal renal function or mild, moderate, or severe renal impairment (excluding patients with estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2, or those with end-stage renal disease requiring haemodialysis or continuous venovenous haemofiltration). The dose of cefiderocol was adjusted for patients with moderate renal impairment to 1500 mg (for body weight ≥34 kg) or 45 mg/kg (for body weight <34 kg), or with severe renal impairment to 1000 mg (for body weight ≥34 kg) or 30 mg/kg (for body weight <34 kg).
- Blood samples were collected at baseline and at prespecified time points for measurement of total plasma cefiderocol concentrations.
- The safety of cefiderocol was evaluated by clinical and laboratory assessment; treatment-emergent adverse events (TEAEs) were reported from the day informed consent was obtained up to the end of the study (i.e., 28 [+7] days after end of treatment).

RESULTS

Baseline demographics

- Patients' baseline demographics and clinical characteristics in the SD and MD phases are shown in **Table 1.**
- In the MD phase, 54 patients receiving cefiderocol ± SOC and 13 patients receiving SOC only had cUTI, and 38 and 8 patients had confirmed Gram-negative infection, respectively.
- Among patients with cUTI, *Escherichia coli* (cefiderocol ± SOC 63.2% [n=24]; SOC only 62.5% [n=5]) was the most frequent pathogen, followed by *Klebsiella pneumoniae* (cefiderocol ± SOC 10.5% [n=4]; SOC only [n=0]) and *Pseudomonas aeruginosa* (cefiderocol ± SOC 7.9% [n=3]; SOC only 37.5% [n=3]). Among five patients with HABP/VABP, *Acinetobacter baumannii-calcoaceticus* complex was found in two patients (cefiderocol ± SOC [n=2]; SOC only [n=0]). Cefiderocol MICs were ≤2 µg/mL for all species.

Table 1. Demographics and baseline clinical characteristics of paediatric patients in the APEKS-PEDI study (Safety/ITT population).

