Amsterdam, 11 December 2025.
EMADOC-1700519818-2517542
Human Medicines Division

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

Fetcroja

cefiderocol

Procedure no: EMA/PAM/0000303390

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	13 October 2025	13 October 2025
☐	CHMP Rapporteur AR	17 November 2025	18 November 2025
☐	CHMP members comments	1 December 2025	N/A
☐	Updated CHMP Rapporteur AR	4 December 2025	N/A
☒	CHMP adoption of conclusions	11 December 2025	11 December 2025

Table of contents

1. Introduction

On 29 September 2025, the MAH submitted a completed paediatric study for Fetcroja, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study 1904R2136, a multicentre, single-arm, open-label study to assess the pharmacokinetics, safety, and tolerability of cefiderocol in hospitalised paediatric patients from birth to < 3 months of age with suspected or confirmed aerobic Gram-negative bacterial infections, is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation used in the study is the same as commercially available Fetcroja, i.e. a powder for concentrate for solution for infusion.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for: Study 1904R2136, a multicentre, single-arm, open-label study to assess the pharmacokinetics, safety, and tolerability of cefiderocol in hospitalised paediatric patients from birth to < 3 months of age with suspected or confirmed aerobic Gram-negative bacterial infections.

2.3.2. Clinical study

Study 1904R2136, A multicentre, single-arm, open-label study to assess the pharmacokinetics, safety, and tolerability of cefiderocol in hospitalized paediatric patients from birth to < 3 months of age with suspected or confirmed aerobic Gram-negative bacterial infections.

Description

Methods

Study participants

- The study enrolled paediatric participants into 6 subgroups based on gestational age (GA) and prenatal age (PNA) (i.e. chronological age, CA):
    - Subgroup 1: GA ≥ 37 weeks and PNA (CA) 28 days to < 3 months
    - Subgroup 2: GA ≥ 37 weeks and PNA (CA) 0 to < 28 days
    - Subgroup 3: GA ≥ 32 to 36 weeks and PNA (CA) ≥ 14 days
    - Subgroup 4: GA ≥ 32 to 36 weeks and PNA (CA) < 14 days
    - Subgroup 5: GA ≥ 26 to < 32 weeks and PNA (CA) ≥ 14 days
    - Subgroup 6: GA ≥ 26 to < 32 weeks and PNA (CA) < 14 days

The study comprised 2 phases: a single-dose and a multiple-dose phase. After obtaining signed informed consent, the screening Visit was conducted within 4 days prior to administration of cefiderocol in both phases.

Potential participants were hospitalised male and female participants from birth to < 3 months of age at the time of evaluation with a suspected or confirmed aerobic Gram-negative infection (including, but not limited to, cUTI, cIAI, HABP/VABP, and BSI/sepsis).

Inclusion Criteria

Participants who met all of the following criteria were eligible to participate in the study:

1. Written informed consent was provided by parent(s)/LAR(s) in accordance with local regulatory requirements.
2. Hospitalised infants from birth to < 3 months (< 90 days) of age at the time written informed consent was provided. Enrolment of premature infants was not excluded, but they must have had a GA ≥ 26 weeks, PNA (CA) of 0 to 3 months, and weight of at least 1 kg.
3. Required systemic IV antibiotic treatment for suspected or confirmed aerobic Gram-negative infections including, but not limited to, cUTI, cIAI, HABP/VABP, and BSI/sepsis.
4. For the multiple-dose phase, within 72 hours of the start of potentially effective treatment with SOC antibiotics for the suspected or confirmed primary aerobic Gram-negative infection.

Exclusion Criteria

Patients who met any of the following criteria were excluded from the study:

1. Documented history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam antibiotic (Note: for β-lactams, a history of a mild rash followed by uneventful re-exposure is not a contraindication to enrolment).
2. Life expectancy of < 72 hours after enrolment.
3. Urine output < 1.0 mL/kg/hour within the 24 hours prior to study intervention administration on day 1 (estimated from the weight of wet diapers).
4. Serum creatinine value greater than the maximum for GA and PNA (CA) shown in Table 1 within the 24 hours prior to study intervention administration on day 1.
5. Neonatal acute kidney injury, defined as a serum creatinine level > 1.5 mg/dL (133 µmol/L) or an increase of 0.3 mg/dL (17 to 27 µmol/L) per day from a previous lower value.
6. Acute kidney injury based on an increase in serum creatinine ≥ 0.3 mg/dL within 48 hours from an established baseline value.
7. Any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the patient or the quality of the study data.
8. Was receiving renal replacement therapy.
9. Received any other investigational medicinal product within 30 days of study intervention administration.
10. Was receiving treatment with a vasopressor at screening.
11. Had a confirmed or strongly suspected infection at screening with a pathogen known to be resistant to cefiderocol or only a Gram-positive pathogen or viral, fungal, or parasitic pathogen as the sole cause of infection.
12. Had an anticipated need for antibacterial therapy longer than 14 days (e.g., osteomyelitis or endocarditis); applicable to both study treatment with cefiderocol, as well as adjunctive IV antibacterial treatment for suspected coinfection with Gram-positive organisms or multidrug-resistant Gram-negative organisms.
13. Had a suspected or confirmed CNS infection, including: participants with suspected CNS infection who did not have a lumbar puncture but who were treated for potential CNS infection; participants who had evidence suggestive of CNS infection based on lumbar puncture results (polymorphonuclear pleocytosis, hypoglycorrhachia, and increased protein concentration), regardless of culture results; and patients with a lumbar puncture with organisms on Gram stain or culture-positive CSF.

Table 1 - Maximum Serum Creatinine by Gestational Age and Postnatal Age

Gestational Age (weeks)	Postnatal Age (Chronological Age)	Maximum Serum Creatinine	
		mg/dL	µmol/L
25 to 27	Birth to 7 days	Serum creatinine not dropping in the first week	
	7 days	1.23	108.73
	10 to 14 days	1.10	97.24
	1 month	0.72	63.65
	2 months	0.51	45.08
28 to 29	Birth to 7 days	Serum creatinine not dropping in the first week	
	7 days	1.18	104.31
	10 to 14 days	1.02	90.17
	1 month	0.64	56.58
	2 months	0.58	51.27
30 to 33	Birth to 7 days	Serum creatinine not dropping in the first week	
	7 days	0.95	83.98
	10 to 14 days	0.84	74.26
	1 month	0.57	50.39
	2 months	0.50[a]	44.20[a]
33 to 42	Birth to 7 days	Serum creatinine not dropping in the first week	
	7 days	0.60	53.04
	10 to 14 days	0.52	45.97
	1 month	0.41	36.24
	2 months	0.37	32.71

a No data to support this.
Source: Adapted from Bateman et al, 2015 and Rao et al, 2017.

In the event a participant's parent(s)/LARS(s) withdrew consent, the participant was discontinued from the study and no further study assessments were performed. If a participant was prematurely discontinued from study intervention by the investigator or designee but consent from the study was not withdrawn, EOT (or early termination) procedures including physical examination, vital signs measurements, and clinical laboratory tests were performed and AEs were recorded through the EOS (28 [+ 7] days after administration of the last dose of study intervention) or follow-up Visit.

Treatments

Cefiderocol

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 Pharma Co., Ltd. Each cefiderocol vial was to be 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 normal saline for injection, 5% dextrose injection, or half- normal saline for injection to prepare an infusion solution with a final concentration of 20 mg/mL for IV administration.

Each dose of cefiderocol was prepared by the study pharmacist or designee and labelled with appropriate information per local standards. A detailed procedure for preparation of the IV infusion solution was provided in a separate pharmacy manual.

Standard-of-Care

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

Selection and Timing of Dose for Each Participant

The dose of cefiderocol administered to each participant was determined by the investigator based on weight, PNA (CA), and GA (Table 2). The dose of study intervention could have been adjusted if the body weight of the participant changed during the treatment phase.

Table 2 - Dosing Recommendations by Postnatal (Chronological and Gestational Age)

Postnatal Age (Chronological Age)	Cefiderocol Dose Per Infusion	
	Gestational Age	
	≥ 32 weeks	< 32 weeks
Birth to < 2 months	40 mg/kg	30 mg/kg
2 to < 3 months	60 mg/kg	40 mg/kg

Single-Dose Phase: On day 1, patients received a single dose of cefiderocol infused IV over 3 hours. Study intervention was administered in combination with an SOC treatment regimen, which may occur at any time during SOC treatment.

