EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 July 2025
EMADOC-1700519818-2101476
Human Medicine Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Fetcroja

International non-proprietary name: Cefiderocol

Procedure no.: EMA/PAM/0000268740

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of Procedure	26 May 2025	26 May 2025
☐	CHMP Rapporteur AR	30 June 2025	30 June 2025
☐	CHMP comments	14 July 2025	N/A
☐	Updated CHMP Rapporteur AR	17 July 2025	N/A
☒	CHMP outcome	24 July 2025	24 July 2025

Table of contents

1. Introduction 4

2. Scientific discussion 4

2.1. Information on the development program 4
2.2. Information on the pharmaceutical formulation used in the study 4
2.3. Clinical aspects 4
2.3.1. Introduction 4
2.3.2. Clinical Study 1704R2133 5
Description 5
Methods 5
Results 8
2.3.3. Discussion on clinical aspects 28

3. Rapporteur's overall conclusion and recommendation 29

Fulfilled: 29

1. Introduction

On 28 April 2025, the MAH submitted a completed paediatric study for Fetcroja, in accordance with Article 46 of Regulation (EC) No1901/2006.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study 1704R2133, An Open-Label Study with a Nonrandomized Single-Dose Phase in Participants With Suspected or Confirmed Aerobic Gram-Negative Bacterial Infections Followed by a Randomized, Multiple-Dose, Active-Controlled Phase in Participants With Suspected or Confirmed Complicated Urinary Tract Infection (cUTI), Hospital-Acquired Bacterial Pneumonia (HABP) or Ventilator-Associated Bacterial Pneumonia (VABP) to Assess the Safety, Tolerability, and Pharmacokinetics of Cefiderocol in Hospitalized Pediatric Participants 3 Months to < 18 Years of Age is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Cefiderocol powder for solution for infusion was supplied in vials containing the equivalent of 1 g cefiderocol as a white to off-white cake or powder, manufactured by Shionogi & Co., Ltd. Each cefiderocol vial was reconstituted in 0.9% sodium chloride (normal saline) injection, 5% dextrose injection, 0.45% sodium chloride (half-normal saline) injection, or water for injection to produce a clear solution and then extracted for further dilution in one of the following: normal saline for injection, 5% dextrose injection, or half-normal saline for injection to prepare an infusion solution with a final concentration of approximately 20 mg/mL for IV administration.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **Study 1704R2133**: An Open-Label Study with a Nonrandomized Single-Dose Phase in Participants With Suspected or Confirmed Aerobic Gram-Negative Bacterial Infections Followed by a Randomized, Multiple-Dose, Active-Controlled Phase in Participants With Suspected or Confirmed Complicated Urinary Tract Infection (cUTI), Hospital-Acquired Bacterial Pneumonia (HABP) or Ventilator-Associated Bacterial Pneumonia (VABP) to Assess the Safety, Tolerability, and Pharmacokinetics of Cefiderocol in Hospitalized Pediatric Participants 3 Months to < 18 Years of Age.

The completed study forms part of a paediatric clinical development plan agreed with regulatory authorities and documented in in the product's US Initial Paediatric Study Plan (iPSP) and EU Paediatric Investigation Plan (PIP) (P/0441/2022).

2.3.2. Clinical Study 1704R2133

Description

The study was a phase 2, open-label study divided into two phases: a non-randomised single-dose phase and a randomised multiple-dose phase with an active control. Participants in the study were 3 months of age to <18 years of age and had a suspected or confirmed infection: complicated urinary tract infection (cUTI), hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP). Participants were stratified by age group prior to randomization.

Methods

Study participants

The study enrolled participants with aerobic Gram-negative pathogens (including but not limited to cUTI, complicated intra-abdominal infection [cIAI], pneumonia, HABP/VABP, and sepsis or bloodstream infections [BSI]) in the single-dose phase. In the single-dose phase up to 6 participants were planned to be enrolled. Evaluable participants who were appropriately distributed across all cohorts being studied were selected. The multiple-dose Phase was specific to participants with cUTI, HABP, or VABP.

Six participants were needed in each single-dose cohort to confirm the dose prior to moving to the Multiple-dose Phase; however, those 6 participants could come from either the single- dose phase of the current study or the single-dose phase of another study (see below), provided they followed the same schedule of assessments. The study therefore also includes data from a total of 7 participants from EU study 1802R2135, A Single-arm, Open-label Study to Assess the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of Cefiderocol in Hospitalized Paediatric Participants 3 Months to < 18 Years of Age with Suspected or Confirmed Aerobic Gram- negative Bacterial Infections. This approach was previously agreed with regulatory authorities and is documented in in the product's US iPSP and EU PIP (P/0441/2022).

Treatments

Cefiderocol was administered as an intravenous infusion over 3 hours, q8h. The dose was adjusted for body weight and renal function and the maximum dose to be administered did not exceed 2000 mg. All participants receiving cefiderocol also received treatment according to standard of care (SOC) unless the participant's cUTI, HABP, or VABP was confirmed to be caused by an aerobic Gram-negative pathogen before starting treatment. Control groups were administered SOC treatment.

The SOC antibiotics administered were selected by the investigator based on the suspected or confirmed pathogen(s) for the infection in accordance with local standards and could be modified at any time during the participant's participation in the study at the investigator's discretion.

Dose selection

The doses used in this study were selected based on age-specific PK parameters estimated for pediatric subjects from a population PK model using PK data from adult subjects to target equivalent systemic exposure (AUC) in pediatric subjects to those in adults. The details of the population PK modelling analysis were not included in the submitted documentation. In short, the model incorporated allometric scaling on clearance and volume of distribution and included a maturation factor on elimination to account for immature glomeruli in very young children.

The single-dose phase of cefiderocol (in Cohorts 2, 3, and 4) was used to confirm the exposure prior to initiating multiple dosing. Cohort 1 (adolescents) did not participate in the single-dose phase as adolescents have a high certainty of similar exposure to adults using weight-based dosing. If the exposures in the Single-dose arms were not as predicted, adjustments to the dosing regimen would have been made by the sponsor prior to initiating the Multiple-dose Phase of the respective cohorts. Dose adjustments at a participant level were made by the investigator reflecting the current creatinine clearance level (CrCL) assessed by eGFR.

Objectives

Primary objectives:

- To assess the safety and tolerability of cefiderocol after single-dose administration in hospitalized paediatric participants 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections;
- To assess the PK of cefiderocol after single- dose administration in hospitalized pediatric participants 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections;
- To assess the safety and tolerability of cefiderocol after multiple-dose administration in hospitalized pediatric participants 3 months to < 18 years of age with suspected or confirmed cUTI, HABP, or VABP;
- To assess the PK of cefiderocol after multiple- dose administration in hospitalized pediatric participants 3 months to < 18 years of age with suspected or confirmed cUTI, HABP, or VABP.

Exploratory objective:

- To estimate the PTA for percent of time that free drug concentrations in plasma exceed the MIC over the dosing interval (%fT>MIC) of ≥ 75% with infections caused by pathogens with MICs ≤ 4 µg/mL;
- Clinical efficacy.

Outcomes/endpoints

Primary endpoints:

- Adverse events
- Vital signs
- Physical examinations
- Clinical laboratory assessments
- C_{max}, $AUC_{0\text{-}inf}$, and $t_{1/2,\,z}$ after single dose
- C_{max}, $AUC_{0\text{-}\tau}$, and $t_{1/2,\,z}$ after a minimum of 4 doses

Exploratory endpoints:

- $\%fT_{>MIC}$ for causative pathogens
- PTA for ≥ 75% $fT_{>MIC}$
- Clinical response
- Microbiological response

Clinical response was characterized based on an evaluation of clinical signs and symptoms by the investigator or designee. Microbiological response was characterized based on microbiological laboratory results.

Sample size

The planned sample size was a minimum of 60 subjects in total and a maximum of 85 subjects. Minimum number of participants in each age cohort was 10. The sample size was driven by the primary PK objective.

Table 1. Cohort Description

Cohort	Age Range	Single-dose Phase	Multiple-dose Phase (minimum per cohort)	Multiple-dose Phase (overall enrollment[e])
1[a]	12 to < 18 yrs	Cohort 1 not included in the single-dose phase	N = 10 (8:2)	Minimum enrollment = 60 (48:12) Maximum overall enrollment = 85 (68:17)
2[b, c]	6 to < 12 yrs	Up to N = 6	N = 10 (8:2)	
3[b, c]	2 to < 6 yrs	Up to N = 6	N = 10 (8:2)	
4[c, d]	3 mos to < 2 yrs	Up to N = 6	N = 10 (8:2)	

mos = months; PK = pharmacokinetic; SOC = standard of care; yrs = years

a Cohort 1 of the multiple-dose phase was initiated in parallel with Cohorts 2 and 3 of the single-dose phase.

b Cohorts 2 and 3 (single-dose) were conducted in parallel with Cohort 1 of the multiple-dose phase.

c Multiple-dose Cohorts 2, 3, and 4 began after safety and PK data from 6 participants in the corresponding single-dose cohort were assessed.

d Cohort 4 (single-dose) began after safety and PK data from at least 6 participants from the single-dose Cohorts 2 and 3 (with a minimum of 3 participants from Cohort 3) were assessed.

e The overall enrollment in the multiple-dose phase included the minimum per cohort (N = 10, 8 cefiderocol:2 SOC).

Randomisation and blinding (masking)

The study was open label, and participants were randomised in a 4:1 ratio to cefiderocol or active control treatment in the multiple dose phase.

Statistical Methods

Analysis Populations

Safety Population included all enrolled participants who received at least 1 dose of investigational intervention. Participants were analyzed according to the treatment they received. The Safety Population was used for all safety analyses.

Pharmacokinetic Concentration (PKC) Population included all enrolled participants who received at least 1 dose of cefiderocol and had at least 1 PK blood sample. This population was used for the PK concentration listing.

Pharmacokinetic Concentration Summary (PKCS) Population included all enrolled participants who received 1 dose of investigational intervention in the single-dose phase and at least 4 doses of cefiderocol in the multiple-dose phase of the study and those who had at least 1 PK blood sample above the limit of quantification. This population was used for plotting of the concentration-time data and summarizing the concentration data.

Intent-to-Treat (ITT) Population only included all randomized participants in the multiple-dose phase who received at least 1 dose of investigational intervention. Participants in this population were analyzed according to the treatment they were randomized to, regardless of treatment they actually received.

Microbiological Intent-to-Treat (MITT) Population included all participants in the ITT Population who had a baseline Gram-negative uropathogen or respiratory pathogen in the multiple-dose phase. The MITT Population was used for summary efficacy data.