	Single-dose phase Cefiderocol + SOC				Multiple-dose phase Cefiderocol ± SOC					SOC only				
	C2 N=5	C3 N=2	C4 N=5	Overall N=12	C1 N=14	C2 N=14	C3 N=17	C4 N=14	Overall N=59	C1 N=3	C2 N=3	C3 N=4	C4 N=3	Overall N=13
Age, median (min; max), years	9.7 (6.7; 11.6)	4.9 (4.9; 4.9)	0.4 (0.3; 0.9)	4.9 (0.3; 11.6)	15 (12.8; 17.7)	9.25 (6.5; 11.3)	3.8 (2.2; 5.8)	0.45 (0.3; 1.7)	5.8 (0.3; 17.7)	15 (14.7; 15.4)	6.8 (6.7; 11.3)	4.2 (3.3; 4.6)	0.6 (0.3; 0.7)	4.6 (0.3; 15.4)
Sex, male, n (%)	3 (60.0)	0	2 (40.0)	5 (41.7)	7 (50.0)	6 (42.9)	3 (17.6)	8 (57.1)	24 (40.7)	1 (33.3)	2 (66.7)	1 (25.0)	2 (66.7)	6 (46.2)
Body weight, n[a]	5	2	5	12	14	14	17	14	59	2	3	3	0	8
Body weight, median (min; max), kg	34.7 (18.9; 37.5)	26.9 (18.6; 35.1)	7.0 (6.8; 7.4)	18.8 (6.8; 37.5)	52.3 (16.0; 83.4)	25.8 (17.2; 48.3)	14.6 (9.4; 27.0)	7.1 (4.9; 12.7)	17.2 (4.9; 83.4)	57.0 (57.0; 57.0)	25.4 (19.9; 72.5)	15.0 (11.9; 15.0)	NA	22.7 (11.9; 72.5)
eGFR grading group, n (%), mL/min/1.73 m^2														
≥120	1 (20.0)	0	1 (20.0)	2 (16.7)	4 (28.6)	3 (21.4)	8 (47.1)	3 (21.4)	18 (30.5)	0	1 (33.3)	1 (25.0)	0	2 (15.4)
90 to <120	2 (40.0)	0	2 (40.0)	4 (33.3)	5 (35.7)	7 (50.0)	5 (29.4)	4 (28.6)	21 (35.6)	0	1 (33.3)	2 (50.0)	1 (33.3)	4 (30.8)
60 to <90	2 (40.0)	2 (100)	2 (40.0)	6 (50.0)	3 (21.4)	2 (14.3)	4 (23.5)	5 (35.7)	14 (23.7)	2 (66.7)	1 (33.3)	0	1 (33.3)	4 (30.8)
30 to <60	0	0	0	0	2 (14.3)	1 (7.1)	0	2 (14.3)	5 (8.5)	0	0	0	0	0
15 to <30	0	0	0	0	0	1 (7.1)	0	0	1 (1.7)	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	1 (33.3)	0	1 (25.0)	1 (33.3)	3 (23.1)
eGFR, n[b]	5	2	5	12	14	14	17	14	59	2	3	3	2	10
eGFR, median (min; max), [mL/min/1.73 m^2]	101.3 (71.6; 171.7)	72.4 (67.5; 77.3)	94.6 (76.2; 146.3)	89.8 (67.5; 171.7)	96.55 (40.4; 469.3)	103.5 (27.3; 308.3)	101.6 (73.5; 165.2)	89 (40.2; 262.8)	97.8 (27.3; 469.3)	68.35 (64.2; 72.5)	108.8 (68.0; 135.1)	119.3 (97.3; 271.4)	84.2 (63.4; 105.0)	101.15 (63.4; 271.4)
Infection, n (%)														
cUTI	2 (40.0)	2 (100)	4 (80.0)	8 (66.7)	10 (71.4)	14 (100)	16 (94.1)	14 (100)	54 (91.5)	3 (100)	3 (100)	4 (100)	3 (100)	13 (100)
HABP/VABP	0	0	0	0	4 (28.6)	0	1 (5.9)	0	5 (8.5)	0	0	0	0	0
cIAI	1 (20.0)	0	0	1 (8.3)	0	0	0	0	0	0	0	0	0	0
BSI	1 (20.0)	0	1 (20.0)	2 (16.7)	0	0	0	0	0	0	0	0	0	0
Sepsis	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other[c]	1 (20.0)	0	0	1 (8.3)	0	0	0	0	0	0	0	0	0	0

BSI, bloodstream infection; C, cohort; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; eGFR, estimated glomerular filtration rate; HABP, hospital-acquired bacterial pneumonia; ITT, intent-to-treat; NA, not available; SOC, standard of care; VABP, ventilator-associated bacterial pneumonia. [a]Number of patients with body weight data available; [b]Number of patients with eGFR data available; [c]Patient had *Pseudomonas aeruginosa* scalp infection.

Treatment exposure and PK

- In the SD phase (n=12), all patients received one dose of cefiderocol and in the MD phase, most patients received cefiderocol ± SOC for 5–14 days (**Table 2**).
  - In the MD phase, three patients received cefiderocol as monotherapy and 56 patients received cefiderocol + SOC antibiotics.
- In the SD phase, cefiderocol maximum concentration at 3 hours (at end of infusion) was 76.0 µg/mL in Cohort 2 (n=4), 341.0 µg/mL in Cohort 3 (n=1), and 87.1 µg/mL in Cohort 4 (n=4) (**Table 3; Figure 1**). At 8 hours, cefiderocol trough concentrations ranged from 6.6 to 14.0 µg/mL across the three cohorts.
- In the MD phase (n=58), cefiderocol maximum concentrations ranged from 84.4 to 108.0 µg/mL at 3 hours (end of infusion), and trough concentrations ranged from 10.6 to 16.2 µg/mL at 8 hours (at end of dosing period) (**Table 3; Figure 1**).