Prior to initiating the multiple-dose phase in participants in the 5 oldest subgroups, PK and safety data were analysed from a minimum of 6 participants who received a single dose of cefiderocol across Subgroups 1 through 5. Prior to initiating the multiple-dose phase in participants in the youngest subgroup, PK and safety data were to be available from at least 2 participants in Subgroup 6 of the single-dose phase.

After administration of cefiderocol in the single-dose phase, dosing recommendations for cefiderocol may have been adjusted by the sponsor prior to initiating enrolment of participants in the multiple-dose phase or for the next subsequent subgroup based on assessment of PK data. The study enrolled only participants in stage 0 according to the Neonatal Kidney Diseases: Improving Global Outcomes Acute Kidney Injury Definition. No dose adjustments for participants in the multiple-dose phase were made based on available data from the single-dose phase.

Multiple-Dose Phase: Participants may have been treated with 1 or more SOC antibiotics for up to 72 hours prior to day 1. The 72-hour interval was for the most recently received effective antibiotic; previous antibiotics to which the infection was resistant were not considered. Participants could receive both SOC antibiotic(s) and cefiderocol at the same time. Cefiderocol was infused IV over 1 or 3 hours q8h for an expected 5 to 14 days. The total duration of treatment with cefiderocol was determined by the investigator based on clinical assessment of each participant's infection status.

Shorter infusion times were allowed in the multiple-dose phase if agreed to by the sponsor via the Request for Shortened Infusion Duration Form and if in the best interest of the patient.

The SOC antibiotic(s) administered were selected by the investigator, based on the suspected or confirmed pathogen(s) 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. In the multiple-dose phase, if the patient's infection was caused by a confirmed aerobic Gram-negative pathogen only and the pathogen was susceptible to cefiderocol, the SOC antibiotics may have been discontinued. Standard-of-care antibiotics were to be continued if an anaerobic or Gram-positive infection was suspected or if sensitivity to cefiderocol was not determined. In participants with infections of polymicrobial aetiology, empiric or definitive treatment aligned with recommended therapies in investigator-preferred clinical guidelines. When polymicrobial growth consisted of pathogens susceptible to cefiderocol, cefiderocol may have been combined with other antimicrobial therapy commonly used in this age group, depending on site of infection and susceptibility results.

Objective, Outcomes and endpoints

Table 3 - Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the PK of cefiderocol after single-dose administration in hospitalized pediatric patients from birth to < 3 months of age with suspected or confirmed aerobic Gram-negative bacterial infections, including but not limited to, cUTI, cIAI, HABP/VABP, and BSI/sepsis • To assess the PK of cefiderocol after multiple-dose administration in hospitalized pediatric patients from birth to < 3 months of age with suspected or confirmed aerobic Gram-negative bacterial infections, including but not limited to, cUTI, cIAI, HABP/VABP, and BSI/sepsis	• C_{max}, $AUC_{0\text{-}inf}$, and $t_{1/2}$ after a single dose • C_{max}, $AUC_{0\text{-}\tau}$, and $t_{1/2}$ after a minimum of 4 doses of cefiderocol
Secondary	
• To assess the safety and tolerability of cefiderocol after single-dose administration in hospitalized pediatric patients from birth to < 3 months 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 patients from birth to < 3 months of age with suspected or confirmed aerobic Gram-negative bacterial infections • To evaluate all-cause mortality at day 28	• Adverse events • Vital signs • Physical examinations • Clinical laboratory assessments • Death
Exploratory	
• To estimate the PTA for the ($\%fT_{>MIC}$) of ≥ 75% with infections caused by pathogens with MICs ≤ 4 µg/mL	• $\%fT_{>MIC}$ for causative pathogens • PTA for ≥ 75% $fT_{>MIC}$
• Multiple-dose phase only: To describe the clinical and microbiological outcomes achieved with cefiderocol in combination with SOC antibiotics to treat suspected or confirmed aerobic Gram-negative bacterial infections in hospitalized pediatric patients from birth to < 3 months of age, at the EOT, posttreatment/TOC, and EOS (or Follow-up) Visits	• Clinical outcome • Microbiological outcome
• To explore the CSF concentration of cefiderocol with respect to plasma concentration if CSF is collected from routine SOC	• To evaluate the ratio of CSF cefiderocol concentration to plasma cefiderocol concentration

$AUC_{0\text{-}inf}$ = area under the concentration-time curve extrapolated from time 0 to infinity; $AUC_{0\text{-}\tau}$ = area under the concentration-time curve over the dosing interval τ; BSI = bloodstream infection; cIAI = complicated intra-abdominal infection; C_{max} = maximum observed plasma concentration; CSF = cerebrospinal fluid; cUTI = complicated urinary tract infection; EOS = end of study; EOT = end of treatment; $fT_{>MIC}$ = fraction of the dosing interval during which free drug concentrations in plasma are above a specified minimum inhibitory concentration; %fT>MIC = percentage of the dosing interval that the free drug concentration in plasma exceeds the specified MIC; HABP/VABP = hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; MIC = minimum inhibitory concentration; PK = pharmacokinetic(s); PTA = probability of target attainment; SOC = standard-of-care; $t_{1/2}$ = elimination half-life; TOC = test of cure

Sample size

In the single-dose phase, a minimum of 12 evaluable participants were planned to be enrolled across the 6 subgroups and receive a single dose of cefiderocol on day 1 (in addition to SOC antibiotics). Prior to initiating the multiple-dose phase in participants in the 5 oldest subgroups, PK and safety data were analysed from a minimum of 6 participants who received a single dose of cefiderocol across Subgroups 1 through 5. Prior to initiating the multiple-dose phase in participants in the youngest subgroup, PK and safety data were available from at least 2 participants in Subgroup 6 of the single-dose phase.

In the multiple-dose phase, a minimum of 18 evaluable participants were planned to be enrolled to receive an initial dose of cefiderocol on day 1 (in addition to and within 72 hours of receiving SOC antibiotics), followed by subsequent cefiderocol doses q8h for an expected 5 to 14 days. Standard-of-care dosing was at the discretion of the investigator consistent with prescribing information.

Randomisation and blinding (masking)

This was an open-label study, no blinding of study intervention was implemented.

Statistical Methods

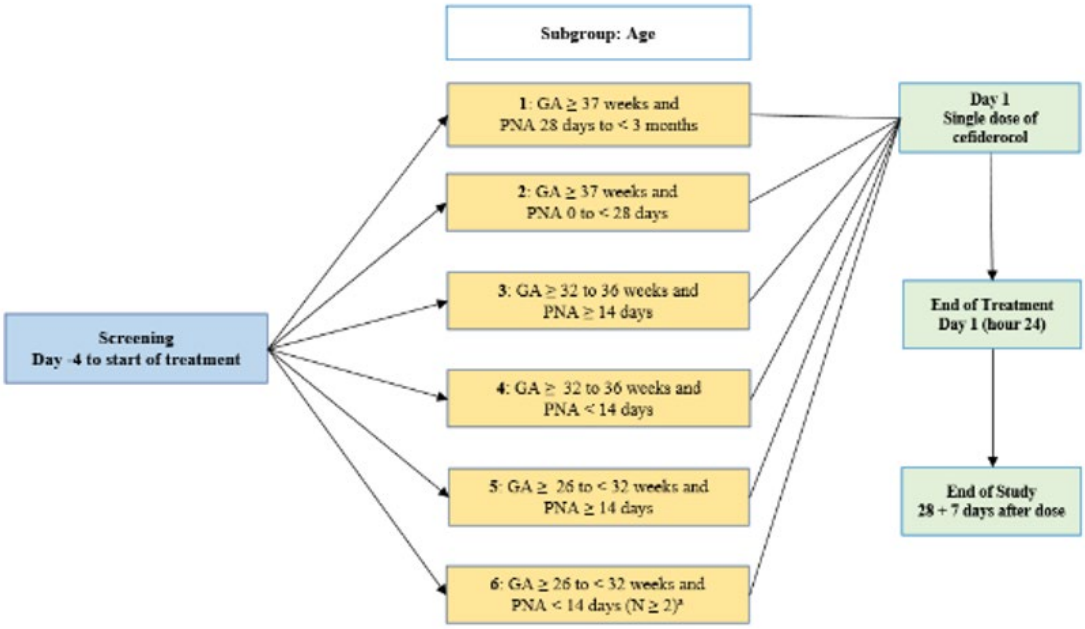
The ITT population was defined only for participants in the multiple-dose phase. There was no overlap of participants between single-dose and multiple-dose phases.