PK Assessment

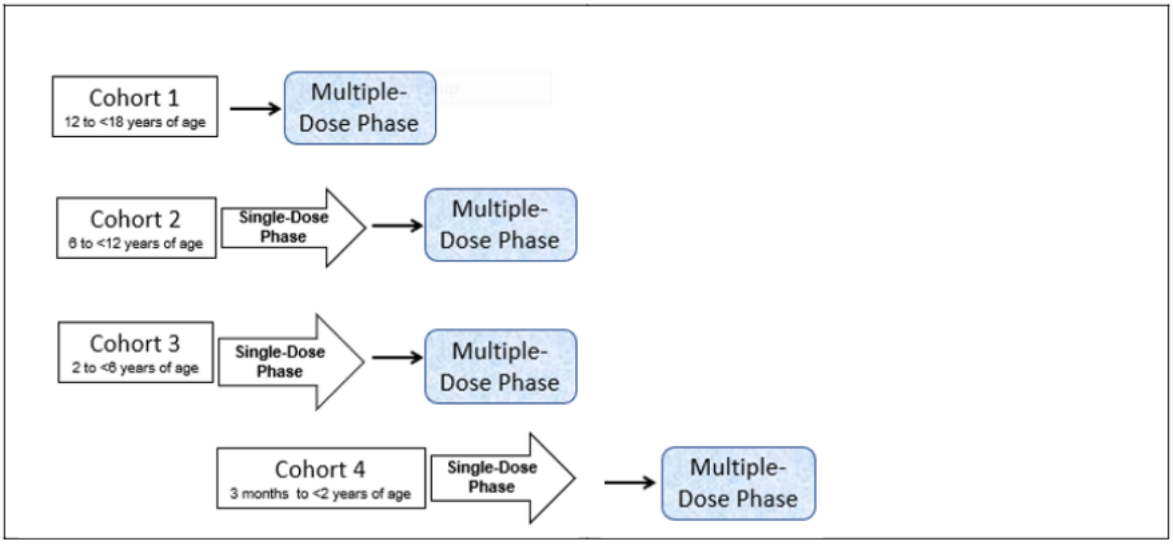
Plasma concentrations of cefiderocol were determined by validated LC-MS/MS method. No samples were below the lower limit of quantification (LLOQ) of 0.100 µg/mL.

Blood was sampled between 1- 8h after the start of drug administration in the single-dose phase and during one of the dosing intervals from the 6th to the 12th dose of cefiderocol in the multiple-dose phase. 5 (cohort 1 and 2) or 3 (cohort 3 and 4) samples were collected from each participant.

Plasma cefiderocol concentrations data were summarized using SAS version 9.4. Additional population PK analysis and estimation of pharmacokinetic parameters (including Cmax, AUC, and t1/2) using nonlinear mixed effects model approach are planned and will be reported separately.

Results

Participant flow



PK = pharmacokinetics
Note: The single-dose phase of Cohorts 2 and 3 were initiated and conducted in parallel to the multiple-dose Cohort 1 (the oldest age group). Cohort 4 (single-dose) began after safety and PK data from at least 6 participants from the single-dose Cohorts 2 and 3 (with a minimum of 3 participants from Cohort 3), were assessed. Multiple-dose cohorts (excluding Cohort 1) commenced after the corresponding single-dose cohort concluded.

Figure 1. Study Schematic

Recruitment

For the current study (1704R2133), 85 participants had informed consent obtained and were screened for participation in the study; 1 (1.2%) failed to meet inclusion/exclusion criteria.

The data from 7 participants enrolled in Study 1802R2135 were included in the single-dose phase. Therefore, a total of 91 participants were analysed in the study: 19 in the single-dose phase (12 participants from the current Study 1704R2133 and 7 participants from Study 1802R2135) and 72 participants in the multiple-dose phase.

Table 2. Participant Disposition (all analyzed participants in the single-dose phase)

	Single-dose Phase – Cefiderocol in Addition to Standard of Care											
	Cohort 2			Cohort 3			Cohort 4			Overall		
	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total
	(N = 5)	(N = 2)	(N = 7)	(N = 2)	(N = 4)	(N = 6)	(N = 5)	(N = 1)	(N = 6)	(N = 12)	(N = 7)	(N = 19)
	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%
Received study treatment	5 (100)	2 (100)	7 (100)	2 (100)	4 (100)	6 (100)	5 (100)	1 (100)	6 (100)	12 (100)	7 (100)	19 (100)
Not treated	0	0	0	0	0	0	0	0	0	0	0	0
Treatment completion status												
Completed study treatment	4 (80.0)	2 (100)	6 (85.7)	2 (100)	4 (100)	6 (100)	5 (100)	1 (100)	6 (100)	11 (91.7)	7 (100)	18 (94.7)
Discontinued study treatment	1 (20.0)	0	1 (14.3)	0	0	0	0	0	0	1 (8.3)	0	1 (5.3)
Withdrawal by participant or parent/responsible adult	1 (20.0)	0	1 (14.3)	0	0	0	0	0	0	1 (8.3)	0	1 (5.3)
Study completion status												
Completed the study [a]	4 (80.0)	2 (100)	6 (85.7)	2 (100)	4 (100)	6 (100)	5 (100)	1 (100)	6 (100)	11 (91.7)	7 (100)	18 (94.7)
Discontinued the study	1 (20.0)	0	1 (14.3)	0	0	0	0	0	0	1 (8.3)	0	1 (5.3)
Other	1 (20.0)	0	1 (14.3)	0	0	0	0	0	0	1 (8.3)	0	1 (5.3)

Cohort 1 (12 to < 18 years); Cohort 2 (6 to < 12 years); Cohort 3 (2 to < 6 years); Cohort 4 (3 months to < 2 years)

Percentage is based on the number of enrolled participants in the single-dose phase.

a Completed study: Participant status was marked as 'Completed' in completion/discontinuation case report form.

Table 3. Participant Disposition (all enrolled participants in multiple-dose phase)

	Multiple-dose Phase					Multiple-dose Phase - SOC Only				
	Cohort 1 (N=14) n%	Cohort 2 (N=14) n%	Cohort 3 (N=17) n%	Cohort 4 (N=14) n%	Total (N=59) n%	Cohort 1 (N=3) n%	Cohort 2 (N=3) n%	Cohort 3 (N=4) n%	Cohort 4 (N=3) n%	Total (N=13) n%
Participants who received study treatment	14 (100)	14 (100)	17 (100)	14 (100)	59 (100)	3 (100)	3 (100)	4 (100)	3 (100)	13 (100)
Participants not treated	0	0	0	0	0	0	0	0	0	0
Treatment completion status										
Completed the study treatment	13 (92.9)	14 (100)	14 (82.4)	11 (78.6)	52 (88.1)	2 (66.7)	3 (100)	3 (75.0)	3 (100)	11 (84.6)
Discontinued the study treatment	1 (7.1)	0	3 (17.6)	3 (21.4)	7 (11.9)	1 (33.3)	0	1 (25.0)	0	2 (15.4)
Adverse event	0	0	0	1 (7.1)	1 (1.7)	0	0	0	0	0
Recovery	1 (7.1)	0	1 (5.9)	0	2 (3.4)	0	0	0	0	0
Withdrawal by participant or parent/responsible adult	0	0	1 (5.9)	0	1 (1.7)	0	0	0	0	0
Other	0	0	1 (5.9)	2 (14.3)	3 (5.1)	1 (33.3)	0	1 (25.0)	0	2 (15.4)
Study completion status										
Completed the study [a]	14 (100)	14 (100)	15 (88.2)	14 (100)	57 (96.6)	3 (100)	3 (100)	4 (100)	3 (100)	13 (100)
Discontinued from the study	0	0	2 (11.8)	0	2 (3.4)	0	0	0	0	0
Adverse event	0	0	1 (5.9)	0	1 (1.7)	0	0	0	0	0
Withdrawal by participant or parent/responsible adult	0	0	1 (5.9)	0	1 (1.7)	0	0	0	0	0

SOC = standard of care

Cohort 1 (12 to < 18 years); Cohort 2 (6 to < 12 years); Cohort 3 (2 to < 6 years); Cohort 4 (3 months to < 2 years)

Percentage is based on the number of randomized participants in the multiple-dose phase.

a Completed study: Participant status was marked as 'Completed' in completion/discontinuation case report form.

Baseline data

For 19 total participants in the Safety Population (including 7 participants from Study 1802R2135), infection types at baseline were cUTI (11 participants, 57.9%; 3 of these were from Study 1802R2135), BSI (2 participants, 10.5%), cIAI (2 participants, 10.5%; 1 from Study 1802R2135), HAP/VAP, sepsis (1 participant 5.3% each; both were from Study 1802R2135) and other infection type (1 participant with Pseudomonas scalp infection, and 1 participant with bronchitis).

Table 4. Infection type at Baseline (Safety and MITT Populations, Multiple-dose Phase)

	Multiple-dose Phase – Cefiderocol					Multiple-dose Phase - SOC Only				
	Cohort 1 (N=14) n%	Cohort 2 (N=14) n%	Cohort 3 (N=17) n%	Cohort 4 (N=14) n%	Total (N=59) n%	Cohort 1 (N=3) n%	Cohort 2 (N=3) n%	Cohort 3 (N=4) n%	Cohort 4 (N=3) n%	Total (N=13) n%
Safety Population										
n	14	14	17	14	59	3	3	4	3	13
cUTI	10 (71.4)	14 (100)	16 (94.1)	14 (100)	54 (91.5)	3 (100)	3 (100)	4 (100)	3 (100)	13 (100)
cIAI	0	0	0	0	0	0	0	0	0	0
HAP/VAP	4 (28.6)	0	1 (5.9)	0	5 (8.5)	0	0	0	0	0
MITT Population										
n	12	10	9	7	38	1	1	3	3	8
cUTI	8 (66.7)	10 (100)	8 (88.9)	7 (100)	33 (86.8)	1 (100)	1 (100)	3 (100)	3 (100)	8 (100)
cIAI	0	0	0	0	0	0	0	0	0	0
HAP/VAP	4 (33.3)	0	1 (11.1)	0	5 (13.2)	0	0	0	0	0

BSI = blood stream infection; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; HAP = hospital-acquired pneumonia; MITT = microbiological intent-to-treat population; VAP = ventilator-associated pneumonia

Cohort 1 (12 to < 18 years); Cohort 2 (6 to < 12 years); Cohort 3 (2 to < 6 years); Cohort 4 (3 months to < 2 years)

Percentage is calculated using the number of participants in the column heading N as the denominator.

