09 November 2023
EMA/513625/2023
Human Medicines Division

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

## Fetcroja

cefiderocol

Procedure no: EMEA/H/C/004829/P46/005

## Note

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

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| Status of this report and steps taken for the assessment | | | |
|---|---|---|---|
| **Current step** | **Description** | **Planned date** | **Actual Date** |
| ☐ | Start of procedure | 11 Sep 2023 | 11 Sep 2023 |
| ☐ | CHMP Rapporteur Assessment Report | 16 Oct 2023 | 17 Oct 2023 |
| ☐ | CHMP members comments | 30 Oct 2023 | 30 Oct 2023 |
| ☐ | Updated CHMP Rapporteur Assessment Report | 06 Nov 2023 | N/A |
| ☒ | CHMP adoption of conclusions | 09 Nov 2023 | 09 Nov 2023 |

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# 1. Introduction

On 11th August 2023, the MAH submitted a completed paediatric study for Fetcroja (cefiderocol), in accordance with Article 46 of Regulation (EC) No1901/2006.

*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 Subjects 3 Months to <18 Years of Age with Suspected or Confirmed Aerobic Gram-negative Bacterial Infections*

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that *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 Subjects 3 Months to <18 Years of Age with Suspected or Confirmed Aerobic Gram-negative Bacterial Infections* is part of an agreed Paediatric Investigation Plan (EMEA-002133-PIP01-17-M02, Decision number EMA/PDCO/8222/2022).

## *2.2. Information on the pharmaceutical formulation used in the study*

The pharmaceutical formulation used in the study is the same as that commercially available.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

*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 Subjects 3 Months to <18 Years of Age with Suspected or Confirmed Aerobic Gram-negative Bacterial Infections*

The chemical structure of cefiderocol is similar to third- to fourth-generation cephalosporins ceftazidime and cefepime, but with the additional presence of a catechol group, resulting in the ability of cefiderocol to act as a siderophore and to be transported across the outer cell membrane of Gram-negative bacteria. As a result, cefiderocol overcomes mechanisms of antibiotic resistance resulting from porin channel mutations or efflux-pump overproduction and demonstrates enhanced stability to hydrolysis by all known classes of BLAs, including serine-carbapenemases and metallo-beta-lactamases. Cefiderocol is being developed to address the unmet medical need to treat carbapenem-resistant infections caused by Gram-negative bacteria, including Enterobacteriaceae and non-fermenters, such as *P. aeruginosa*, *S. maltophilia*, and *A. baumannii*.

In 2019, Fetcroja received marketing authorisation in the EU for treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

The paediatric development plan for Fetcroja as per the agreed Paediatric Investigation Plan (EMEA-002133-PIP01-17-M02, Decision number EMA/PDCO/8222/2022) comprises one quality measure, one

non-clinical juvenile toxicity study and two paediatric clinical studies (of which the first concerns this submission), alongside a modelling and simulation study and an extrapolation measure.

## 2.3.2. Clinical study

### 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 Subjects 3 Months to <18 Years of Age with Suspected or Confirmed Aerobic Gram-negative Bacterial Infections

## Description

The primary purpose of the study was to provide safety data commensurate with the intended duration of treatment and obtain pharmacokinetic (PK) data to confirm dosing recommendations supporting the safe and effective use of cefiderocol in paediatric participants 3 months to <18 years of age with suspected or confirmed aerobic Gram-negative infections. The PK data for cefiderocol from this study will be used for the planned modelling and simulations, to estimate the probability of target attainment (PTA) and determine the efficacious dose (and dosing regimen) of cefiderocol for this age range. The clinical efficacy of cefiderocol is established from the PK/PD data package and as such this study was not designed to conclude on paediatric clinical efficacy.

## Methods

***Study participants***

Hospitalised paediatric participants 3 months to < 18 years of age (in 4 separate cohorts) with a suspected or confirmed aerobic Gram-negative pathogen, including but not limited to complicated urinary tract infections (cUTI), complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP)/ventilator-acquired pneumonia (VAP), and sepsis or bloodstream infection (BSI), caused by a suspected or confirmed aerobic Gram-negative pathogen requiring systemic antibiotics for an expected 5 to 14 days.

Premature babies were not restricted but must have had an adjusted or postnatal age of 3 months.

As discussed and agreed with the EMA's PDCO, Cohort 1 (adolescents) did not participate in the Multiple-dose Phase because adolescent PK data may be extrapolated from available and adequate adult PK data.

***Main inclusion criteria***

- Hospitalised participants 3 months to < 18 years of age.
- Suspected or confirmed infection (including but not limited to cUTI, cIAI, HAP/VAP, sepsis, or BSI) that required hospitalisation for treatment with IV antibiotics.