Clinical and microbiological outcomes were exploratory endpoints for the multiple-dose phase. This study was not designed or powered to determine the effectiveness of cefiderocol; therefore, no inferential statistical testing for efficacy was performed. Clinical and microbiological outcomes were summarised by the number and percent of participants and 95% CI in the respective outcome category at each timepoint for the multiple-dose phase. The 95% CI was calculated using the Clopper-Pearson method for overall group only.

Clinical and microbiological outcome data were presented in detailed participant listings. The clinical and microbiological outcome listings were composed of data from all timepoints besides EOT and posttreatment Visit. Additional clinical response data were listed.

Results - Participant flow

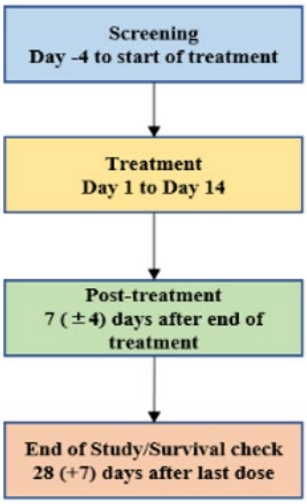
Figure 1 - Single-Dose Phase



GA = gestational age; PNA = postnatal age

A minimum of 12 evaluable participants will be enrolled across the 6 subgroups, with at least 2 participants enrolled in Subgroup 6.

Figure 2 - Multiple-Dose Phase



Recruitment

A total of 40 participants were screened for participation in the study. Two (5.0%) participants discontinued during screening, and 8 (20.0%) failed to meet eligibility criteria. Therefore, a total of 30 participants were enrolled in the study: 12 in the single-dose phase and 18 participants in the multiple-dose phase.

Single-Dose Phase

A total of 12 participants were enrolled:

- Subgroup 1 (GA ≥ 37 weeks and PNA 28 days to < 3 months): 1 participant
- Subgroup 2 (GA ≥ 37 weeks and PNA 0 to < 28 days): 2 participants
- Subgroup 3 (GA ≥ 32 to 36 weeks and PNA ≥ 14 days): 3 participants
- Subgroup 4 (GA ≥ 32 to 36 weeks and PNA < 14 days): 0 participants
- Subgroup 5 (GA ≥ 26 to < 32 weeks and PNA ≥ 14 days): 3 participants
- Subgroup 6 (GA ≥ 26 to < 32 weeks and PNA < 14 days): 3 participants

All 12 participants received and completed treatment with study intervention and completed the study.

Multiple-Dose Phase

A total of 18 participants were enrolled:

- Subgroup 1 (GA ≥ 37 weeks and PNA 28 days to < 3 months): 0 participants
- Subgroup 2 (GA ≥ 37 weeks and PNA 0 to < 28 days): 6 participants
- Subgroup 3 (GA ≥ 32 to 36 weeks and PNA ≥ 14 days): 1 participant
- Subgroup 4 (GA ≥ 32 to 36 weeks and PNA < 14 days): 5 participants
- Subgroup 5 (GA ≥ 26 to < 32 weeks and PNA ≥ 14 days): 2 participants
- Subgroup 6 (GA ≥ 26 to < 32 weeks and PNA < 14 days): 4 participants

All 18 participants received study intervention; 12 (66.7%) completed treatment. Reasons for discontinuation of study intervention were recovery from infection/antibiotic treatment no longer required (3 participants, 16.7%); investigator decision (2 participants, 11.1%); and adverse event (1 participant, 5.6%). All 18 participants completed the study.

Baseline data

Baseline demographics for the safety population are summarised for the single-dose and multiple-dose phases in Table 4.

Single-Dose Phase

For the 12 participants in the single-dose phase, the median GA was 31.5 weeks (range: 26 to 41 weeks) and the median PNA was 16.5 days (range: 4 to 60 days). A total of 58.3% of participants were male and 41.7% were female. The majority of participants were Black/African-American (66.7%); none were Hispanic/Latino (Table 4). As expected, the median height (length) and weight varied accordingly across cohorts by age.

Multiple-Dose Phase

For the 18 participants in the multiple-dose phase, the median age was 33.0 weeks (range: 28 to 41 weeks) and the median PNA was 5.5 days (range: 2 to 25 days). A total of 50.0% of participants were male. Most participants were Black/African-American (55.6%) or Asian (27.8%); 1 (5.6%) was Hispanic/Latino (Table 4). As expected, the median height (length) and weight varied accordingly across cohorts by age (Table 4).

Table 4 - Demographics and Baseline Characteristics (Safety Population)

	Single-dose Phase							Multiple-dose Phase						
	S 1 (N = 1)	S 2 (N = 2)	S 3 (N = 3)	S 4 (N = 0)	S 5 (N = 3)	S 6 (N = 3)	Overall (N = 12)	S 1 (N = 0)	S 2 (N = 6)	S 3 (N = 1)	S 4 (N = 5)	S 5 (N = 2)	S 6 (N = 4)	Overall (N = 18)
GA (weeks), n	**1**	**2**	**3**	**0**	**3**	**3**	**12**	**0**	**6**	**1**	**5**	**2**	**4**	**18**
Mean (SD)	38.1 (N/A)	40.7 (0.4)	34.1 (1.9)	0	28.0 (1.8)	30.3 (1.2)	33.1 (4.9)	0	39.8 (1.6)	35.0 (N/A)	33.0 (1.2)	29.5 (2.1)	29.1 (1.4)	34.1 (4.7)
Median	38.1	40.7	34.7	0	28.3	31.0	31.5	0	40.4	35.0	33.0	29.5	28.8	33.0
Min, max	38, 38	40, 41	32, 36	0	26, 30	29, 31	26, 41	0	37, 41	35, 35	32, 35	28, 31	28, 31	28, 41
PNA (days), n	**1**	**2**	**3**	**0**	**3**	**3**	**12**	**0**	**6**	**1**	**5**	**2**	**4**	**18**
Mean (SD)	33.0 (N/A)	9.0 (5.7)	26.7 (9.5)	0	45.3 (24.5)	9.0 (4.6)	24.5 (19.2)	0	6.0 (6.5)	25.0 (N/A)	4.4 (2.3)	19.0 (2.8)	7.5 (4.1)	8.4 (7.3)
Median	33.0	9.0	30.0	0	59.0	10.0	16.5	0	3.5	25.0	5.0	19.0	7.0	5.5
Min, max	33, 33	5, 13	16, 34	0	17, 60	4, 13	4, 60		2, 19	25, 25	2, 7	17, 21	4, 12	2, 25
Sex, n (%)														
Male	1 (100.0)	2 (100.0)	3 (100.0)	0	1 (33.3)	0	7 (58.3)	0	3 (50.0)	1 (100.0)	1 (20.0)	2 (100.0)	2 (50.0)	9 (50.0)
Female	0	0	0	0	2 (66.7)	3 (100.0)	5 (41.7)	0	3 (50.0)	0	4 (80.0)	0	2 (50.0)	9 (50.0)
Race, n (%)														
White	0	0	1 (33.3)	0	0	0	1 (8.3)	0	1 (16.7)	0	0	0	0	1 (5.6)
Black/African-American	0	1 (50.0)	1 (33.3)	0	3 (100.0)	3 (100.0)	8 (66.7)	0	2 (33.3)	1 (100.0)	3 (60.0)	2 (100.0)	2 (50.0)	10 (55.6)
Asian	1 (100.0)	0	1 (33.3)	0	0	0	2 (16.7)	0	2 (33.3)	0	1 (20.0)	0	2 (50.0)	5 (27.8)
Other	0	1 (50.0)	0	0	0	0	1 (8.3)	0	1 (16.7)	0	1 (20.0)	0	0	2 (11.1)
Ethnicity, n (%)														
Hisp./Latino	0	0	0	0	0	0	0	0	0	0	1 (20.0)	0	0	1 (5.6)

GA = gestational age; Hisp. = Hispanic; PNA = postnatal age (chronological age); S = subgroup; SD = standard deviation
Subgroup 1: GA ≥ 37 weeks and PNA 28 days to < 3 months; Subgroup 2: GA ≥ 37 weeks and PNA 0 to < 28 days; Subgroup 3: GA ≥ 32 to 36 weeks and PNA ≥ 14 days; Subgroup 4: GA ≥ 32 to 36 weeks and PNA < 14 days; Subgroup 5: GA ≥ 26 to < 32 weeks and PNA ≥ 14 days; Subgroup 6: GA ≥ 26 to < 32 weeks and PNA < 14 days.