Table 5. Demographic Characteristics (Safety Population, Single-dose Phase)

	Cohort 2			Cohort 3			Cohort 4			Overall		
	APEKS-PEDI (N = 5) n%	PEDI-CEFI (N = 2) n%	Total (N = 7) n%	APEKS-PEDI (N = 2) n%	PEDI-CEFI (N = 4) n%	Total (N = 6) n%	APEKS-PEDI (N = 5) n%	PEDI-CEFI (N = 1) n%	Total (N = 6) n%	APEKS-PEDI (N = 12) n%	PEDI-CEFI (N = 7) n%	Total (N = 19) n%
Age (years)												
Mean	9.22	9.85	9.40	4.90	2.35	3.20	0.50	1.80	0.72	4.87	4.41	4.70
SD	1.83	1.48	1.64	0.00	0.19	1.33	0.23	-	0.57	4.30	3.77	4.01
Median	9.70	9.85	9.70	4.90	2.40	2.50	0.40	1.80	0.45	4.90	2.50	2.50
Minimum	6.7	8.8	6.7	4.9	2.1	2.1	0.3	1.8	0.3	0.3	1.8	0.3
Maximum	11.6	10.9	11.6	4.9	2.5	4.9	0.9	1.8	1.8	11.6	10.9	11.6
Sex (n, %)												
Male	3 (60.0)	1 (50.0)	4 (57.1)	0	2 (50.0)	2 (33.3)	2 (40.0)	0	2 (33.3)	5 (41.7)	3 (42.9)	8 (42.1)
Female	2 (40.0)	1 (50.0)	3 (42.9)	2 (100)	2 (50.0)	4 (66.7)	3 (60.0)	1 (100)	4 (66.7)	7 (58.3)	4 (57.1)	11 (57.9)
Race												
White	3 (60.0)	2 (100)	5 (71.4)	2 (100)	2 (50.0)	4 (66.7)	5 (100)	1 (100)	6 (100)	10 (83.3)	5 (71.4)	15 (78.9)
Black/African American	1 (20.0)	0	1 (14.3)	0	1 (25.0)	1 (16.7)	0	0	0	1 (8.3)	1 (14.3)	2 (10.5)
Asian	0	0	0	0	1 (25.0)	1 (16.7)	0	0	0	0	1 (14.3)	1 (5.3)
Other	1 (20.0)	0	1 (14.3)	0	0	0	0	0	0	1 (8.3)	0	1 (5.3)
Ethnicity (n, %)												
Hispanic/Latino	2 (40.0)	0	2 (28.6)	0	0	0	1 (20.0)	0	1 (16.7)	3 (25.0)	0	3 (15.8)
Not Hispanic or Latino	3 (60.0)	2 (100)	5 (71.4)	2 (100)	4 (100)	6 (100)	3 (60.0)	1 (100)	4 (66.7)	8 (66.7)	7 (100)	15 (78.9)
Not reported	0	0	0	0	0	0	1 (20.0)	0	1 (16.7)	1 (8.3)	0	1 (5.3)
BMI												
Mean	15.59	17.84	16.24	21.89	17.71	19.10	15.82	9.18	14.71	16.74	16.53	16.66
SD	3.07	0.60	2.74	8.61	3.49	5.18	1.06	-	2.87	4.05	4.08	3.95

	Cohort 2			Cohort 3			Cohort 4			Overall		
	APEKS-PEDI (N = 5) n%	PEDI-CEFI (N = 2) n%	Total (N = 7) n%	APEKS-PEDI (N = 2) n%	PEDI-CEFI (N = 4) n%	Total (N = 6) n%	APEKS-PEDI (N = 5) n%	PEDI-CEFI (N = 1) n%	Total (N = 6) n%	APEKS-PEDI (N = 12) n%	PEDI-CEFI (N = 7) n%	Total (N = 19) n%
Median	14.78	17.84	17.42	21.89	16.81	17.06	16.07	9.18	15.96	15.96	17.42	16.07
Minimum	12.1	17.4	12.1	15.8	14.8	14.8	14.1	9.2	9.2	12.1	9.2	9.2
Maximum	19.8	18.3	19.8	28.0	22.4	28.0	17.0	9.2	17.0	28.0	22.4	28.0
eGFR grading group (n, %) [a]												
≥ 120 mL/min/1.73 m^2	1 (20.0)	1 (50.0)	2 (28.6)	0	2 (50.0)	2 (33.3)	1 (20.0)	0	1 (16.7)	2 (16.7)	3 (42.9)	5 (26.3)
90 to < 120 mL/min/1.73 m^2	2 (40.0)	0	2 (28.6)	0	2 (50.0)	2 (33.3)	2 (40.0)	0	2 (33.3)	4 (33.3)	2 (28.6)	6 (31.6)
60 to < 90 mL/min/1.73 m^2	2 (40.0)	1 (50.0)	3 (42.9)	2 (100)	0	2 (33.3)	2 (40.0)	1 (100)	3 (50.0)	6 (50.0)	2 (28.6)	8 (42.1)
eGFR (mL/min/1.73 m^2)												
Mean	108.74	121.50	112.39	72.40	132.38	112.38	100.06	60.10	93.40	99.07	118.94	106.39
SD	39.62	78.49	45.96	6.93	44.10	46.21	27.25	-	29.33	31.90	51.95	40.23
Median	101.30	121.50	101.30	72.40	121.50	105.70	94.60	60.10	89.75	89.75	119.90	94.60
Minimum	71.6	66.0	66.0	67.5	91.5	67.5	76.2	60.1	60.1	67.5	60.1	60.1
Maximum	171.7	177.0	177.0	77.3	195.0	195.0	146.3	60.1	146.3	171.7	195.0	195.0

BMI = body mass index; eGFR = estimated glomerular filtration rate; SD = standard deviation
Cohort 1 (12 to < 18 years); Cohort 2 (6 to < 12 years); Cohort 3 (2 to < 6 years); Cohort 4 (3 months to < 2 years)
a For ages ≥ 3 months to < 1 year, eGFR = 0.45 × (height/Scr); For ages ≥ 1 year to < 18 years, eGFR = 0.413 × (height/Scr). where height is expressed in centimeters and Scr is standardized serum creatinine in mg/dL.
Percentage is calculated using the number of participants in the column heading N as the denominator.

Table 6. Demographic Characteristics (Safety Population, Multiple-dose Phase)

	Multiple-dose Phase – Cefiderocol					Multiple-dose Phase - SOC Only				
	Cohort 1 (N=14) n%	Cohort 2 (N=14) n%	Cohort 3 (N=17) n%	Cohort 4 (N=14) n%	Total (N=59) n%	Cohort 1 (N=3) n%	Cohort 2 (N=3) n%	Cohort 3 (N=4) n%	Cohort 4 (N=3) n%	Total (N=13) n%
Age (years)										
Mean	15.28	9.13	3.94	0.76	7.11	15.03	8.27	4.08	0.53	6.75
Standard deviation	1.73	1.66	1.05	0.53	5.61	0.35	2.63	0.57	0.21	5.57
Median	15.00	9.25	3.80	0.45	5.80	15.00	6.80	4.20	0.60	4.60
Minimum	12.8	6.5	2.2	0.3	0.3	14.7	6.7	3.3	0.3	0.3
Maximum	17.7	11.3	5.8	1.7	17.7	15.4	11.3	4.6	0.7	15.4
Sex										
Male	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)
Female	7 (50.0)	8 (57.1)	14 (82.4)	6 (42.9)	35 (59.3)	2 (66.7)	1 (33.3)	3 (75.0)	1 (33.3)	7 (53.8)
Race										
White	14 (100)	14 (100)	16 (94.1)	14 (100)	58 (98.3)	3 (100)	3 (100)	4 (100)	3 (100)	13 (100)
Not collected in this country	0	0	1 (5.9)	0	1 (1.7)	0	0	0	0	0
Ethnicity										
Hispanic or Latino	2 (14.3)	8 (57.1)	11 (64.7)	4 (28.6)	25 (42.4)	0	2 (66.7)	2 (50.0)	1 (33.3)	5 (38.5)
Not Hispanic or Latino	12 (85.7)	6 (42.9)	6 (35.3)	10 (71.4)	34 (57.6)	3 (100)	1 (33.3)	2 (50.0)	2 (66.7)	8 (61.5)
BMI (kg/m^2), n	14	14	17	14	59	2	3	3	0	8
Mean	19.84	15.99	14.84	16.33	16.65	20.57	18.51	13.76	---	17.24
Standard deviation	6.12	2.09	1.75	2.25	3.86	0.52	5.02	0.37	---	4.04
Median	19.58	15.78	14.65	16.37	16.20	20.57	16.52	13.87	---	15.65
Minimum	9.5	13.7	12.0	11.9	9.5	20.2	14.8	13.3	---	13.3
Maximum	29.9	22.1	17.8	21.4	29.9	20.9	24.2	14.1	---	24.2
eGFR grading group (n, %) [a]										
≥ 120 mL/min/1.73 m^2	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 mL/min/1.73 m^2	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 mL/min/1.73 m^2	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 mL/min/1.73 m^2	2 (14.3)	1 (7.1)	0	2 (14.3)	5 (8.5)	0	0	0	0	0
15 to < 30 mL/min/1.73 m^2	0	1 (7.1)	0	0	1 (1.7)	0	0	0	0	0
Missing	0	0	0	0	0	1 (33.3)	0	1 (25.0)	1 (33.3)	3 (23.1)
eGFR (mL/min/1.73 m^2), n	14	14	17	14	59	2	3	3	2	10
Mean	129.92	108.64	112.48	104.01	113.69	68.35	103.97	162.67	84.20	110.50
Standard deviation	107.66	65.30	29.08	58.86	68.24	5.87	33.81	94.81	29.42	61.82
Median	96.55	103.50	101.60	89.00	97.80	68.35	108.80	119.30	84.20	101.15
Minimum	40.4	27.3	73.5	40.2	27.3	64.2	68.0	97.3	63.4	63.4
Maximum	469.3	308.3	165.2	262.8	469.3	72.5	135.1	271.4	105.0	271.4

BMI = body mass index; eGFR = estimated glomerular filtration rate
Cohort 1 (12 to < 18 years); Cohort 2 (6 to < 12 years); Cohort 3 (2 to < 6 years); Cohort 4 (3 months to < 2 years)
a For ages ≥ 3 months to < 1 year, eGFR = 0.45 × (height/Scr); For ages ≥ 1 year to < 18 years, eGFR = 0.413 × (height/Scr). where height is expressed in centimeters and Scr is standardized serum creatinine in mg/dL.
Percentage is calculated using the number of participants in the column heading N as the denominator.

Number analysed

Single-dose Phase

In the current Study 1704R2133, 11 of 12 (91.7%) participants were included in the PKC and PKCS Populations; 1 (8.3%) participant in Cohort 2 did not have at least 1 PK blood sample. All 12 patients (100%) were included in the Safety Population (Table 6). Of the 19 total participants analysed, 18 (94.7%) participants (11 from the current Study 1704R2133 and 7 from Study 1802R2135) were included in the PKC and PKCS Populations; 1 (5.3%) participant in Cohort 2 of the current Study 1704R2133 did not have at least 1 PK blood sample. All 19 patients (100%) were included in the Safety Population.

Multiple-dose Phase

All participants in the multiple-dose phase were randomized and treated and, therefore, were included in the ITT and Safety Populations. Of the 59 patients assigned to cefiderocol in the multiple-dose phase, 38 (64.4%) participants were included in the MITT Population (21 [35.6%] participants did not have a baseline Gram-negative pathogen). Fifty-eight (98.3%) participants were included in PKC and PKCS Populations (1 [1.7%] participant did not receive adequate doses of cefiderocol, ie, at least 4 doses of cefiderocol). Of the 13 participants assigned to SOC only, 8 (61.5%) participants were included in the MITT Population (5 [38.5%] participants did not have a baseline Gram-negative pathogen). Pharmacokinetics testing was not performed for participants who received SOC only.

Pharmacokinetic results

Observed plasma concentrations of cefiderocol from the single-dose phase and multiple-dose phase, respectively, are summarized below. Pharmacokinetic parameters including maximum observed plasma concentration (Cmax), area under the concentration-time curve (AUC), and half-life (t1/2) will be estimated in the planned population PK analysis and reported separately.

Single-dose Phase

18 (94.7%) of the 19 enrolled participants in the Single-dose Phase were included in the PKC and PKCS Populations. One participant did not have any PK blood samples. Plasma cefiderocol concentrations are summarized in Table 7. Mean plasma concentration-time profiles for the PKCS Population are shown in Figure 2 for Study 1704R2133 and in Figure 3 for combined Studies 1704R2133 and 1802R2135. The plasma cefiderocol concentration profiles after the single dose were similar among the 3 age cohorts.