Safety

- In the SD phase, five patients (41.7%) experienced 20 TEAEs (**Table 4**).
  - Minor treatment-related TEAEs occurred in three patients.
  - No deaths, serious adverse events (SAEs), or TEAEs leading to withdrawal of cefiderocol were reported.
- In the MD phase, 44 (74.6%) of 59 patients who received cefiderocol ± SOC antibiotics experienced 221 TEAEs, and eight (61.5%) of 13 patients who received SOC alone experienced 38 TEAEs (**Table 4**).
  - One patient (1.7%) treated with cefiderocol ± SOC experienced two treatment-related TEAEs (thrombocytosis and transaminases increased). No treatment-related SAEs were reported.
  - Two patients (3.4%) who received cefiderocol ± SOC experienced three TEAEs leading to withdrawal of cefiderocol; one patient (1.7%) had two events considered treatment related (thrombocytosis and transaminases increased) and one patient experienced unrelated electrolyte imbalance leading to withdrawal of cefiderocol ± SOC.
  - No TEAEs in those receiving SOC alone led to withdrawal from treatment.

References

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Conflict of interest

ER has received no personal funding. His institution has received research grants from Shionogi, Pfizer, and Merck. ER, OM, MA, TB, TK, BJ, MPL, and SP are/were employees of Shionogi during the conduct of the study. JSB has received no personal funding from Shionogi for any work, including the development of this poster. His employer, the Regents of the University of California, has received funding from Shionogi for the conduct of paediatric clinical trials and for consulting for cefiderocol.

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Table 2. Extent of exposure to, and compliance with, cefiderocol treatment in the single- and multiple-dose phases (Safety population).

	Single-dose phase Cefiderocol + SOC				Multiple-dose phase Cefiderocol ± SOC				
	C2 N=5 n (%)	C3 N=2[b] n (%)	C4 N=5 n (%)	Overall N=12 n (%)	C1 N=14 n (%)	C2 N=14 n (%)	C3 N=17 n (%)	C4 N=14 n (%)	Overall N=59 n (%)
Extent of exposure, days[a]									
Median	1.0	1.0	1.0	1.0	10.0	9.0	7.0	5.5	8.0
Minimum	1	1	1	1	4	5	1	2	1
Maximum	1	1	1	1	19	14	13	13	19
Extent of exposure, days, categorical, n (%)									
1	5 (100)	2 (100)	5 (100)	12 (100)	0	0	1 (5.9)	0	1 (1.7)
2–4	0	0	0	0	2 (14.3)	0	2 (11.8)	6 (42.9)	10 (16.9)
5–14	0	0	0	0	10 (71.4)	14 (100)	14 (82.4)	8 (57.1)	46 (78.0)
>14–21	0	0	0	0	2 (14.3)	0	0	0	2 (3.4)
>21	0	0	0	0	0	0	0	0	0
Total number of doses received									
Median	1.0	1.0	1.0	1.0	30.0	27.0	21.0	16.5	24.0
Minimum	1	1	1	1	10	15	1	6	1
Maximum	1	1	1	1	57	40	38	37	57