Infection Type at Baseline

Single-Dose Phase

For the 12 participants in the safety population, infection types at baseline were cIAI (4 participants, 33.3%), sepsis (2 participants, 16.7%), HABP/VABP (2 participants, 16.7%), and 4 (33.3%) participants with other infection type (2 with UTI and 2 with hospital-acquired IAI).

Multiple-Dose Phase

For the 18 participants in the safety population, infection types at baseline were HABP/VABP (4 participants, 22.2%), BSI (3 participants, 16.7%), sepsis (2 participants, 11.1%), and other infection

types (9 participants, 50.0%). Other infection types were congenital pneumonia (3 participants); gastrointestinal infection (1 participant); neonatal early onset sepsis (4 participants); and hospital-acquired IAI (1 participant).

Number analysed

Single-Dose Phase

Of the 16 participants in the single-dose phase, 12 (75.0%) participants comprised the safety, pharmacokinetic concentration (PKC), and pharmacokinetic concentration summary (PKCS) populations. Four (25.0%) participants who did not receive at least 1 dose of cefiderocol were excluded from the safety and PKC populations, and 4 (25.0%) participants who did not receive a sufficient dose of cefiderocol were excluded from the PKCS population.

Multiple-Dose Phase

Of the 24 participants in the multiple-dose phase, 18 (75.0%) participants comprised the safety, PKC, PKCS, and ITT populations. Six (25.0%) participants who did not receive at least 1 dose of cefiderocol were excluded from the safety, PKC, and ITT populations and 6 (25.0%) participants who did not receive a sufficient dose of cefiderocol were excluded from the PKCS population.

Pharmacokinetic results

Single-Dose Phase

In the single-dose phase, 12 of 16 (75.0%) participants comprised the PKCS population; 4 (25.0%) participants who did not receive a sufficient dose of cefiderocol were excluded from the PKCS population.

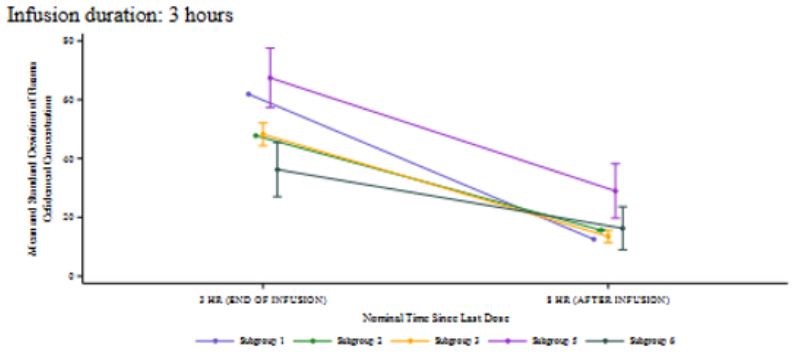
Plasma cefiderocol concentration for the PKCS population are summarised in Table 5. Mean plasma concentration-time profiles for the PKCS population are shown in Figure 3 and Figure 4. For the 11 participants analysed in the in the PKCS population, the geometric mean concentrations at 3 hours after the start of the infusion (the end of infusion) and 8 hours after the start of infusion were 35.5 to 66.9 and 12.6 to 28.2 µg/mL, respectively, in the 5 subgroups (Subgroups 1, 2, 3, 5, and 6).

Table 5 - Summary of Plasma Cefiderocol Concentration by Timepoint and Infusion Duration (Single-Dose Phase - PKCS Population)

Infusion Duration Nominal Hour	Subgroup 1 (N = 1)	Subgroup 2 (N = 2)	Subgroup 3 (N = 3)	Subgroup 4 (N = 0)	Subgroup 5 (N = 3)	Subgroup 6 (N = 3)	Overall (N = 12)
3-Hour Infusion Duration 3 Hours (end of infusion)							
N	1	1	3	0	3	3	11
n	1	1	3	0	3	3	11
Mean (SD)	61.9 (N/A)	47.8 (N/A)	48.2 (3.9)	N/A	67.4 (10.1)	36.2 (9.2)	51.4 (14.2)
% CV	N/A	N/A	8.0	N/A	15.0	25.4	27.6
Geom. Mean (% Geom. CV)	61.9 (N/A)	47.8 (N/A)	48.1 (8.0)	N/A	66.9 (15.5)	35.5 (24.5)	49.5 (29.5)
Median	61.9	47.8	48.4	N/A	69.2	32.0	48.4
Min, Max	61.9, 61.9	47.8, 47.8	44.3, 52.0	N/A	56.5, 76.5	29.9, 46.8	29.9, 76.5
8 Hours (after infusion)							
N	1	2	3	0	2	3	11
n	1	2	3	0	2	3	11
Mean (SD)	12.6 (N/A)	15.6 (0.0)	13.5 (2.1)	N/A	29.0 (9.3)	16.3 (7.3)	17.4 (7.4)
% CV	N/A	0.2	15.5	N/A	31.9	45.1	42.7
Geom. Mean (% Geom. CV)	12.6 (N/A)	15.6 (0.2)	13.4 (16.4)	N/A	28.2 (33.4)	15.3 (44.0)	16.3 (37.5)
Median	12.6	15.6	14.5	N/A	29.0	12.9	14.9
Min, Max	12.6, 12.6	15.6, 15.6	11.1, 14.9	N/A	22.4, 35.5	11.2, 24.7	11.1, 35.5

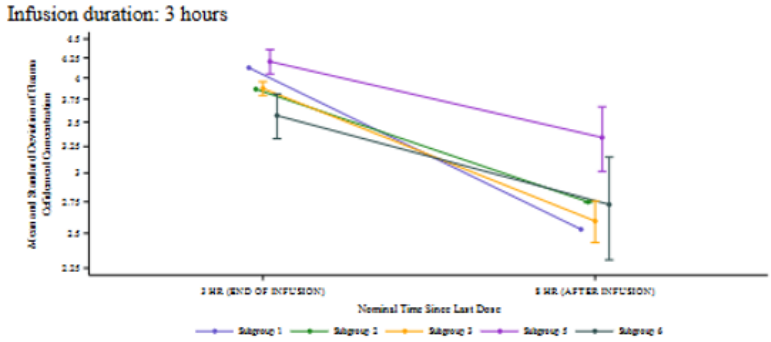
CV = coefficient of variation; GA = gestational age; Geom = geometric; N/A = not applicable;
PKCS = pharmacokinetic concentration summary (population); PNA = postnatal age (chronological age);
SD = standard deviation
Subgroup 1: GA ≥ 37 weeks and PNA 28 days to < 3 months; Subgroup 2: GA ≥ 37 weeks and PNA 0 to < 28 days;
Subgroup 3: GA ≥ 32 to 36 weeks and PNA ≥ 14 days; Subgroup 4: GA≥ 32 to 36 weeks and PNA < 14 days;
Subgroup 5: GA ≥ 26 to < 32 weeks and PNA ≥ 14 days; Subgroup 6: GA ≥ 26 to < 32 weeks and PNA < 14 days.
N is the number of participants with samples collected at each timepoint. n is the number of samples collected at each timepoint.
Geom. Mean = exp(mean(log(x))), Geom. CV (%) = 100*sqrt(exp((log(Geom. Sd)))-1), where Geom. SD = exp(sd(log(x))).
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 (%).