For the 18 total participants analyzed, which includes 7 participants from Study 1802R2135, the geometric mean concentrations at 3 hours after the start of the infusion (the end of infusion) and 8 hours after the start of infusion were 87.7 to 109 and 9.44 to 10.8 µg/mL, respectively. For the participants analyzed in the current Study 1704R2133 (11 of 18), the plasma cefiderocol, the geometric mean concentrations at 3 hours after the start of the infusion (the end of infusion) and 8 hours after the start of infusion were 76.0 to 341 and 6.59 to 14.0 µg/mL, respectively.

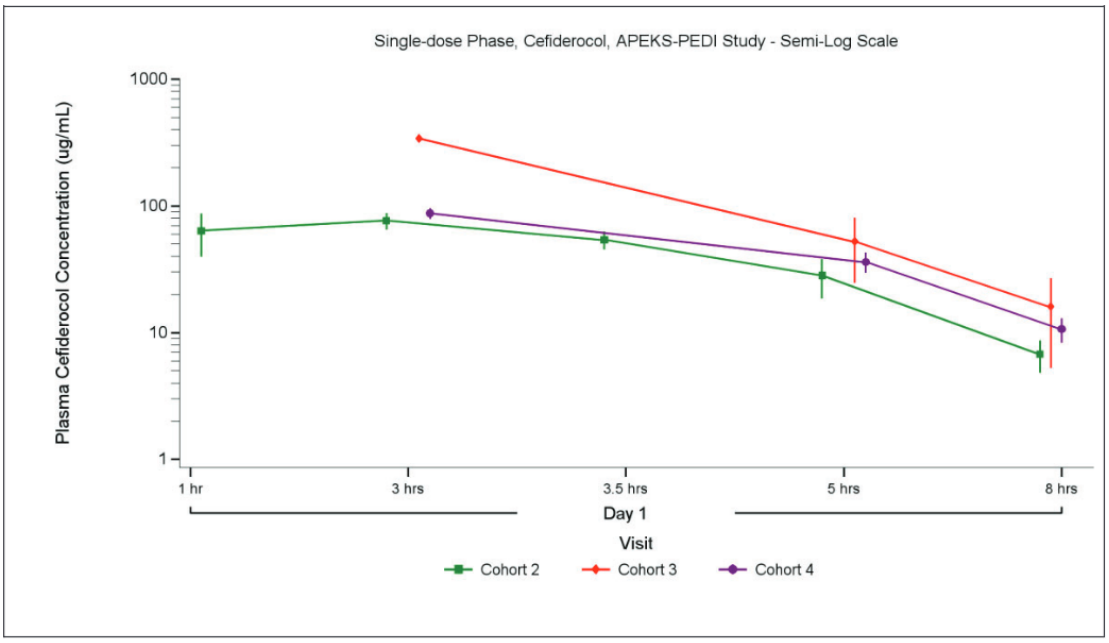
Table 7: Plasma Cefiderocol Concentrations – Single dose phase (PKCS Population)

	Cohort 2			Cohort 3			Cohort 4			Overall		
	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total
	(N = 4)	(N = 2)	(N = 6)	(N = 2)	(N = 4)	(N = 6)	(N = 5)	(N = 1)	(N = 6)	(N = 11)	(N = 7)	(N = 18)
	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%
Day 1: 1 h after start of inf., n	4	2	6							4	2	6
Mean (SD)	63.6 (23.4)	70.1 (32.0)	65.8 (23.3)							63.6 (23.4)	70.1 (32.0)	65.8 (23.3)
CV (%)	36.8	45.6	35.5							36.8	45.6	35.5
Median	60.7	70.1	60.7							60.7	70.1	60.7
Min, Max	38.7, 94.2	47.5, 92.7	38.7, 94.2							38.7, 94.2	47.5, 92.7	38.7, 94.2
Geometric Mean	60.4	66.3	62.3							60.4	66.3	62.3
Geometric SD	1.45	1.61	1.43							1.45	1.61	1.43
Geometric CV (%)	38.5	50.1	37.3							38.5	50.1	37.3
Day 1: 3 h after start of inf., n	4	2	6	1	4	5	4	1	5	9	7	16
Mean (SD)	76.7 (11.1)	124 (56.6)	92.3 (36.1)	342 (NE)	83.4 (17.5)	135 (116)	87.5 (8.10)	92.9 (NE)	88.6 (7.42)	111 (87.1)	96.2 (32.4)	104 (67.2)
CV (%)	14.5	45.8	39.1	---	20.9	86.3	9.3	---	8.4	78.5	33.7	64.4
Median	78.0	124	83.9	342	81.5	83.2	90.1	92.9	92.7	87.4	83.6	85.8
Min, Max	63.4, 87.4	83.6, 164	63.4, 164	342, 342	64.1, 106	64.1, 342	76. 93.7	92.9, 92.9	76.0, 93.7	63.4, 342	64.1, 164	63.4, 342
Geometric Mean	76.0	116	87.7	341	82.0	109	87.1	92.8	88.2	95.4	92.3	94.1
Geometric SD	1.16	1.61	1.39	NE	1.23	1.94	1.10	NE	1.09	1.64	1.34	1.50
Geometric CV (%)	14.9	50.3	33.7	---	21.0	74.3	9.6	---	8.8	52.7	30.2	42.5
Day 1: 3.5 h after start of inf., n	4	2	6							4	2	6

	Cohort 2			Cohort 3			Cohort 4			Overall		
	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total
	(N = 4)	(N = 2)	(N = 6)	(N = 2)	(N = 4)	(N = 6)	(N = 5)	(N = 1)	(N = 6)	(N = 11)	(N = 7)	(N = 18)
	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%
Mean (SD)	54.0 (8.55)	101 (37.4)	69.6 (30.1)							54.0 (8.55)	101 (37.4)	69.6 (30.1)
CV (%)	15.8	37.1	43.3							15.8	37.1	43.3
Median	53.5	101	59.7							53.5	101	59.7
Min, Max	44.0 64.9	74.3, 127	44.0, 127							44.0, 64.9	74.3, 127	44.0, 127
Geometric Mean	53.4	97.2	65.2							53.4	97.2	65.2
Geometric SD	1.17	1.46	1.45							1.17	1.46	1.45
Geometric CV (%)	16.0	39.4	38.7							16.0	39.4	38.7
Day 1: 5 h after start of inf., n	3	2	5	2	4	6	5	1	6	10	7	17
Mean (SD)	28.3 (9.64)	77.3 (11.2)	47.9 (28.3)	52.4 (27.7)	23.8 (13.9)	33.3 (22.1)	36.2 (6.38)	31.4 (NE)	35.4 (6.03)	37.1 (14.2)	40.2 (27.7)	38.3 (20.1)
CV (%)	34.1	14.5	59.0	52.9	58.5	66.3	17.6		17.0	38.4	69.0	52.5
Median (min, max)	22.8	77.3	39.4	52.4	27.6	31.4	37.6	31.4	36.1	36.1	31.4	34.7
Min, Max	22.6, 39.4	69.3, 85.2	22.6, 85.2	32.8, 71.9	3.96, 35.9	3.96, 71.9	26.0, 41.6	31.4, 31.4	26.0, 41.6	22.6, 71.9	3.96, 85.2	3.96, 85.2
Geometric Mean	27.2	76.8	41.2	48.5	18.1	25.1	35.7	31.4	34.9	35.0	29.6	32.6
Geometric SD	1.37	1.16	1.85	1.74	2.78	2.65	1.21	NE	1.20	1.41	2.71	1.95
Geometric CV (%)	32.6	14.7	67.8	60.1	136.0	126.0	19.4	---	18.1	35.4	130.0	75.0
Day 1: 8 h after start of inf., n	4	2	6	2	4	6	5	1	6	11	7	18
Mean (SD)	6.76 (1.89)	23.8 (7.64)	12.5 (9.57)	16.0 (10.7)	9.12 (5.27)	11.4 (7.22)	10.6 (2.30)	13.4 (NE)	11.1 (2.34)	10.2 (5.12)	13.9 (8.47)	11.7 (6.65)
CV (%)	28.0	32.0	76.8	66.8	57.8	63.3	21.7	---	21.1	50.1	60.8	57.1
Median	5.97	23.8	7.87	16.0	9.52	10.4	10.7	13.4	11.7	9.49	13.4	10.1

	Cohort 2			Cohort 3			Cohort 4			Overall		
	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total
	(N = 4)	(N = 2)	(N = 6)	(N = 2)	(N = 4)	(N = 6)	(N = 5)	(N = 1)	(N = 6)	(N = 11)	(N = 7)	(N = 18)
	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%
Min, Max	5.53, 9.58	18.4, 29.2	5.53, 29.2	8.44, 23.6	3.01, 14.4	3.01, 23.6	7.40, 13.0	13.4, 13.4	7.40, 13.4	5.53, 23.6	3.01, 29.2	3.01 29.2
Geometric Mean	6.59	23.2	10.0	14.0	7.72	9.44	10.4	13.3	10.8	9.32	11.4	10.0
Geometric SD	1.29	1.39	2.00	2.07	2.04	2.04	1.26	NE	1.26	1.53	2.10	1.75
Geometric CV (%)	25.7	33.5	78.7	83.3	81.7	81.4	23.3	---	23.2	44.6	85.3	60.3

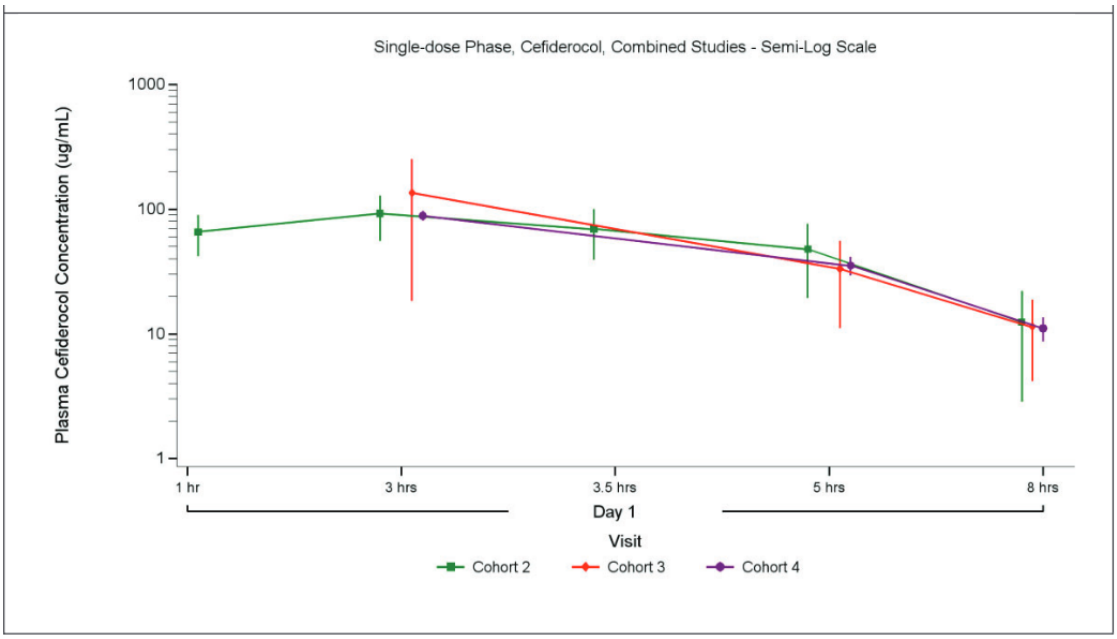
C = cohort; CV = coefficient of variation; inf. = infusion; PKCS = pharmacokinetic concentration summary; SD = standard deviation
Cohort 2 = 6 to < 12 years; Cohort 3 = 2 to < 6 years; Cohort 4 = 3 months to < 2 years
CV (%) = SD/mean × 100, Geometric Mean = exp(mean(log(x))), Geometric CV (%) = 100*sqrt(exp(sd(ln(x))^2)-1), where Geometric Sd = Standard deviation of Natural log (ln)-transformed data. Plasma concentrations below lower limit of quantitation were treated as 0 for calculations of mean, SD, CV (%), median, minimum, and maximum and treated as missing for calculations of Geom. Mean and Geom. CV (%). Plasma concentration presented in µg/mL.



hrs = hours; PKCS = pharmacokinetics concentration summary

The plot displays the means and standard deviation (error bars) for plasma cefiderocol concentration. Error bars below zero are not displayed.