The suspected or confirmed aerobic Gram-negative infection type (including but not limited to cUTI, cIAI, HAP/VAP, and sepsis or BSI) was specified and recorded in the electronic case report form (eCRF):

- **Complicated urinary tract infection** was defined as a clinical syndrome characterised by pyuria and a microbial pathogen in the urine in the context of the following underlying features: recurrent urinary tract infections (2 or more in a 12-month period); obstructive uropathy; a functional or anatomical abnormality of the urinary tract, including anatomical

malformations or neurogenic bladder; vesicoureteric reflux; urinary tract catheterisation; an invasive urogenital procedure, such as cystoscopy or urogenital surgery; or azotemia caused by intrinsic renal disease. In addition, paediatric participants should have had at least 2 of the following signs and symptoms depending on their age:

    - For participants < 2 years of age: Fever defined as body temperature ≥ 38.0°C, failure to thrive, recent weight loss, irritability, poor feeding, lack of normal level of activity, abdominal pain/tenderness on physical examination, vomiting, or jaundice
    - For participants ≥ 2 to < 18 years: Fever defined as body temperature ≥ 38.0°C, chills or rigors, dysuria, urinary urgency, urinary frequency, new-onset urinary incontinence, suprapubic pain, flank pain, abdominal pain, pelvic pain, suprapubic tenderness or costovertebral angle tenderness on physical examination, nausea, or vomiting

- **Hospital-acquired pneumonia** was defined as an acute infection of the pulmonary parenchyma associated with clinical signs and symptoms, such as fever or hypothermia, chills, rigors, cough, purulent sputum production, chest pain, or dyspnoea, accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient hospitalised for more than 48 hours or developing within 7 days after discharge from a hospital. Patients with HAP may or may not require intubation and mechanical ventilation.
- **Ventilator-associated pneumonia** was defined as an acute infection of the pulmonary parenchyma associated with clinical signs and symptoms, such as fever or hypothermia, chills, rigors, purulent respiratory secretions, and increased oxygen requirements. These signs and symptoms are in addition to laboratory abnormalities, such as leucocytosis accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient on mechanical ventilation for a minimum of 48 hours.

***Main exclusion criteria***

- Suspected or confirmed central nervous system (CNS) infection (eg, meningitis, brain abscess, shunt infection) or osteomyelitis (which required prolonged antibiotic therapy).
- Medical history of cystic fibrosis.
- Documented history of any hypersensitivity or allergic reaction to any β-lactam antibiotic (history of a mild rash followed by uneventful re- exposure not a contraindication to enrolment).
- Multiple-dose only: infection caused only by a confirmed Gram- positive pathogen.
- Single-dose Phase: moderate or severe renal impairment based on estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2 at screening.
- Multiple-dose Phase: eGFR < 15 mL/min/1.73 m2 at screening.
- End-stage renal disease, haemodialysis, continuous venovenous hemofiltration.
- Shock in the prior month or at screening.
- Severe neutropenia or severely immunocompromised.
- Multiorgan failure.
- Vasopressor therapy at screening.
- Life expectancy of < 30 days due to severity of a concurrent illness. V

***Treatments***

Cefiderocol infused intravenously over 3 hours, q8h.

Treatment began within 72 hours of the start of other potentially effective treatment with SOC antibiotics (in accordance with local standards, modifiable at any time) for infection and continued for an expected 5 to 14 days (in addition to SOC).

If the participant's infection was confirmed to be Gram-negative before starting treatment, monotherapy with cefiderocol was allowed.

In special circumstances, treatment beyond 14 days was allowed.

Single-dose Phase (Cohorts 1, 2, 3, and 4), normal renal function or mild renal impairment.

The dose of cefiderocol was determined based on body weight; the maximum dose to be administered did not exceed 2000 mg. On Day 1 of the Single-dose Phase, participants were administered a single dose of cefiderocol infused IV over 3 hours at any time during the SOC treatment. After review of data from administration of cefiderocol in the Single-dose Phase, dosing recommendations for cefiderocol may have been adjusted by the sponsor prior to administration in the Multiple-dose Phase or for the next subsequent cohort based on ongoing assessment of PK data. All revised dosing recommendations were provided by the sponsor, discussed with the investigator, and documented.

Multiple-dose Phase (Cohorts 2, 3, and 4).

The dose of cefiderocol administered to each participant was based on both body weight and renal function, not exceeding 2000 mg of cefiderocol.