Figure 3 - Linear Plot of Mean Plasma Cefiderocol Concentration by Nominal Time and Infusion Duration (Single-Dose Phase - PKCS Population)



Hr = hour; PKCS = pharmacokinetic concentration summary (population)

Figure 4 - Semi-Log Plot of Mean Plasma Cefiderocol Concentration by Nominal Time and Infusion Duration (Single-Dose Phase - PKCS Population)



Hr = hour; PKCS = pharmacokinetic concentration summary (population)

Multiple-Dose Phase

In the multiple-dose phase, 18 (75.0%) participants comprised the PKC and PKCS populations. Six (25.0%) participants who did not receive at least 1 dose of cefiderocol were excluded from the PKC population and 6 (25.0%) participants who did not receive a sufficient dose of cefiderocol were excluded from the PKCS population. Plasma cefiderocol concentration for the PKCS population are summarised in Table 6. Mean plasma concentration-time profiles for the PKCS Population are shown in Figure 5.

The geometric mean concentrations at the end of infusion and 8 hours after the start of infusion (before the next infusion) were 59.0 to 128 and 7.95 to 27.7 µg/mL, respectively, with a 1-hour infusion in the 4 subgroups (Subgroups 2, 4, 5, and 6) and 70.3 to 129 and 34.1 to 47.0 µg/mL, respectively, with a 3-hour infusion in the 3 subgroups (Subgroups 2, 4, and 6).

Of note, the plasma concentrations at 3 hours (end of infusion) and 8 hours in 1 participant were 0.407 and 0.168 µg/mL, respectively, which were much lower than those of the other 3 participants in the same cohort (Cohort 3). There were no dosing deviations from the protocol-specified dose. The plasma concentration data in this participant were deemed to be anomalous and were excluded from the concentration summary. The plasma concentration at end of infusion in a second participant was 986.514 µg/mL. Given that it was much higher than those of the other participants, the plasma concentration at end of infusion in this participant were deemed to be anomalous and were excluded for the concentration summary. However, the plasma concentration at 8 hours in this participant was comparable to those of the other participants and retained in the summary (Table 6). Cerebrospinal fluid samples were collected from a limited number of participants. The 3 CSF samples were available from 2 patients. The CSF concentrations and the ratios of CSF to plasma concentrations were 1.51 to 85.5 µg/mL and 0.029 to 14.546 µg/mL, respectively.

Table 6 - Summary of Plasma Cefiderocol Concentration by Timepoint and Infusion Duration (Multiple-Dose Phase - PKCS Population)

Infusion Duration Nominal Hour	Subgroup 1 (N = 0)	Subgroup 2 (N = 6)	Subgroup 3 (N = 1)	Subgroup 4 (N = 5)	Subgroup 5 (N = 2)	Subgroup 6 (N = 4)	Overall (N = 18)
1-Hour Infusion Duration							
End of infusion							
N	0	3	0	2	2	2	9
n	0	3	0	2	2	2	9
Mean (SD)	N/A	114.1 (15.8)	N/A	85.8 (0.3)	59.7 (13.0)	154.7 (122.5)	104.7 (56.7)
% CV	N/A	13.8	N/A	0.3	21.8	79.2	54.1
Geom. Mean (% Geom. CV)	N/A	113.3 (14.5)	N/A	85.8 (0.3)	59.0 (22.3)	128.2 (110.8)	94.7 (47.7)
Median	N/A	121.6	N/A	85.8	59.7	154.7	86.0
Min, Max	N/A	96.0, 124.7	N/A	86.0, 86.0	50.5, 68.9	68.1, 241.4	50.5, 241.4
8 Hours (after infusion)							
N	0	3	0	3	2	2	10
n	0	3	0	3	2	2	10
Mean (SD)	N/A	27.9 (3.8)	N/A	26.2 (4.5)	8.3 (3.2)	20.0 (4.2)	21.9 (8.4)
% CV	N/A	13.5	N/A	17.1	38.8	20.8	38.5
Geom. Mean (% Geom. CV)	N/A	27.7 (14.2)	N/A	26.0 (16.7)	8.0 (41.5)	19.8 (21.2)	19.8 (56.8)
Median	N/A	29.8	N/A	24.6	8.3	20.0	23.3
Min, Max	N/A	23.5, 30.3	N/A	22.8, 31.3	6.0, 10.6	17.1, 23.0	6.0, 31.3
CSF Timepoint							
N	0	1	0	1	0	0	2
n	0	2	0	1	0	0	3
Mean (SD)	N/A	50.6 (1.3)	N/A	5.9 (N/A)	N/A	N/A	35.7 (25.9)
% CV	N/A	2.6	N/A	N/A	N/A	N/A	72.4
Geom. Mean (% Geom. CV)	N/A	50.6 (2.6)	N/A	5.9 (N/A)	N/A	N/A	24.7 (192.2)
Median	N/A	50.6	N/A	5.9	N/A	N/A	49.7
Min, Max	N/A	49.7, 51.6	N/A	5.9, 5.9	N/A	N/A	5.9, 51.6
3-Hour Infusion Duration							
End of infusion							
N	0	2	0	2	0	2	6
n	0	2	0	2	0	2	6
Mean (SD)	N/A	180.2 (177.8)	N/A	96.3 (82.3)	N/A	71.5 (17.9)	116.0 (101.7)
% CV	N/A	98.7	N/A	85.4	N/A	25.0	87.7
Geom. Mean (% Geom. CV)	N/A	129.1 (185.2)	N/A	76.7 (128.9)	N/A	70.3 (25.7)	88.6 (89.9)
Median	N/A	180.205	N/A	96.272	N/A	71.465	71.465
Min, Max	N/A	54.5, 306.0	N/A	38.1, 154.4	N/A	58.8, 84.1	38.1, 305.9

Infusion Duration Nominal Hour	Subgroup 1 (N = 0)	Subgroup 2 (N = 6)	Subgroup 3 (N = 1)	Subgroup 4 (N = 5)	Subgroup 5 (N = 2)	Subgroup 6 (N = 4)	Overall (N = 18)
8 Hours (after infusion)							
N	0	3	0	2	0	2	7
n	0	3	0	2	0	2	7
Mean (SD)	N/A	62.5 (58.2)	N/A	68.8 (76.0)	N/A	35.2 (12.4)	56.5 (48.3)
% CV	N/A	93.2	N/A	110.3	N/A	35.2	85.6
Geom. Mean (% Geom. CV)	N/A	47.0 (112.3)	N/A	43.1 (280.9)	N/A	34.1 (37.2)	41.8 (98.6)
Median	N/A	35.4	N/A	68.8	N/A	35.2	35.4
Min, Max	N/A	22.7, 129.3	N/A	15.1, 122.5	N/A	26.4, 43.9	15.1, 129.3

CSF = cerebrospinal fluid; CV = coefficient of variation; GA = gestational age; Geom = geometric; N/A = not applicable; PKCS = pharmacokinetic concentration summary (population); PNA = postnatal age (chronological age); SD = standard deviation

Subgroup 1: GA ≥ 37 weeks and PNA 28 days to < 3 months; Subgroup 2: GA ≥ 37 weeks and PNA 0 to < 28 days; Subgroup 3: GA ≥ 32 to 36 weeks and PNA ≥ 14 days; Subgroup 4: GA≥ 32 to 36 weeks and PNA < 14 days; Subgroup 5: GA ≥ 26 to < 32 weeks and PNA ≥ 14 days; Subgroup 6: GA ≥ 26 to < 32 weeks and PNA < 14 days.

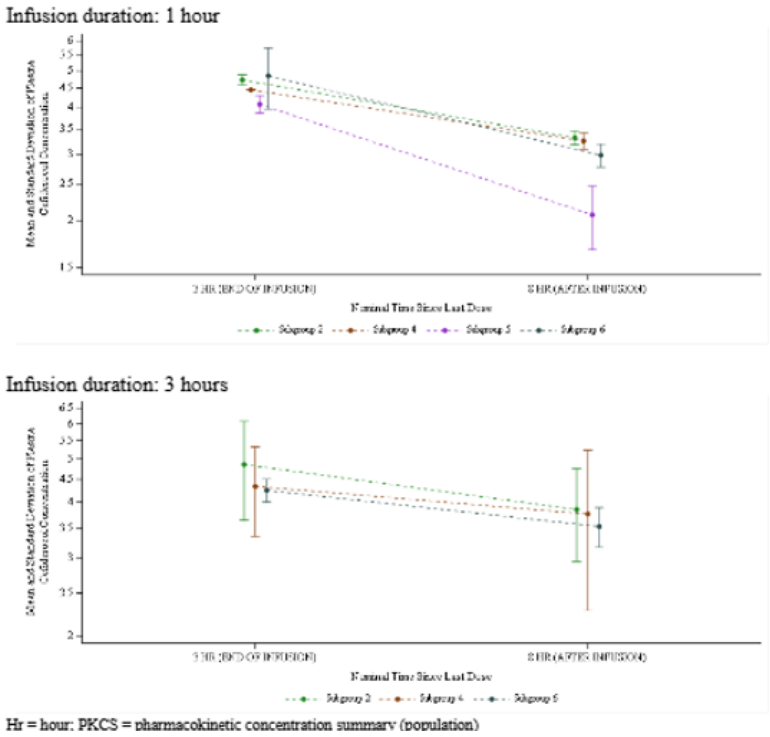
N is the number of participants with samples collected at each timepoint. n is the number of samples collected at each timepoint.