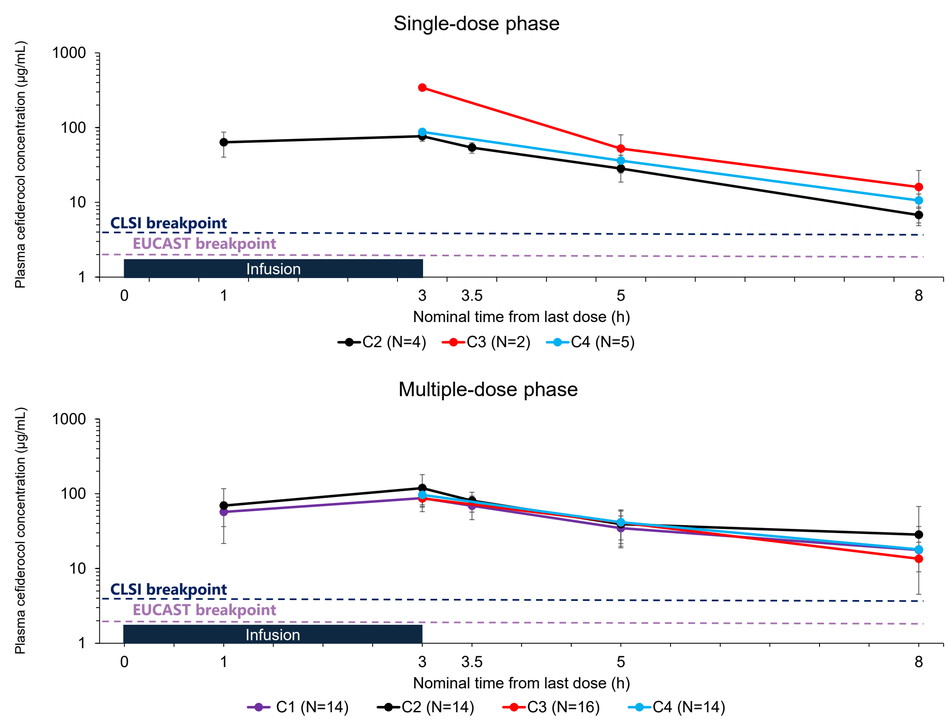
C, cohort; SOC, standard of care. [a]Extent of exposure to study drug (days) = round up to an integer of (the stop date and time (HH:MM) of the last dose – the start date and time (HH:MM) of the first dose / [60×60×24]). [b]Both patients in the single-dose phase in C3 had dosing errors.

Table 3. Pharmacokinetics of cefiderocol in the single- and multiple-dose phases (PKCS population).

DAY 1	Total cefiderocol concentration (µg/mL) Geometric mean (geometric CV %) Single-dose phase				
	C1	C2[a] N=4	C3[b] N=2	C4[b] N=5	Overall N=11
Time after start of infusion					
1 h	NA	60.4 (38.5) [n=4]	NA	NA	60.4 (38.5) [n=4]
3 h (end of infusion)		76.0 (14.9) [n=4]	341.0 (–) [n=1][c]	87.1 (9.6) [n=4]	95.4 (52.7) [n=9]
3.5 h		53.4 (16.0) [n=4]	NA	NA	53.4 (16.0) [n=4]
5 h		27.2 (32.6) [n=3]	48.5 (60.1) [n=2]	35.7 (19.4) [n=5]	35 (35.4) [n=10]
8 h (end of dosing interval)		6.6 (25.7) [n=4]	14.0 (83.3) [n=2]	10.4 (23.3) [n=5]	9.3 (44.6) [n=11]
DAY 3 or 4	Multiple-dose phase				
	C1[a] N=14	C2[a] N=14	C3[b] N=16	C4[b] N=14	Overall N=58
Time after start of infusion					
1 h	50.2 (74.4) [n=14]	54.5 (92.9) [n=14]	NA	NA	52.3 (81.9) [n=28]
3 h (end of infusion)	85.2 (25.0) [n=13]	108.0 (45.8) [n=13]	84.4 (24.5) [n=14]	93.6 (27.5) [n=9]	92.2 (32.7) [n=49]
3.5 h	65.4 (35.4) [n=14]	77.2 (33.1) [n=14]	NA	NA	71.0 (34.8) [n=28]
5 h	31.8 (44.9) [n=14]	34.8 (56.5) [n=14]	36.8 (53.3) [n=16]	37.8 (50.1) [n=14]	35.3 (50.4) [n=58]
8 h (end of dosing interval)	13.6 (73.1) [n=10]	15.6 (148.0) [n=12]	10.6 (84.0) [n=16]	16.2 (48.4) [n=13]	13.6 (88.2) [n=51]

C, cohort; CV, coefficient of variance of the geometric mean; NA, not applicable; N, number of patients in the PKCS population; n, number of non-missing concentrations for analysis of geometric mean and geometric CV %; PKCS, pharmacokinetic concentration summary. [a]Blood samples were collected at five time points in Cohort 2 in the single-dose phase, and in Cohorts 1 and 2 in the multiple-dose phase. [b]Blood samples were collected at three time points in both Cohorts 3 and 4 in the SD phase and the MD phase. [c]The patient had an overdose of 2106 g cefiderocol (major protocol deviation).