Figure 2: Mean and SD Plasma Cefiderocol Concentration Over Time for Single-dose Cohort, PKCS Population of Study 1704R2133



hrs = hours; PKCS = pharmacokinetics concentration summary

The plot displays the means and standard deviation (error bars) for plasma cefiderocol concentration. Error bars below zero are not displayed.

Figure 3: Mean and SD Plasma Cefiderocol Concentration Over Time for Single-dose Cohort, PKCS Population, Combined Studies 1704R2133 and 1802R2135

Multiple-dose Phase

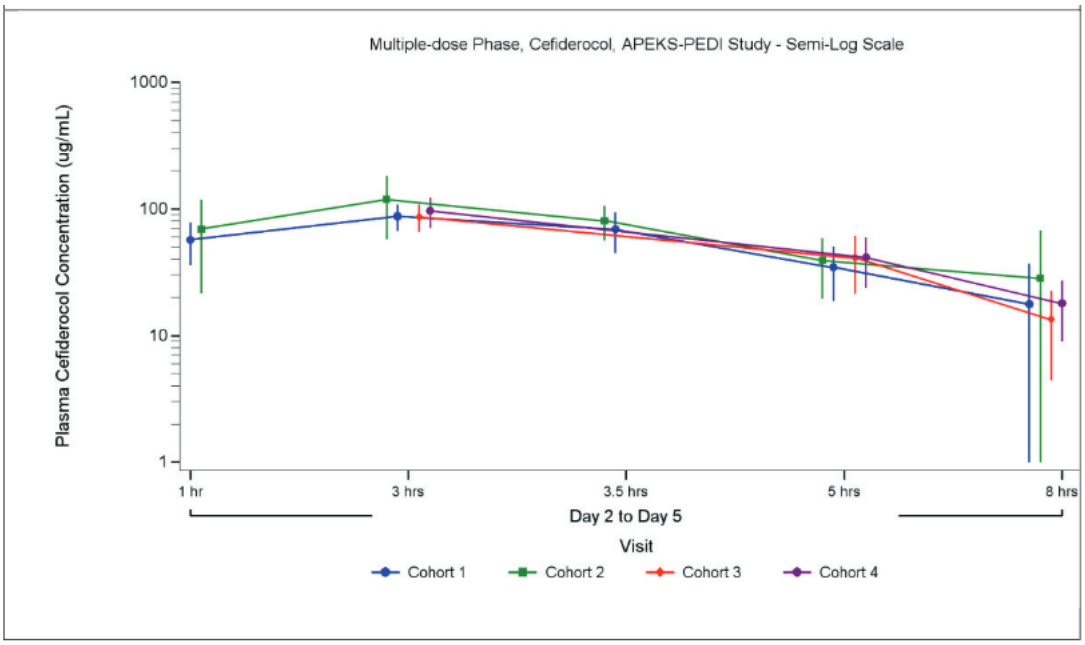
In the Multiple-dose Phase, the PKC and the PKCS Populations included 59 (98.3%) participants. One enrolled participant did not have ≥ 4 PK blood samples. Plasma cefiderocol concentrations are summarized in Table 8 and Figure 4. The plasma cefiderocol concentration profiles after the multiple doses were similar among the 4 cohorts. The geometric mean concentrations at 3 hours after the start of infusion (the end of infusion) and 8 hours after the start of infusion (before the next infusion) were 84.4 to 108 and 10.6 to 16.2 µg/mL, respectively, in the 4 cohorts.

Table 8: Plasma Cefiderocol Concentrations – Multiple dose phase (PKCS Population)

Visit - Blood Sampling Time Statistics	Cohort 1 N = 14	Cohort 2 N = 14	Cohort 3 N = 16	Cohort 4 N = 14	Overall N = 58
Day 2 to Day 5 - 1 hour after the start of infusion					
N	14	14	0	0	28
Mean (SD)	57.1 (20.7)	69.3 (47.7)	Not applicable		63.2 (36.6)
CV (%)	36.2	68.8			57.9
Median	58.6	64.5			61.2
Minimum, maximum	5.82, 89.1	8.42, 201			5.82, 201
Geometric Mean (SD)	50.2 (1.94)	54.5 (2.20)			52.3 (2.05)
Geometric CV (%)	74.4	92.9			81.9
Day 2 to Day 5 - 3 hours after the start of infusion					
N	13	13	14	9	49
Mean (SD)	87.5 (20.0)	119 (61.4)	86.8 (20.6)	96.6 (25.5)	97.4 (38.1)
CV (%)	22.9	51.5	23.7	26.4	39.2
Median	84.2	111	86.2	94.8	92.7
Minimum, maximum	47.4, 121	45.1, 299	53.8, 127	60.6, 143	45.1, 299
Geometric Mean (SD)	85.2 (1.28)	108 (1.55)	84.4 (1.27)	93.6 (1.31)	92.2 (1.38)
Geometric CV (%)	25.0	45.8	24.5	27.5	32.7
Day 2 to Day 5 - 3.5 hours after the start of infusion					
N	14	14	--	--	28
Mean (SD)	69.1 (24.1)	80.8 (24.0)	Not applicable		74.9 (24.3)
CV (%)	34.9	29.7			32.5
Median	63.9	77.9			73.4
Minimum, maximum	34.8, 125	33.1, 141			33.1, 141
Geometric Mean (SD)	65.4 (1.41)	77.2 (1.38)			71.0 (1.40)
Geometric CV (%)	35.4	33.1			34.8
Day 2 to Day 5 - 5 hours after the start of infusion					
N	14	14	16	14	58
Mean (SD)	34.7 (15.8)	39.3 (19.5)	41.2 (19.7)	41.5 (17.4)	39.3 (17.9)
CV (%)	45.4	49.6	47.7	42.0	45.7
Median	33.5	33.8	38.7	35.6	34.2
Minimum, maximum	16.6, 73.5	11.7, 79.2	15.7, 74.8	10.6, 85.2	10.6, 85.2
Geometric Mean (SD)	31.8 (1.53)	34.8 (1.69)	36.8 (1.65)	37.8 (1.61)	35.3 (1.61)
Geometric CV (%)	44.9	56.5	53.3	50.1	50.4

Visit - Blood Sampling Time Statistics	Cohort 1 N = 14	Cohort 2 N = 14	Cohort 3 N = 16	Cohort 4 N = 14	Overall N = 58
Day 2 to Day 5 - 8 hours after the start of infusion					
N	10	12	16	13	51
Mean (SD)	17.7 (18.8)	28.4 (39.2)	13.5 (8.98)	18.0 (8.97)	19.0 (21.8)
CV (%)	105.9	138.0	66.8	49.8	115.1
Median	12.1	10.0	11.6	16.6	13.0
Minimum, maximum	6.05, 70.2	3.10, 143	3.01, 34.4	8.13, 38.4	3.01, 143
Geometric Mean (SD)	13.6 (1.92)	15.6 (2.94)	10.6 (2.08)	16.2 (1.58)	13.6 (2.13)
Geometric CV (%)	73.1	148.0	84.0	48.4	88.2

C = cohort; CV = coefficient of variation; inf. = infusion; mos = months; PKCS = pharmacokinetic concentration summary; SD = standard deviation; yrs = years
Cohort 1 = 12 to < 18 yrs; Cohort 2 = 6 to < 12 yrs; Cohort 3 = 2 to < 6 yrs; Cohort 4 = 3 mos to < 2 yrs
CV (%) = SD/mean × 100, Geometric Mean = exp(mean(log(x))), Geometric CV (%) = 100*sqrt(exp(sd(ln(x))^2)-1) , where Geometric Sd = Standard deviation of Natural log (ln)-transformed data.
Plasma concentrations below lower limit of quantitation were treated as 0 for calculations of mean, SD, CV (%), median, minimum, and maximum and treated as missing for calculations of Geom. Mean and Geom. CV (%).
Plasma concentration presented in µg/mL.



hrs = hours; PKCS = pharmacokinetics concentration summary

The plot displays the means and standard deviation (error bars) for plasma cefiderocol concentration. Error bars below zero are not displayed.

Figure 4: Mean and SD Plasma Cefiderocol Concentration Over Time for Multiple-dose Cohort, PKCS Population

Efficacy results

Analysis of Efficacy

The objective of this study was to assess safety and PK of cefiderocol; however, microbiological and clinical outcome data were collected and reported descriptively for the multiple- dose phase, as an exploratory objective.

Clinical Outcomes

Table 9 below shows a summary of clinical outcomes by participant and timepoint for all participants in the ITT population in the multiple-dose phase.

- For participants who received cefiderocol, at EOT, Posttreatment, and EOS, respectively, clinical cure was achieved by 55 (93.2%), 54 (91.5%), and 48 (81.4%) participants. The clinical failure rates were 2 (3.4%), 4 (6.8%), and 0, respectively, and the indeterminate rates were 2 (3.4%), 1 (1.7%), and 11 (18.6%), respectively.
- For participants who received SOC only, at EOT, Posttreatment, and EOS, respectively, clinical cure was achieved by 11 (84.6%), 12 (92.3%), and 9 (69.2%) participants. The clinical failure rate was 0 at all timepoints, and the indeterminate rates were 2 (15.4%), 1 (7.7%), and 4 (30.8%), respectively. Clinical outcomes for the MITT population are provided in Table 9.

- In the MITT population, for participants who received cefiderocol, at EOT, Posttreatment, and EOS, respectively, clinical cure was achieved by 34 (89.5%), 33 (86.8%), and 29 (76.3%) participants.
- In the MITT population, for participants who received SOC only, at EOT, Posttreatment, and EOS, respectively, clinical cure was achieved by 7 (87.5%), 8 (100%), and 6 (75.0%) participants.