Geom. Mean = exp(mean(log(x))), Geom. CV (%) = 100*sqrt(exp((log(Geom. Sd)))-1), where Geom. SD = exp(sd(log(x))).

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 (%).

Source: Table 14.4.1.2

Figure 5 - Semi-Log Plot of Mean Plasma Cefiderocol Concentration by Nominal Time and Infusion Duration (Multiple-Dose Phase - PKCS Population)



Hr = hour; PKCS = pharmacokinetic concentration summary (population)

Efficacy results

Clinical Outcomes

Clinical response was characterised based on an evaluation of clinical signs and symptoms by the investigator or designee. Table 7 shows a summary of clinical outcomes by participant and timepoint for all participants in the ITT population in the multiple-dose phase. At EOT, posttreatment, and EOS, respectively, clinical cure was achieved by 16 (88.9%), 15 (83.3%), and 3 (16.7%) participants. The clinical failure rate was 1 (5.6%) at all timepoints, which was observed in Subgroup 6 only, and the indeterminate rates were 1 (5.6%), 2 (11.1%), and 14 (77.8%), respectively.
Indeterminate clinical outcomes include participants for whom the source specimen was unavailable for culture.

Table 7 - Summary of Clinical Outcomes by Timepoint (Multiple-Dose Phase; Intent-to-Treat Population)

Timepoint Outcome	Subgroup 1 (N = 0)	Subgroup 2 (N = 6)	Subgroup 3 (N = 1)	Subgroup 4 (N = 5)	Subgroup 5 (N = 2)	Subgroup 6 (N = 4)	Overall (N = 18) [95% CI]
End of Treatment							
Clinical Cure n (%)	0	6 (100.0)	1 (100.0)	5 (100.0)	1 (50.0)	3 (75.0)	16 (88.9) [65.29, 98.62]
Clinical Failure n (%)	0	0	0	0	0	1 (25.0)	1 (5.6) [0.14, 27.29]
Indeterminate (LTFU) n (%)	0	0	0	0	1 (50.0)	0	1 (5.6) [0.14, 27.29]
Posttreatment							
Clinical Cure n (%)	0	6 (100.0)	1 (100.0)	3 (60.0)	2 (100.0)	3 (75.0)	15 (83.3) [58.58, 96.42]
Clinical Failure n (%)	0	0	0	0	0	1 (25.0)	1 (5.6) [0.14, 27.29]
Indeterminate (LTFU) n (%)	0	0	0	2 (40.0)	0	0	2 (11.1) [1.38, 34.71]
End of Study [a]							
Clinical Cure n (%)	0	2 (33.3)	1 (100.0)	0	0	0	3 (16.7) [3.58, 41.42]
Clinical Failure n (%)	0	0	0	0	0	1 (25.0)	1 (5.6) [0.14, 27.29]
Indeterminate (LTFU) n (%)	0	4 (66.7)	0	5 (100.0)	2 (100.0)	3 (75.0)	14 (77.8) [52.36, 93.59]

GA = gestational age; LTFU = lost to follow-up; PNA = postnatal age (chronological age)
Subgroup 1: GA ≥ 37 weeks and PNA 28 days to < 3 months; Subgroup 2: GA ≥ 37 weeks and PNA 0 to < 28 days;
Subgroup 3: GA ≥ 32 to 36 weeks and PNA ≥ 14 days; Subgroup 4: GA ≥ 32 to 36 weeks and PNA < 14 days;
Subgroup 5: GA ≥ 26 to < 32 weeks and PNA ≥ 14 days; Subgroup 6: GA ≥ 26 to < 32 weeks and PNA < 14 days
a Clinical outcomes were collected at the end-of-study Visit only if the participants were enrolled under Protocol Version 2, Amendment 1 (04 Oct 2024).
The 95% CI is calculated using the Clopper-Pearson method.
Clinical cure: Participants who improved ≥1 baseline sign with no new or worsening signs of infection, but had insufficient improvement to allow switch to oral therapy (standard-of-care).
Clinical failure: No apparent response to therapy; persistence or worsening of baseline signs or reappearance of signs; development of new signs requiring antibiotic therapy other than, or in addition to, study treatment therapy; or death.
Indeterminate: Missing or lost to follow-up such that a determination of clinical cure/failure could not be made.

Microbiological Outcomes

Microbiological response was characterised based on microbiological laboratory results. Table 8 shows a summary of microbiological outcomes by participant and timepoint for all participants in the ITT population in the multiple-dose phase. At EOT, posttreatment, and EOS, respectively, eradication was achieved by 16 (88.9%), 15 (83.3%), and 3 (16.7%) participants. The persistence rate was 0% at all timepoints, and the indeterminate rates were 2 (11.1%), 3 (16.7%), and 15 (83.3%), respectively. Indeterminate microbiological outcomes include participants for whom the source specimen was unavailable for culture.

Table 8 - Summary of Microbiological Outcomes by Timepoint (Multiple-Dose Phase; Intent-to-Treat Population)

Timepoint Outcome	Subgroup 1 (N = 0)	Subgroup 2 (N = 6)	Subgroup 3 (N = 1)	Subgroup 4 (N = 5)	Subgroup 5 (N = 2)	Subgroup 6 (N = 4)	Overall (N = 18) [95% CI]
End of Treatment							
Eradication n (%)	0	6 (100.0)	1 (100.0)	5 (100.0)	1 (50.0)	3 (75.0)	16 (88.9) [65.29, 98.62]
Persistence n (%)	0	0	0	0	0	0	0 (0.0) [0.00, 18.53]
Indeterminate n (%)	0	0	0	0	1 (50.0)	1 (25.0)	2 (11.1) [1.38, 34.71]
Posttreatment							
Eradication n (%)	0	6 (100.0)	1 (100.0)	3 (60.0)	2 (100.0)	3 (75.0)	15 (83.3) [58.58, 96.42]
Persistence n (%)	0	0	0	0	0	0	0 (0.0) [0.00, 18.53]
Indeterminate n (%)	0	0	0	2 (40.0)	0	1 (25.0)	3 (16.7) [3.58, 41.42]
End of Study [a]							
Eradication n (%)	0	2 (33.3)	1 (100.0)	0	0	0	3 (16.7) [3.58, 41.42]
Persistence n (%)	0	0	0	0	0	0	0 (0.0) [0.00, 18.53]
Indeterminate n (%)	0	4 (66.7)	0	5 (100.0)	2 (100.0)	4 (100.0)	15 (83.3) [58.58, 96.42]

GA = gestational age; PNA = postnatal age (chronological age)
Subgroup 1: GA ≥ 37 weeks and PNA 28 days to < 3 months; Subgroup 2: GA ≥ 37 weeks and PNA 0 to < 28 days; Subgroup 3: GA ≥ 32 to 36 weeks and PNA ≥ 14 days; Subgroup 4: GA ≥ 32 to 36 weeks and PNA < 14 days; Subgroup 5: GA ≥ 26 to < 32 weeks and PNA ≥ 14 days; Subgroup 6: GA ≥ 26 to < 32 weeks and PNA < 14 days
a Microbiological outcomes were collected at the end-of-study Visit only if the participants were enrolled under Protocol Version 2, Amendment 1 (04 Oct 2024).
The 95% CI is calculated using the Clopper-Pearson method.
Eradication: All baseline Gram-negative pathogens eradicated or presumed eradicated. If it was not possible to obtain an appropriate clinical culture and the participant had a successful clinical outcome, the response was presumed to be eradication. In the presence of colonizing Gram-negative pathogens and the participant had a successful clinical outcome, the response was presumed to be eradication.
Persistence: Any baseline Gram-negative pathogen with persistence, presumed persistence, or persistence with increasing minimum inhibitory concentration.
Indeterminate: Missing or source specimen unavailable for culture and the participant's clinical outcome was assessed as indeterminate.