Figure 1. Arithmetic mean and standard deviation plasma cefiderocol concentrations over time in the single-dose phase and the multiple-dose phase (PKCS population).



The plot displays the means and standard deviations (error bars) for plasma cefiderocol concentration. PKCS, pharmacokinetic concentration summary. PKCS population: all enrolled patients who received at least one dose of cefiderocol in the single-dose phase and at least four doses of cefiderocol in the multiple-dose phase and had at least one evaluable blood sample for pharmacokinetic analysis.

Table 4. Treatment-emergent adverse events following administration of cefiderocol in paediatric patients (Safety population).

	Single-dose phase Cefiderocol + SOC					SOC only
	C1	C2 N=5 n (%)	C3 N=2 n (%)	C4 N=5 n (%)	Overall N=12 n (%)	NA
Any TEAEs	NA	2 (40.0)	1 (50.0)	2 (40.0)	5 (41.7)	NA
Treatment-related TEAEs[a]		1 (20.0)	1 (50.0)	1 (20.0)	3 (25.0)	
Treatment-emergent SAEs		0	0	0	0	
Treatment-related SAEs		0	0	0	0	
Drug withdrawn due to TEAEs		0	0	0	0	
Drug withdrawn due to related TEAEs		0	0	0	0	
TEAEs leading to death		0	0	0	0	

	Multiple-dose phase Cefiderocol ± SOC					SOC only				
	C1 N=14 n (%)	C2 N=14 n (%)	C3 N=17 n (%)	C4 N=14 n (%)	Overall N=59 n (%)	C1 N=3 n (%)	C2 N=3 n (%)	C3 N=4 n (%)	C4 N=3 n (%)	Overall N=13 n (%)
Any TEAEs	8 (57.1)	11 (78.6)	13 (76.5)	12 (85.7)	44 (74.6)	2 (66.7)	3 (100)	2 (50.0)	1 (33.3)	8 (61.5)
Treatment-related TEAEs	0	0	0	1 (7.1)[b]	1 (1.7)	0	0	0	0	0
Treatment-emergent SAEs	0	2 (14.3)	2 (11.8)	4 (28.6)	8 (13.6)	1 (33.3)	0	0	0	1 (7.7)
Treatment-related SAEs	0	0	0	0	0	0	0	0	0	0
Drug withdrawn due to TEAEs	0	0	1 (5.9)[c]	1 (7.1)[b]	2 (3.4)	0	0	0	0	0
Drug withdrawn due to related TEAEs	0	0	0	1 (7.1)[b]	1 (1.7)	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0	0	0	0	0

Percentages are based on number of patients within each column header N; n refers to the number of patients in each category. TEAEs are defined as adverse events reported after the initial dose of study drug. Adverse events are coded using MedDRA version 23.0.
C, cohort; NA, not applicable; SAE, serious adverse event; SOC, standard of care; TEAE, treatment-emergent adverse event.
[a]One patient in Cohort 2 had infusion-site pain, one patient in Cohort 3 had infusion-site pain, and one patient in Cohort 4 had neutropenia.
[b]One patient had thrombocytosis and transaminases increased; patient received cefiderocol + ciprofloxacin, cefuroxime as SOC antibiotics.
[c]One patient had unrelated electrolyte imbalance; event resolved after withdrawal of both cefiderocol + meropenem as SOC antibiotic.

CONCLUSION

- Cefiderocol (± SOC) treatment for 5–14 days in this study was well tolerated. The safety profile was similar to that of other β-lactam antibiotics and without unexpected adverse effects.
- Total plasma trough cefiderocol concentrations remained above 4 µg/mL (i.e., susceptibility breakpoint for Enterobacterales, *P. aeruginosa*, and *Acinetobacter* spp. by the Clinical and Laboratory Standards Institute) and 2 µg/mL (i.e., susceptibility breakpoint for Enterobacterales and *P. aeruginosa* by EUCAST) for the whole dosing period in all age cohorts.
- Cefiderocol may be a treatment option in the paediatric population for the treatment of multidrug-resistant Gram-negative infections.