***Objectives and Outcomes/endpoints***

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To assess the safety and tolerability of cefiderocol after single-dose administration in hospitalized pediatric participants 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative bacterial infections | • Adverse events<br>• Vital signs measurements<br>• Physical examination findings<br>• Clinical laboratory assessments |
| • To assess the safety and tolerability of cefiderocol after multiple-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 PK of cefiderocol after single-dose administration of cefiderocol in hospitalized pediatric participants 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative bacterial infections | • $C_{max}$, $AUC_{0\text{-}inf}$, and $t_{1/2}$ after single dose<br>• $C_{max}$, $AUC_{0\text{-}\tau}$, and $t_{1/2}$ after a minimum of 4 doses |
| • To assess the PK of cefiderocol after multiple-dose administration in hospitalized pediatric participants 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections | |
| Secondary | |
| • Multiple-dose Phase only: When cefiderocol is administered alone, to assess the clinical response at the Posttreatment visit (7 [±◦4] days following EOT) and at the EOS visit, AND to assess the microbiological response at the Posttreatment visit (7 [±◦4] days) following EOT and EOS (if available) | • Clinical outcome<br>• Microbiological outcome |
| Exploratory | |
| • 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 | • %$fT_{>MIC}$ for causative pathogens<br>• PTA for 75% $fT_{>MIC}$ |
| • Multiple-dose Phase only: To describe the clinical outcome of cefiderocol when given alone or in combination with SOC antibiotics to treat infections caused by aerobic Gram-negative pathogens in hospitalized pediatric participants 3 months to < 12 years of age at the Posttreatment visit, EOT, and EOS | • Clinical outcome |
| • Multiple-dose Phase only: To describe the microbiological outcome of cefiderocol when given alone or in combination with SOC antibiotics to treat infections caused by aerobic Gram-negative pathogens in hospitalized pediatric participants 3 months to < 12 years of age at the Posttreatment visit, EOT, and EOS | • Microbiological outcome |

%$fT$>MIC = percentage of time of the dosing interval required for plasma concentrations to be above the mean inhibitory concentration; $AUC_{0\text{-}inf}$ = area under the plasma-concentration-time curve extrapolated from time 0 to infinity; $AUC_{0\text{-}\tau}$ = area under the concentration-time curve over the dosing interval τ; $C_{max}$ = maximum plasma concentration; EOS = end of study; EOT = end of treatment; $fT_{>MIC}$ = time during which plasma concentrations are above the mean inhibitory concentration; MIC = minimum inhibitory concentration; PK = pharmacokinetics; PTA = probability of target attainment; SOC = standard of care; $t_{1/2}$ = half-life

**ENDPOINT DEFINITIONS**

**Safety**

- Physical examination
- Vital signs
- Mandatory clinical laboratory tests (haematology, blood chemistry, urinalysis) via central laboratory
- eGFR
- Microbiological culture
- Pregnancy test
- Adverse events (from the time signed informed consent/assent was obtained through the EOS visit or 28 (+ 7) days after administration of the last dose of the study drug)
- Liver event form

**Efficacy (Multiple-dose Phase Only)**

*Physician Clinical Response*

Cure or failure based on the clinical outcome as assessed by the investigator, considering objective data (e.g., body temperature, white blood cell count, urinalysis).

The following clinical outcomes in the Multiple-dose Phase were characterised at EOT, at the Posttreatment visit, and at EOS (conducted on site or as a phone call).

- **Complicated Urinary Tract Infection**
  - Clinical Cure: Resolution or substantial improvement of baseline signs and symptoms of cUTI, or return to pre-infection baseline if known, such that no antibiotic therapy was required for the treatment of the current infection.
  - Clinical Failure: No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of cUTI; or reappearance of signs and/or symptoms of cUTI; development of new signs and/or symptoms of cUTI requiring antibiotic therapy other than, or in addition to, study treatment therapy; or death due to cUTI.
  - Indeterminate: Lost to follow-up such that a determination of clinical cure/failure could not be made.
- **HAP/VAP/cIAI**
  - Clinical Cure: Resolution or substantial improvement of baseline signs and symptoms of pneumonia/cIAI.
  - Clinical Failure: No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of pneumonia/cIAI; reappearance of signs and/or symptoms of pneumonia/cIAI; development of new signs and/or symptoms of pneumonia/cIAI requiring antibiotic therapy other than, or in addition to, study treatment therapy; progression of chest radiographic abnormalities; or death due to pneumonia/cIAI.
  - Indeterminate: Lost to follow-up such that a determination of clinical cure/failure could not be made.
- **BSI/Sepsis**
  - Clinical Cure: Resolution or substantial improvement of baseline signs and symptoms. Participants with bacteraemia must have had eradication of bacteraemia caused by the Gram-negative pathogen.
  - Clinical Failure: No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms, reappearance of signs and/or symptoms development of new signs and/or symptoms requiring antibiotic therapy other than, or in addition to, study treatment therapy; or death due to BSI/sepsis.

- Indeterminate: Lost to follow-up such that a determination of clinical cure/failure could not be made.