Table 9. Summary of clinical outcome by Participant and Timepoint, Multiple-dose Phase (ITT Population)

	Cefiderocol					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 (%)	Difference	95% CI
End of Treatment												
Clinical cure	11 (78.6)	14 (100)	16 (94.1)	14 (100)	55 (93.2)	2 (66.7)	2 (66.7)	4 (100)	3 (100)	11 (84.6)	8.6	(-6.1, 36.2)
Clinical failure	2 (14.3)	0	0	0	2 (3.4)	0	0	0	0	0		
Indeterminate	1 (7.1)	0	1 (5.9)	0	2 (3.4)	1 (33.3)	1 (33.3)	0	0	2 (15.4)		
Posttreatment												
Clinical cure	11 (78.6)	13 (92.9)	16 (94.1)	14 (100)	54 (91.5)	2 (66.7)	3 (100)	4 (100)	3 (100)	12 (92.3)	-0.8	(-13.2, 25.7)
Clinical failure	3 (21.4)	1 (7.1)	0	0	4 (6.8)	0	0	0	0	0		
Indeterminate	0	0	1 (5.9)	0	1 (1.7)	1 (33.3)	0	0	0	1 (7.7)		
End of Study												
Clinical cure	8 (57.1)	11 (78.6)	15 (88.2)	14 (100)	48 (81.4)	2 (66.7)	1 (33.3)	3 (75.0)	3 (100)	9 (69.2)	12.1	(-9.9, 40.8)
Clinical failure	0	0	0	0	0	0	0	0	0	0		
Indeterminate	6 (42.9)	3 (21.4)	2 (11.8)	0	11 (18.6)	1 (33.3)	2 (66.7)	1 (25.0)	0	4 (30.8)		

CI = confidence interval; ITT = intent-to-treat; SOC = standard of care; mos = months; N = number of participants in the analysis set; n = number of participants within the clinical outcome category; SOC = standard of care; yr = year

C1 = Cohort 1 (12 to < 18 yrs); C2 = Cohort 2 (6 to < 12 yrs); C3 = Cohort 3 (2 to < 6 yrs); C4 = Cohort 4 (3 mos to < 2 yrs)

Indeterminate includes participants lost to follow-up such that a determination of clinical cure/failure could not be made.

Percentage was calculated using N as the denominator for each visit.

The difference in the clinical cure rate between the 2 treatment arms (cefiderocol minus SOC only) and 95% CIs (2-sided) were calculated using a Miettinen and Nurminen method.

Similarly, in the MITT population:

- For participants who received cefiderocol, at EOT, Posttreatment, and EOS, respectively, clinical cure was achieved by 34 (89.5%), 33 (86.8%), and 29 (76.3%) participants.
- For participants who received SOC only, at EOT, Posttreatment, and EOS, respectively, clinical cure was achieved by 7 (87.5%), 8 (100%), and 6 (75.0%) participants.

Microbiological Outcomes

The results of microbiological outcomes by time point for the MITT population are summarized in Table 10 below.

For participants who received cefiderocol, at EOT, Posttreatment, and EOS, respectively, eradication was achieved by 23 (60.5%), 27 (71.1%), and 13 (34.2%) participants in the MITT Population.

For participants who received SOC only, at EOT, Posttreatment, and EOS, respectively, eradication was achieved by 5 (62.5%), 7 (87.5%), and 3 (37.5%) participants in the MITT Population.

Table 10. Summary of Microbiological outcome per Participant by Timepoint (MITT Population)

	Multiple-dose Phase Cefiderocol					Multiple-dose Phase SOC Only						
Time Point Microbiological Outcome, n (%)	Cohort 1 N=12	Cohort 2 N=10	Cohort 3 N=9	Cohort 4 N=7	Overall N=38	Cohort 1 N=1	Cohort 2 N=1	Cohort 3 N=3	Cohort 4 N=3	Overall N=8	Difference (%)	95% CI
End of Treatment												
Eradication	7 (58.3)	9 (90.0)	6 (66.7)	1 (14.3)	23 (60.5)	1 (100)	0	2 (66.7)	2 (66.7)	5 (62.5)	-2.0	(-32.2, 34.2)
Persistence	1 (8.3)	0	0	0	1 (2.6)	0	0	0	0	0		
Indeterminate	4 (33.3)	1 (10.0)	3 (33.3)	6 (85.7)	14 (36.8)	0	1 (100)	1 (33.3)	1 (33.3)	3 (37.5)		
Post Treatment												
Eradication	9 (75.0)	7 (70.0)	7 (77.8)	4 (57.1)	27 (71.1)	1 (100)	1 (100)	3 (100)	2 (66.7)	7 (87.5)	-16.4	(-37.2, 21.0)
Persistence	1 (8.3)	0	1 (11.1)	0	2 (5.3)	0	0	0	0	0		
Indeterminate	2 (16.7)	3 (30.0)	1 (11.1)	3 (42.9)	9 (23.7)	0	0	0	1 (33.3)	1 (12.5)		
End of Study												
Eradication	3 (25.0)	4 (40.0)	4 (44.4)	2 (28.6)	13 (34.2)	1 (100)	0	0	2 (66.7)	3 (37.5)	-3.3	(-39.2, 26.8)
Persistence	0	0	0	0	0	0	0	0	0	0		
Indeterminate	9 (75.0)	6 (60.0)	5 (55.6)	5 (71.4)	25 (65.8)	0	1 (100)	3 (100)	1 (33.3)	5 (62.5)		

CI = confidence interval; MITT = microbiological intent-to-treat; mos = months; N = number of participants in the analysis population; n = number of participants within the microbiological outcome category; SOC = standard of care; yr = year
Cohort 1 = 12 to < 18 yrs; Cohort 2 = 6 to < 12 yrs; Cohort 3 = 2 to < 6 yrs; Cohort 4 = 3 mos to < 2 yrs
Indeterminate includes participants lost to follow-up such that a determination of clinical eradication/persistence could not be made.
Percentage was calculated using N as the denominator for each visit.
The difference in the eradication rate between the 2 treatment arms (cefiderocol minus SOC only) and 95% CIs (2-sided) were calculated using a Miettinen and Nurminen method.

Microbiological outcomes by baseline Gram-negative pathogen and timepoint are summarized for the MITT Population in Table 11. For participants with E. coli at baseline, eradication was achieved by 62.5% at EOT and 75.0% posttreatment for participants who received cefiderocol (N = 24) and 40.0% at EOT and 60.0% posttreatment for participants who received SOC only (N = 5).

Microbiological outcomes for all other Gram-negative baseline pathogens are shown in Table 11. However, due to the small number of participants in each category (N ≤ 5), definitive conclusions cannot be made.

Table 11. Summary of Microbiological outcome per Baseline Gram-negative pathogen by timepoint (MITT Population)

	Cefiderocol	SOC Only		
Gram-negative Pathogen [a] **Time Point** **Microbiological Outcome, n (%)**	**Overall N=38**	**Overall N=8**	**Difference (%)**	**95% CI**
Acinetobacter calcoaceticus-Baumannii Complex	**N'=2**	**N'=0**		
End of Treatment				
Eradication	1 (50.0)	0	-	-
Persistence	1 (50.0)	0		
Post Treatment				
Eradication	1 (50.0)	0	-	-
Indeterminate	1 (50.0)	0		
Escherichia coli	**N'=24**	**N'=5**		
End of Treatment				
Eradication	15 (62.5)	2 (40.0)	22.5	(-21.4, 58.2)
Indeterminate	9 (37.5)	3 (60.0)		
Post Treatment				
Eradication	18 (75.0)	3 (60.0)	15.0	(-21.5, 56.6)
Persistence	1 (4.2)	1 (20.0)		
Indeterminate	5 (20.8)	1 (20.0)		
Haemophilus influenzae	**N'=1**	**N'=0**		
End of Treatment				
Eradication	1 (100)	0	-	-
Post Treatment				
Eradication	1 (100)	0	-	-
Klebsiella oxytoca	**N'=1**	**N'=0**		
End of Treatment				
Indeterminate	1 (100)	0		
Post Treatment				
Eradication	1 (100)	0	-	-
Klebsiella pneumoniae	**N'=5**	**N'=0**		
End of Treatment				
Eradication	5 (100)	0	-	-
Post Treatment				
Eradication	5 (100)	0	-	-

Proteus mirabilis	**N'=3**	**N'=0**		
End of Treatment				
Eradication	1 (33.3)	0	-	-
Persistence	1 (33.3)	0		
Indeterminate	1 (33.3)	0		
Post Treatment				
Eradication	2 (66.7)	0	-	-
Persistence	1 (33.3)	0		
Providencia rettgeri	**N'=1**	**N'=0**		
End of Treatment				
Eradication	1 (100)	0	-	-
Post Treatment				
Eradication	1 (100)	0	-	-
Pseudomonas aeruginosa	**N'=4**	**N'=3**		
End of Treatment				
Eradication	2 (50.0)	2 (66.7)	-16.7	(-71.6, 52.4)
Persistence	1 (25.0)	0		

	Cefiderocol	**SOC Only**		
Gram-negative Pathogen [a] **Time Point** **Microbiological Outcome, n (%)**	**Overall N=38**	**Overall N=8**	**Difference (%)**	**95% CI**
Indeterminate	1 (25.0)	1 (33.3)		
Post Treatment				
Eradication	3 (75.0)	3 (100)	-25.0	(-72.4, 43.8)
Indeterminate	1 (25.0)	0		
Raoultella ornithinolytica	**N'=1**	**N'=0**		
End of Treatment				
Eradication	1 (100)	0	-	-
Post Treatment				
Eradication	1 (100)	0	-	-
Persistence	0	0		

CI = confidence interval; MITT = microbiological intent-to-treat; mos = months; N = number of participants in the analysis population; n = number of participants within the microbiological outcome category; SOC = standard of care; yr = year
Cohort 1 = 12 to < 18 yrs; Cohort 2 = 6 to < 12 yrs; Cohort 3 = 2 to < 6 yrs; Cohort 4 = 3 mos to < 2 yrs
a Gram-negative pathogens are based on data from the central microbiology laboratory (if available).
Indeterminate includes participants lost to follow-up such that a determination of clinical cure/failure could not be made. The difference in the eradication rate between the 2 treatment arms (cefiderocol minus SOC only) and 95% CIs (2-sided) were calculated using a Miettinen and Nurminen method.

Safety results

Adverse Events

Single-dose Phase

For the 12 participants in the single-dose phase of the current Study 1704R2133, a total of 5 (41.7%) participants experienced 20 TEAEs. Three (25.0%) participants experienced treatment-related TEAEs. No trends were observed in the incidence of TEAEs across cohorts. No deaths, SAEs, or TEAEs leading to withdrawal from investigational intervention were reported.

For the 19 total participants in the single-dose phase, which includes 7 participants from Study 1802R2135, a total of 8 (42.1%) participants experienced 27 TEAEs. Three (15.8%) participants experienced treatment-related TEAEs. No trends were observed in the incidence of TEAEs across

cohorts. No deaths, SAEs, or TEAEs leading to withdrawal from investigational intervention were reported.

Multiple-dose Phase

In the multiple-dose phase, the incidence of TEAEs was higher in participants who received cefiderocol.

A total of 44 (74.6%) participants who received cefiderocol experienced 221 TEAEs and 8 (61.5%) participants who received SOC only experienced 38 TEAEs. One (1.7%) cefiderocol -treated participant experienced 3 treatment- related TEAEs. Eight (13.6%) participants who received cefiderocol experienced 9 SAEs and 1 (7.7%) participant who received SOC only experienced 2 SAEs. No treatment related SAEs were reported in the multiple-dose phase.