Safety results

Single-Dose Phase

Of the 16 participants enrolled in the single-dose phase, 12 (75.0%) participants comprised the safety population. Four (25.0%) participants did not receive at least 1 dose of cefiderocol and were excluded from the safety population.

Multiple-Dose Phase

Of the 24 participants in the multiple-dose phase, 18 (75.0%) participants comprised the safety population. Six (25.0%) participants did not receive at least 1 dose of cefiderocol and were excluded from the safety population (Section 11.1). For the 18 participants in the ITT population, the median duration of exposure was 6.0 days (range: 2 to 13 days). Five (27.8%) participants received 5 to < 15 infusions, and 13 (72.2%) participants received 15 or more infusions.

Display of Adverse Events

Single-Dose Phase

Of the 12 participants in the safety population, a total of 5 (41.7%) participants experienced 38 TEAEs. The only TEAE preferred term reported for > 1 participant was anaemia, which was reported for 2 (16.7%) participants (Table 9). No treatment-related AEs were reported in the single-dose phase.

Table 9 - Treatment-Emergent Adverse Events by System Organ Class and Preferred Terms Reported for > 1 Participant (Single-Dose Phase - Safety Analysis Population)

System Organ Class Preferred Term	Subgroup 1 (N = 1) n (%)	Subgroup 2 (N = 2) n (%)	Subgroup 3 (N = 3) n (%)	Subgroup 4 (N = 0) n (%)	Subgroup 5 (N = 3) n (%)	Subgroup 6 (N = 3) n (%)	Overall (N = 12) n (%)
Total number of TEAEs	3	1	4	0	30	0	38
Number of participants with at least 1 TEAE	1 (100.0)	1 (50.0)	1 (33.3)	0	2 (66.7)	0	5 (41.7)
Blood and Lymphatic System Disorders	0	1 (50.0)	1 (33.3)	0	2 (66.7)	0	4 (33.3)
Anaemia	0	0	0	0	2 (66.7)	0	2 (16.7)
Gastrointestinal Disorders	1 (100.0)	0	1 (33.3)	0	2 (66.7)	0	4 (33.3)
Infections and Infestations	1 (100.0)	0	1 (33.3)	0	1 (33.3)	0	3 (25.0)
Vascular Disorders	0	0	0	0	2 (66.7)	0	2 (16.7)
Congenital, Familial and Genetic Disorders	0	0	0	0	1 (33.3)	0	1 (8.3)
General Disorders and Administration Site Conditions	0	0	0	0	1 (33.3)	0	1 (8.3)
Hepatobiliary Disorders	0	0	0	0	1 (33.3)	0	1 (8.3)
Injury, Poisoning and Procedural Complications	0	0	0	0	1 (33.3)	0	1 (8.3)
Metabolism and Nutrition Disorders	0	0	0	0	1 (33.3)	0	1 (8.3)
Renal and Urinary Disorders	0	0	0	0	1 (33.3)	0	1 (8.3)
Respiratory, Thoracic, and Mediastinal Disorders	0	0	0	0	1 (33.3)	0	1 (8.3)
Skin and Subcutaneous Tissue Disorders	1 (100.0)	0	0	0	0	0	1 (8.3)

GA = gestational age; PNA = postnatal age (chronological age); TEAE = treatment-emergent adverse event
Subgroup 1: GA ≥ 37 weeks and PNA 28 days to < 3 months; Subgroup 2: GA ≥ 37 weeks and PNA 0 to < 28 days;
Subgroup 3: GA ≥ 32 to 36 weeks and PNA ≥ 14 days; Subgroup 4: GA ≥ 32 to 36 weeks and PNA < 14 days;
Subgroup 5: GA ≥ 26 to < 32 weeks and PNA ≥ 14 days; Subgroup 6: GA ≥ 26 to < 32 weeks and PNA < 14 days.
A treatment-emergent adverse event (TEAE) is an adverse event with onset after the first dose of study intervention.
The total number of TEAEs counts all TEAEs for participants. At each level of participant summarization, a participant is counted once if the participant reported 1 or more events. Adverse Events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 26.0.

Multiple-Dose Phase

Of the 18 participants in the safety population, a total of 16 (88.9%) participants experienced 50 TEAEs. TEAE preferred terms reported for > 1 participant were bacterial conjunctivitis, fungal sepsis, neonatal sepsis, hypoglycaemia, hypomagnesemia, neonatal anaemia, normochromic normocytic anaemia, bronchopulmonary dysplasia, tachycardia, and glycosuria, which were each reported for 2 (11.1%) participants (Table 10). Treatment-related AEs were reported for 2 (11.1%) participants: leukopenia (1 participant, 5.6%) and oral candidiasis (1 participant, 5.6%).

Table 10 - Treatment-Emergent Adverse Events by System Organ Class and Preferred Terms Reported for > 1 Participant (Multiple-Dose Phase - Safety Analysis Population)

System Organ Class Preferred Term	Subgroup 1 (N = 0) n (%)	Subgroup 2 (N = 6) n (%)	Subgroup 3 (N = 1) n (%)	Subgroup 4 (N = 5) n (%)	Subgroup 5 (N = 2) n (%)	Subgroup 6 (N = 4) n (%)	Overall (N = 18) n (%)
Total number of TEAEs	0	16	1	3	14	16	50
Number of participants with at least 1 TEAE	0	6 (100.0)	1 (100.0)	3 (60.0)	2 (100.0)	4 (100.0)	16 (88.9)
Infections and Infestations	0	5 (83.3)	0	1 (20.0)	2 (100.0)	3 (75.0)	11 (61.1)
Conjunctivitis bacterial	0	2 (33.3)	0	0	0	0	2 (11.1)
Fungal sepsis	0	1 (16.7)	0	0	1 (50.0)	0	2 (11.1)
Sepsis neonatal	0	1 (16.7)	0	0	1 (50.0)	0	2 (11.1)
Metabolism and Nutrition Disorders	0	2 (33.3)	0	0	2 (100.0)	2 (50.0)	6 (33.3)
Hypoglycaemia	0	1 (16.7)	0	0	0	1 (25.0)	2 (11.1)
Hypomagnesaemia	0	1 (16.7)	0	0	0	1 (25.0)	2 (11.1)
Blood and Lymphatic System Disorders	0	0	0	1 (20.0)	2 (100.0)	2 (50.0)	5 (27.8)
Anaemia neonatal	0	0	0	0	1 (50.0)	1 (25.0)	2 (11.1)
Normochromic normocytic anaemia	0	0	0	0	1 (50.0)	1 (25.0)	2 (11.1)
Respiratory, Thoracic and Mediastinal Disorders	0	1 (16.7)	0	0	1 (50.0)	2 (50.0)	4 (22.2)
Bronchopulmonary dysplasia	0	1 (16.7)	0	0	1 (50.0)	0	2 (11.1)
Cardiac Disorders	0	1 (16.7)	0	0	1 (50.0)	1 (25.0)	3 (16.7)
Tachycardia	0	1 (16.7)	0	0	1 (50.0)	0	2 (11.1)
Gastrointestinal Disorders	0	1 (16.7)	0	0	2 (100.0)	0	3 (16.7)
Investigations	0	1 (16.7)	1 (100.0)	0	0	1 (25.0)	3 (16.7)
Renal and Urinary Disorders	0	1 (16.7)	0	1 (20.0)	1 (50.0)	0	3 (16.7)
Glycosuria	0	0	0	1 (20.0)	1 (50.0)	0	2 (11.1)
General Disorders and Administration Site Conditions	0	1 (16.7)	0	0	1 (50.0)	0	2 (11.1)

GA = gestational age; PNA = postnatal age (chronological age); TEAE = treatment-emergent adverse event
Subgroup 1: GA ≥ 37 weeks and PNA 28 days to < 3 months; Subgroup 2: GA ≥ 37 weeks and PNA 0 to < 28 days; Subgroup 3: GA ≥ 32 to 36 weeks and PNA ≥ 14 days; Subgroup 4: GA ≥ 32 to 36 weeks and PNA < 14 days; Subgroup 5: GA ≥ 26 to < 32 weeks and PNA ≥ 14 days; Subgroup 6: GA ≥ 26 to < 32 weeks and PNA < 14 days.
A treatment-emergent adverse event (TEAE) is an adverse event with onset after the first dose of study intervention.
The total number of TEAEs counts all TEAEs for participants. At each level of participant summarization, a participant is counted once if the participant reported 1 or more events. Adverse Events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 26.0.