Two (3.4%) participants who received cefiderocol experienced 3 TEAEs leading to withdrawal of investigational intervention; 1 (1.7%) participant had 2 events considered treatment-related. No TEAEs leading to withdrawal of investigational intervention were reported in participants who received SOC only. No deaths were reported in the multiple-dose phase.

Table 12. Overall Summary of Treatment emergent Adverse Events (Safety Population – multiple-dose phase))

	Multiple-dose Phase – Cefiderocol									
	Cohort 1 N=14		Cohort 2 N=14		Cohort 3 N=17		Cohort 4 N=14		Overall N=59	
	Participants n (%)	Events m	Participants n (%)	Events m	Participants n (%)	Events m	Participants n (%)	Events m	Participants n (%)	Events m
Any TEAEs	8 (57.1)	57	11 (78.6)	30	13 (76.5)	70	12 (85.7)	64	44 (74.6)	221
Treatment-related TEAEs	0	0	0	0	0	0	1 (7.1)	3	1 (1.7)	3
TEAEs leading to death	0	0	0	0	0	0	0	0	0	0
Treatment-emergent SAEs	0	0	2 (14.3)	2	2 (11.8)	3	4 (28.6)	4	8 (13.6)	9
Treatment-related SAEs	0	0	0	0	0	0	0	0	0	0
Drug withdrawn due to TEAEs	0	0	0	0	1 (5.9)	1	1 (7.1)	2	2 (3.4)	3
Drug withdrawn due to related TEAEs	0	0	0	0	0	0	1 (7.1)	2	1 (1.7)	2
	Multiple-dose Phase - SOC Only									
	Cohort 1 N=3		Cohort 2 N=3		Cohort 3 N=4		Cohort 4 N=3		Overall N=13	
	Participants n (%)	Events m	Participants n (%)	Events m	Participants n (%)	Events m	Participants n (%)	Events m	Participants n (%)	Events m
Any TEAEs	2 (66.7)	21	3 (100)	7	2 (50.0)	4	1 (33.3)	6	8 (61.5)	38
Treatment-related TEAEs	0	0	0	0	0	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0	0	0	0	0
Treatment-emergent SAEs	1 (33.3)	2	0	0	0	0	0	0	1 (7.7)	2
Treatment-related SAEs	0	0	0	0	0	0	0	0	0	0
Drug withdrawn due to TEAEs	0	0	0	0	0	0	0	0	0	0
Drug withdrawn due to related TEAEs	0	0	0	0	0	0	0	0	0	0

N = number of participants in each category; m = number of evens; SAE = serious adverse event; TEAE = treatment-emergent adverse events
Percentages are based on number of subjects within each column header N. n refers to the number of subjects in each category and m refer to the number of events accordingly.
TEAEs are defined as adverse events reported after the initial dose of study drug.

Table 13. Treatment-emergent Adverse Events – Differences in Percentage (Multiple-dose Phase, Safety Population)

	Multiple-dose Phase Cefiderocol (N=59)		Multiple-dose Phase SOC only (N=13)		
	Participants n (%)	Events m	Participants n (%)	Events m	Difference of Percentage (95% CI) [a]
Any TEAEs	44 (74.6)	221	8 (61.5)	38	13.0 (-11.7, 41.5)
Treatment-related TEAEs	1 (1.7)	3	0	0	1.7 (-21.5, 9.1)
TEAEs leading to death	0	0	0	0	-
Treatment-emergent SAEs	8 (13.6)	9	1 (7.7)	2	5.9 (-20.9, 19.4)
Treatment-related SAEs	0	0	0	0	-
Drug withdrawn due to TEAEs	2 (3.4)	3	0	0	3.4 (-19.8, 11.6)
Drug withdrawn due to Related TEAEs	1 (1.7)	2	0	0	1.7 (-21.5, 9.1)

CI = confidence interval; SOC = standard of care; TEAE = treatment-emergent adverse events
Percentages are based on number of participants within each column header N.
Adverse events are coded using MedDRA version 23.0. A participant is counted only once for multiple events within a Preferred Term/System Organ Class. The same participant may appear in different categories.
TEAEs are defined as adverse events reported after the initial dose of study drug.
a Confidence Intervals are calculated for difference in percentage (Cefiderocol minus SOC only in multiple-dose phase) by Miettinen and Nurminen method.

Display of Adverse Events

Single-dose Phase

For the 12 participants in the single-dose phase of the current Study 1704R2133, the only AE preferred term reported for > 1 participant was infusion site pain, which was reported for 2 (16.7%) participants. Treatment-related AEs were reported for 3 (25.0%) participants and included infusion site pain (2 participants, 16.7%) and neutropenia (1 participant, 8.3%).

For the 19 total participants in the single-dose phase, which includes 7 participants from Study 1802R2135, few AE preferred terms were reported for > 1 participant. Abdominal pain, hematochezia, pyrexia, and infusion site pain were each reported for 2 (10.5%) participants. In the single-dose phase, treatment-related AEs were reported for 3 (15.8%) participants and included infusion site pain (2 participants, 10.5%) and neutropenia (1 participant, 16.7%).

Multiple-dose Phase

In the multiple-dose phase, for participants who received cefiderocol, the system organ class of Infections and Infestations had the highest incidence of AEs (40.7%). The most frequently reported AE preferred terms (> 10%) were thrombocytosis (11 participants, 18.6%) and asymptomatic bacteriuria (6 participants, 10.2%). One (1.7%) participant who received cefiderocol experienced treatment-related thrombocytosis and transaminases increased.

For participants who received SOC only, the system organ classes of Blood and Lymphatic System Disorders and Infections and Infestations had the highest incidence of AEs (38.5%). The most frequently reported AE preferred terms (> 10%) were anaemia, thrombocytopenia, gamma-glutamyltransferase increased, and fibrin D dimer increased (2 participants, 15.4%). No treatment-related AEs were reported for participants who received SOC only.

Table 14. Treatment Emergent Adverse Events – Preferred Terms Reported for > 1 Participant (Safety Population Single-dose Phase - Cefiderocol)

System Organ Class Preferred Term	Cohort 2			Cohort 3			Cohort 4			Overall		
	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total	APEKS-PEDI	PEDI-CEFI	Total
	(N = 5)	(N = 2)	(N = 7)	(N = 2)	(N = 4)	(N = 6)	(N = 5)	(N = 1)	(N = 6)	(N = 12)	(N = 7)	(N = 19)
	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%	n%
Any TEAE	2 (40.0)	1 (50.0)	3 (42.9)	1 (50.0)	2 (50.0)	3 (50.0)	2 (40.0)	0	2 (33.3)	5 (41.7)	3 (42.9)	8 (42.1)
Gastrointestinal Disorders	1 (20.0)	1 (50.0)	2 (28.6)	1 (50.0)	1 (25.0)	2 (33.3)	0	0	0	2 (16.7)	2 (28.6)	4 (21.1)
Abdominal pain	1 (20.0)	1 (50.0)	2 (28.6)	0	0	0	0	0	0	1 (8.3)	1 (14.3)	2 (10.5)
Haematochezia	1 (20.0)	0	1 (14.3)	0	1 (25.0)	1 (16.7)	0	0	0	1 (8.3)	1 (14.3)	2 (10.5)
General disorders and administration site conditions	2 (40.0)	0	2 (28.6)	1 (50.0)	1 (25.0)	2 (33.3)	0	0	0	3 (25.0)	1 (14.3)	4 (21.1)
Pyrexia	1 (20.0)	0	1 (14.3)	0	1 (25.0)	1 (16.7)	0	0	0	1 (8.3)	1 (14.3)	2 (10.5)
Infusion site pain	1 (20.0)	0	1 (14.3)	1 (50.0)	0	1 (16.7)	0	0	0	2 (16.7)	0	2 (10.5)

TEAE = treatment-emergent adverse event
Cohort 2 (6 to < 12 years); Cohort 3 (2 to < 6 years); Cohort 4 (3 months to < 2 years)
Percentages are based on number of participants within each column header N. Adverse events are coded using Medical Dictionary for Regulatory Activities version 23.0. A participant is counted only once for multiple events within a Preferred Term/System Organ Class. The same participant may appear in different categories. TEAEs are defined as adverse events reported after the initial dose of study drug.

Table 15. Treatment-emergent Adverse Events – Preferred Terms Reported for >1 Participant in Either Treatment Group (Safety population, Multiple -dose Phase)

	Multiple-dose Phase Cefiderocol					Multiple-dose Phase SOC Only				
	Cohort 1 (N=14) n%	Cohort 2 (N=14) n%	Cohort 3 (N=17) n%	Cohort 4 (N=14) n%	Total (N=59) n%	Cohort 1 (N=3) n%	Cohort 2 (N=3) n%	Cohort 3 (N=4) n%	Cohort 4 (N=3) n%	Total (N=13) n%
Participants with 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)
Blood and lymphatic system disorders	1 (7.1)	1 (7.1)	5 (29.4)	7 (50.0)	14 (23.7)	2 (66.7)	1 (33.3)	2 (50.0)	0	5 (38.5)
Thrombocytosis	0	0	5 (29.4)	6 (42.9)	11 (18.6)	0	0	1 (25.0)	0	1 (7.7)
Anaemia	0	1 (7.1)	1 (5.9)	2 (14.3)	4 (6.8)	2 (66.7)	0	0	0	2 (15.4)
Leukopenia	1 (7.1)	0	0	1 (7.1)	2 (3.4)	0	0	0	0	0
Thrombocytopenia	1 (7.1)	0	0	0	1 (1.7)	2 (66.7)	0	0	0	2 (15.4)
Cardiac disorders	1 (7.1)	0	1 (5.9)	1 (7.1)	3 (5.1)	1 (33.3)	0	0	0	1 (7.7)
Bradycardia	1 (7.1)	0	1 (5.9)	0	2 (3.4)	0	0	0	0	0
Endocrine disorders	2 (14.3)	0	0	1 (7.1)	3 (5.1)	0	0	0	0	0
Hypothyroidism	2 (14.3)	0	0	1 (7.1)	3 (5.1)	0	0	0	0	0
Gastrointestinal disorders	1 (7.1)	2 (14.3)	4 (23.5)	2 (14.3)	9 (15.3)	1 (33.3)	0	0	1 (33.3)	2 (15.4)
Vomiting	0	1 (7.1)	3 (17.6)	1 (7.1)	5 (8.5)	0	0	0	1 (33.3)	1 (7.7)
Infections and infestations	4 (28.6)	5 (35.7)	9 (52.9)	6 (42.9)	24 (40.7)	1 (33.3)	2 (66.7)	1 (25.0)	1 (33.3)	5 (38.5)
Asymptomatic bacteriuria	0	1 (7.1)	4 (23.5)	1 (7.1)	6 (10.2)	0	0	1 (25.0)	0	1 (7.7)
Bacteriuria	1 (7.1)	2 (14.3)	1 (5.9)	0	4 (6.8)	0	0	0	0	0
Urinary tract infection	1 (7.1)	1 (7.1)	1 (5.9)	1 (7.1)	4 (6.8)	0	0	0	0	0
Nasopharyngitis	0	1 (7.1)	2 (11.8)	0	3 (5.1)	0	1 (33.3)	0	0	1 (7.7)
Pyuria	2 (14.3)	1 (7.1)	0	0	3 (5.1)	0	0	0	0	0
Upper respiratory tract infection	0	1 (7.1)	1 (5.9)	0	2 (3.4)	0	0	0	0	0
Viral infection	0	0	1 (5.9)	1 (7.1)	2 (3.4)	0	0	0	0	0
Investigations	3 (21.4)	1 (7.1)	5 (29.4)	5 (35.7)	14 (23.7)	2 (66.7)	1 (33.3)	0	0	3 (23.1)
Alanine aminotransferase increased	0	1 (7.1)	3 (17.6)	1 (7.1)	5 (8.5)	0	1 (33.3)	0	0	1 (7.7)
Blood urea increased	2 (14.3)	0	2 (11.8)	0	4 (6.8)	0	0	0	0	0
Aspartate aminotransferase increased	0	1 (7.1)	1 (5.9)	1 (7.1)	3 (5.1)	0	1 (33.3)	0	0	1 (7.7)
Gamma-glutamyltransferase increased	0	1 (7.1)	1 (5.9)	0	2 (3.4)	2 (66.7)	0	0	0	2 (15.4)
Blood creatinine increased	1 (7.1)	0	1 (5.9)	0	2 (3.4)	0	0	0	0	0
Blood lactate dehydrogenase increased	0	0	0	2 (14.3)	2 (3.4)	0	0	0	0	0
Transaminases increased	1 (7.1)	0	0	1 (7.1)	2 (3.4)	0	0	0	0	0
Fibrin D dimer increased	0	0	0	0	0	2 (66.7)	0	0	0	2 (15.4)
Metabolism and nutrition disorders	1 (7.1)	2 (14.3)	3 (17.6)	4 (28.6)	10 (16.9)	1 (33.3)	0	1 (25.0)	0	2 (15.4)
Hypomagnesaemia	1 (7.1)	0	1 (5.9)	1 (7.1)	3 (5.1)	0	0	0	0	0
Hypophosphataemia	1 (7.1)	0	1 (5.9)	1 (7.1)	3 (5.1)	0	0	0	0	0
Hypocalcaemia	0	2 (14.3)	0	0	2 (3.4)	1 (33.3)	0	0	0	1 (7.7)
Hypernatraemia	1 (7.1)	0	0	1 (7.1)	2 (3.4)	0	0	0	0	0
Hyponatraemia	0	0	1 (5.9)	1 (7.1)	2 (3.4)	0	0	0	0	0
Nervous system disorders	1 (7.1)	1 (7.1)	2 (11.8)	1 (7.1)	5 (8.5)	1 (33.3)	0	0	0	1 (7.7)
Headache	0	1 (7.1)	1 (5.9)	0	2 (3.4)	1 (33.3)	0	0	0	1 (7.7)
Seizure	0	0	1 (5.9)	1 (7.1)	2 (3.4)	0	0	0	0	0
Renal and urinary disorders	3 (21.4)	2 (14.3)	0	0	5 (8.5)	0	1 (33.3)	0	0	1 (7.7)
Haematuria	1 (7.1)	1 (7.1)	0	0	2 (3.4)	0	0	0	0	0
Leukocyturia	2 (14.3)	0	0	0	2 (3.4)	0	0	0	0	0
Skin and subcutaneous tissue disorders	1 (7.1)	1 (7.1)	3 (17.6)	2 (14.3)	7 (11.9)	0	0	0	0	0
Dermatitis	0	0	1 (5.9)	1 (7.1)	2 (3.4)	0	0	0	0	0
Dermatitis diaper	0	0	1 (5.9)	1 (7.1)	2 (3.4)	0	0	0	0	0
Rash	1 (7.1)	0	0	1 (7.1)	2 (3.4)	0	0	0	0	0
Vascular disorders	1 (7.1)	2 (14.3)	1 (5.9)	1 (7.1)	5 (8.5)	0	1 (33.3)	0	0	1 (7.7)
Hypotension	1 (7.1)	2 (14.3)	1 (5.9)	0	4 (6.8)	0	0	0	0	0
Hypertension	0	1 (7.1)	0	1 (7.1)	2 (3.4)	0	0	0	0	0

SOC = standard of care; TEAE = treatment-emergent adverse event
Cohort 1 (12 to < 18 years); Cohort 2 (6 to < 12 years); Cohort 3 (2 to < 6 years); Cohort 4 (3 months to < 2 years)
Percentages are based on number of participants within each column header N. Adverse events are coded using Medical Dictionary for Regulatory Activities version 23.0. A participant is counted only once for multiple events within a Preferred Term/System Organ Class. The same participant may appear in different categories. TEAEs are defined as adverse events reported after the initial dose of study drug.

Treatment-emergent Adverse Events by Severity

Single-dose Phase

No severe TEAEs were reported. Two (10.5%) participants experienced TEAEs which were moderate in severity and 6 (31.6%) participants experienced TEAEs which were mild in severity. Moderate TEAEs

include anaemia, neutropenia, and bradycardia (1 event reported for each). All other TEAEs were mild in severity.

Multiple-dose Phase

For participants who received cefiderocol, 4 (6.8%) participants had severe TEAEs, 9 (15.3%) had moderate TEAEs, and 31 (52.5%) had mild TEAEs. Severe TEAEs included 2 (3.4%) participants with severe urinary tract infection, 1 (1.7%) with transaminases increased, and 1 (1.7%) with intraventricular haemorrhage. Moderate TEAEs included moderate thrombocytosis reported for 2 (3.4%) participants, and upper respiratory tract infection, bacterial pyelonephritis, CNS ventriculitis, Enterobacter bacteraemia, febrile infection, Klebsiella bacteraemia, pneumonia, pneumonia viral, pyelonephritis acute, Enterococcal UTI, nerve injury, postprocedural haemorrhage, prolonged activated partial thromboplastin time, hepatic enzyme increased, and pleural effusion each reported for 1 (1.7%) participant.

For participants who received SOC only, 1 (7.7%) participant had severe TEAEs, 7 had moderate TEAEs, and 7 (53.8%) had mild TEAEs. The severe TEAE was 1 (7.7%) participant with severe sepsis. Moderate TEAEs included thrombocytopenia, bronchopulmonary aspergillosis, cytomegalovirus infection, lung abscess, wound dehiscence, GGT increased, and fibrin D dimer increased, each reported for 1 (7.7%) participant.

Treatment-emergent Adverse Events by Outcome

Single-dose Phase

For the 12 participants in the single-dose phase of the current Study 1704R2133, 1 participant had unresolved TEAE as of the end of the study: 1 event of mild, unrelated donor site complication (verbatim term: right thigh skin donor site itching.

For the 19 total participants in the single-dose phase, which includes 7 participants from Study 1802R2135, 2 participants had unresolved TEAEs as of the end of the study: 1 event of mild, unrelated, donor site complication (see above); and 1 event of moderate, unrelated bradycardia in a participant from Study 1802R2135.

Multiple-dose Phase

For participants who received cefiderocol, the following TEAEs were unresolved as of the end of the study:

- Mild, unrelated TEAEs (each reported once) of UTI, hypofibrinogenemia, elevated urea, hypomagnesemia, hypoalbuminemia, leukocyturia, thrombocytosis, hypertriglyceridemia, elevation of C-protein, worsening of anemia; and mild, unrelated TEAEs (each reported for 2 participants) of hypothyroidism and anemia.
- Moderate, unrelated TEAEs (each reported once) of nerve injury (verbatim term: damage of fibular and sural nerve), thrombocytosis, and hepatic enzyme increased (verbatim term: increased liver enzymes).

For participants who received SOC only, the following TEAEs were unresolved as of the end of the study: mild unrelated thrombocytosis, asymptomatic bacteriuria, COVID-19 infection, and K. pneumoniae UTI (each reported once).

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths

No deaths were reported during the study.

Other Serious Adverse Events

Single-dose Phase

No serious adverse events were reported in the single-dose phase.

Multiple-dose Phase

Eight (13.6%) participants who received cefiderocol experienced SAEs. All SAEs were singular events with the exception of 2 (3.4%) participants who experienced urinary tract infection. No SAEs were considered treatment related by the investigator. One (7.7%) participant who received SOC only experienced an SAE of wound dehiscence. The event was not considered treatment related by the investigator.

Other Significant Adverse Events

No AEs leading to discontinuation of cefiderocol were reported in the single-dose phase. Two (3.4%) participants who received cefiderocol experienced 3 AEs leading to discontinuation of cefiderocol. One participant experienced thrombocytosis (moderate, related to cefiderocol) and transaminases increased (severe, related to cefiderocol), both of which let to withdrawal of cefiderocol. Both events resolved without treatment. Another participant experienced electrolyte imbalance (mild, unrelated) which led to discontinuation of cefiderocol. The participant was put on total parenteral nutrition and the event resolved.

Adverse Events of Special Interest

No AEs of special interest were identified for this study.

2.3.3. Discussion on clinical aspects

The study was a phase 2, open-label study with two phases: a non-randomised single-dose phase including data from two studies and a randomised multiple-dose phase with an active control. Participants in the study were 3 months of age to <18 years of age and had a suspected or confirmed complicated urinary tract infection (cUTI), hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP). Participants were stratified by age group prior to randomization.

The single-dose phase was designed to confirm the exposure of cefiderocol in each age cohort. The multiple-dose phase of the study was designed to address a primary objective of pharmacokinetics, coprimary objectives of safety and exploratory objectives of efficacy. Participants on active treatment received cefiderocol as add-on to SOC treatment as determined by investigators based on the investigator's local standards.

Pharmacokinetics

The cefiderocol pharmacokinetics has been studied across the age range of 3 months to 18 years. The summarised plasma concentrations display similar concentrations across the 4 age cohorts, with age groups between 3 months to < 18 years.

The primary PK endpoints, Cmax, AUC, and t1/2, will be reported separately in a population PK analysis report. A full report is expected at the application for a paediatric indication, including reporting of the actual dosing levels and exposure comparison with the adult reference population.

Efficacy

While descriptive data on clinical and microbiological outcomes were collected during the multiple dose phase, comparisons are based on numerical similarity alone. Further, given that all participants received SOC regardless of cefiderocol administration, very limited conclusions can be drawn from the data. Numerically, participants on cefiderocol and SOC had a higher rate of clinical cure at end of treatment, posttreatment and end of study visits than SOC alone. Overall microbiological eradication rate was numerically similar between groups at end of treatment and end of study visits, although worse at the posttreatment visit; this difference appears to be driven by differences in indeterminates, i.e. missing information.

Safety

Participants that received both cefiderocol and SOC reported numerically more TEAEs than participants on SOC only. Eight participants on cefiderocol reported SAEs, and two participants discontinued cefiderocol. None of the SAEs were considered related to cefiderocol. Given that all participants received SOC regardless of cefiderocol administration, very limited conclusions can be drawn from the data. Reported adverse events in the cefiderocol group were similar to the SOC group and/or consistent with the known safety profile of cefiderocol or beta-lactam antibiotics. No new safety concerns were noted.

3. Rapporteur's overall conclusion and recommendation

The completed study1704R2133 submitted and assessed in this procedure forms part of a paediatric clinical development plan agreed with regulatory authorities and documented in in the product's US iPSP and EU PIP (P/0441/2022). Additional data from other ongoing and planned paediatric clinical studies, and modelling and simulation measures, are anticipated in due course at the time of application for a paediatric indication.

From the submitted data, no need for regulatory action at this time has been identified.

☒ **Fulfilled:**

No regulatory action required.