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

One death was reported in Subgroup 5 (GA ≥ 26 to < 32 weeks and PNA ≥ 14 days) of the single-dose phase. A Black/African-American male participant (GA 28 weeks, PNA 60 days) with cIAI experienced Grade 4 multiple organ dysfunction syndrome beginning on day 13 and Grade 5 sepsis on day 39. Both events were considered not related to study intervention and resulted in death on day 39 of the study.

The incidence of all-cause mortality through day 28 is summarised in Table 11.

Table 11 - Incidence of All-Cause Mortality Through Day 28 (Safety Population)

Infection Type All-Cause Mortality Rate	Single-Dose Phase Overall (N = 12) n (%) [95% CI]	Multiple-Dose Phase Overall (N = 18) n (%) [95% CI]
BSI		
N'	0	3
Day 28	0	0 (0.00) [0.00, 70.76]
Sepsis		
N'	2	2
Day 28	0 (0.00) [0.00, 84.19]	0 (0.00) [0.00, 84.19]
cIAI		
N'	4	0
Day 28	0 (0.00) [0.00, 60.24]	0
HABP/VABP		
N'	2	4
Day 28	0 (0.00) [0.00, 84.19]	0 (0.00) [0.00, 60.24]
Other		
N'	4	9
Day 28	0 (0.00) [0.00, 60.24]	0 (0.00) [0.00, 33.63]

BSI = blood stream infection; cIAI = complicated intra-abdominal infection; GA = gestational age; HABP/VABP = hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; PNA = postnatal age (chronological age)
Subgroup 1: GA ≥ 37 weeks and PNA 28 days to < 3 months; Subgroup 2: GA ≥ 37 weeks and PNA 0 to < 28 days; Subgroup 3: GA ≥ 32 to 36 weeks and PNA ≥ 14 days; Subgroup 4: GA ≥ 32 to 36 weeks and PNA < 14 days; Subgroup 5: GA ≥ 26 to < 32 weeks and PNA ≥ 14 days; Subgroup 6: GA ≥ 26 to < 32 weeks and PNA < 14 days.
Percentage was calculated using N' as the denominator where N' is the number of participants who had the specified infection type. Any participant without a reported death was treated as alive.
The 95% CI was calculated using Clopper-Pearson method.

Other Serious Adverse Events

Single-Dose Phase

Two (16.7%) participants in the safety population experienced a total of 3 serious TEAEs. One participant experienced Grade 3 necrotising enterocolitis neonatal on day 19, which was considered not related to study intervention and resolved on day 39. A second participant had Grade 4 multiple organ dysfunction syndrome beginning on day 13 and Grade 5 sepsis beginning on day 39. Both events were considered not related to study intervention and resulted in death on day 39.

Multiple-Dose Phase

Five (27.8%) participants in the safety population experienced a total of 5 serious TEAEs, including Grade 4 neonatal sepsis, Grade 1 subcutaneous abscess, Grade 2 vascular device infection, Grade 2 diarrhoea, and Grade 4 small intestinal perforation. All events were considered not related to study intervention and all were considered recovered or resolved.

Treatment-Emergent Adverse Events Leading to Discontinuation of Study Intervention

Single-Dose Phase

No TEAEs leading to discontinuation of cefiderocol were reported.

Multiple-Dose Phase

One participant in Subgroup 6 (GA ≥ 26 to < 32 weeks and PNA < 14 days) experienced a nonserious, Grade 2 TEAE of candida infection leading to discontinuation of cefiderocol. The event was considered not related to cefiderocol. Study intervention was withdrawn and the event resolved.

Treatment-Emergent Adverse Events Leading to Discontinuation from the Study

No participant experienced a TEAE leading to discontinuation from the study.

Laboratory Values

Formal statistical analysis of laboratory parameters was not performed. Visual review of the data did not reveal any consistent or clinically meaningful trends over time.

Individual Participant Changes

Postdosing abnormal laboratory values are summarised below.

Single-Dose Phase

- Haemoglobin: 4 (40.0%) participants had a decrease from baseline of ≥ 1.5 g/dL.
- Platelet count: 2 (20.0%) participants had a decrease from baseline of ≥ 25% and value < lower limit of normal (LLN).
- White blood cell count: 1 (10.0%) participant had an increase from baseline of ≥ 20% and value > ULN.
- Total bilirubin: 3 (30.0%) participants had a value > 2 × ULN.

Multiple-Dose Phase

- Haemoglobin: 13 (76.5%) participants had a decrease from baseline of ≥ 1.5 g/dL.
- Platelet count: 3 (17.6%) participants had a decrease from baseline of ≥ 25% and value < LLN; 2 (11.8%) participants had an increase from baseline of ≥ 100% and value > ULN.
- White blood cell count: 3 (17.6%) participants had a decrease from baseline of ≥ 50% and value < LLN; 5 (29.4%) participants had an increase from baseline of ≥ 20% and value > ULN.
- ALT: 1 (5.6%) participant had a value > 3 × ULN.
- Total bilirubin: 9 (50.0%) participants had a value > 2 × ULN.
- Blood urea nitrogen: 1 (25.0%) participant had an increase from baseline of ≥ 50% and value > ULN.
- • Alanine phosphatase: 2 (11.1%) participants had an increase from baseline of ≥ 50% and value > ULN.

Vital Sign Measurements, Physical Findings, and Other Observations Related to Safety

No formal statistical testing was performed on the vital signs measurements, but visual inspection of the data suggests that there were no apparent trends in vital signs measurements over time (blood pressure [systolic and diastolic], heart rate, respiratory rate, SpO2, and body temperature).

2.3.3. Discussion on clinical aspects

This study evaluated the safety and tolerability of cefiderocol when used in addition to SOC in paediatric participants from birth to < 3 months of age with suspected or confirmed aerobic Gram-negative bacterial infections. Cefiderocol was administered either as a single dose or in multiple doses. The treatment was generally well-tolerated, with approximately 28% of participants receiving 5 to < 15 infusions and approximately 72% of participants receiving 15 or more infusions.

In the single-dose phase, no treatment-related AEs, treatment-related serious AEs, or TEAEs leading to discontinuation from cefiderocol or from the study were reported. Two participants experienced a serious TEAE; 1 was fatal (Grade 5, unrelated sepsis). In the multiple-dose phase, no treatment-related serious AEs, TEAEs leading to discontinuation from the study, or TEAEs leading to death were reported. Five participants experienced a serious TEAE, 2 participants experienced treatment-related AEs, and 1 participant experienced a TEAE leading to cefiderocol discontinuation. The safety profile of cefiderocol in combination with SOC was consistent with that expected for a β-lactam antibiotic, with

no unexpected safety concerns identified. Geometric mean plasma concentrations were 8 µg/mL or above in all age cohorts with 1-hour or 3-hour infusion times.

PK results have been provided in a very basic way, but the MAH will update the popPK model for a future application for a paediatric indication. This is considered acceptable for this procedure. The MAH is asked to present future simulations and PK results in a useful and easy interoperable way in the future variation (please see Modelling and simulation Q&A). Modelling and simulation: questions and answers | European Medicines Agency (EMA).

3. CHMP's overall conclusion and recommendation

The completed study 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 PSP and EU PIP (P/0441/2022). The cefiderocol PK results from this study will be used for modelling and simulations to estimate a potentially efficacious dose (and dosing regimen) of cefiderocol and appropriate updates to the Fetcroja marketing authorisation to include a paediatric indication are anticipated in due course.

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

☒ **Fulfilled:**

No regulatory action required.