*Microbiological Response*

Determined at the Posttreatment Visit (7 [± 4] days) following EOT and EOS (if available) for each baseline Gram-negative pathogen. Emergent (ie, non-baseline) pathogens were considered separately, and did not affect the per-participant microbiological outcome.

- **Complicated Urinary Tract Infection**
  - Eradication: A urine culture showed the baseline Gram-negative uropathogen found at entry at ≥ 105 colony forming units (CFU)/mL was reduced to < 103 CFU/mL.
  - Persistence: A urine culture showed that the baseline Gram-negative uropathogen found at entry at ≥ 105 CFU/mL remained at ≥ 103 CFU/mL.
  - Indeterminate: No urine culture obtained or additional antibiotic therapy for the treatment of the current infection including missed sampling.
- **HAP/VAP/cIAI and BSI/Sepsis**
  - Eradication: Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen. 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.
  - Persistence: Continued presence of the baseline Gram-negative pathogen from an appropriate clinical specimen.
  - Indeterminate: No culture obtained from an appropriate clinical specimen or additional antibiotic therapy for the treatment of the current infection including missed sampling.

***Sample size***

This primary purpose of this study was to assess the PK and safety of cefiderocol in paediatric participants 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative infections. Therefore, the sample size calculation did not consider efficacy endpoints.

Overall, at least 54 evaluable paediatric participants were planned to be enrolled in the study across all 4 cohorts.

**Table 9-1 Cohort Description**

| Cohort | Age Range | Single-dose Phase (minimum per cohort) | Multiple-dose Phase (minimum per cohort) |
|---|---|---|---|
| 1[a] | 12 to < 18 years | N = 6 | No Multiple-dose Phase for this cohort |
| 2[a, b] | 6 to < 12 years | N = 6 | N = 10 |
| 3[a, b] | 2 to < 6 years | N = 6 | N = 10 |
| 4[c] | 3 months to < 2 years | N = 6 | N = 10 |

PK = pharmacokinetic

a Cohorts 1, 2, and 3 of the Single-dose Phase were initiated in parallel.

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

c Cohort 4 (single dose) began after safety and PK data from at least 6 participants from single-dose Cohorts 1, 2, and 3 (with a minimum of 3 participants from Cohort 3) were assessed.

***Randomisation and blinding***

This was an open-label study.

***Statistical Methods***

No inferential statistical testing was performed.

**Safety Population** included all enrolled participants who received at least 1 dose of cefiderocol. 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 concentration listing.

**Pharmacokinetic Concentration Summary (PKCS) Population** included all enrolled participants who received 1 dose of cefiderocol in the Single-dose Phase and ≥ 4 doses of cefiderocol in the Multiple-dose Phase and those who had at least 1 PK blood sample above the limit of quantification. This population was used for the concentration summary and for plotting the concentration-time data and the concentration data summary.

**ITT population** included all enrolled participants who received at least 1 dose of cefiderocol. The ITT Population was used for summary efficacy data.

**MITT population** included all participants in the ITT population who had a baseline Gram-negative pathogen from any specimen from a baseline infection site (Multiple-dose Phase only). The MITT Population was used for summary efficacy data.

(The Intent-to-treat (ITT) and Microbiological ITT (MITT) Populations were defined only for participants in the Multiple-dose Phase.)

## Results

***Participant flow***

**Table 10-1 Participant Disposition (All Enrolled Participants)**

| | Single-dose Phase | | | | | Multiple-dose Phase | | | |
|---|---|---|---|---|---|---|---|---|---|
| | C1 N = 6 n (%) | C2 N = 6 n (%) | C3 N = 6 n (%) | C4 N = 6 n (%) | Overall N = 24 n (%) | C2 N = 12 n (%) | C3 N = 11 n (%) | C4 N = 6 n (%) | Overall N = 29 n (%) |
| Received treatment | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 24 (100) | 12 (100) | 11 (100) | 6 (100) | 29 (100) |
| Treatment completion status | | | | | | | | | |
| Completed study treatment | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 24 (100) | 11 (91.7) | 9 (81.8) | 6 (100) | 26 (89.7) |
| Discontinued treatment | 0 | 0 | 0 | 0 | 0 | 1 (8.3) | 2 (18.2) | 0 | 3 (10.3) |
| Other | 0 | 0 | 0 | 0 | 0 | 1 (8.3) | 2 (18.2) | 0 | 3 (10.3) |
| Study completion status | | | | | | | | | |
| Completed the study [a] | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 24 (100) | 12 (100) | 10 (90.9) | 6 (100) | 28 (96.6) |
| Discontinued from the study | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (3.4) |
| Protocol deviation | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (3.4) |

C = cohort; mos = months; yr = year

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

Percentage is based on the number of enrolled participants. 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).

Source: Table 14.1.1.2

***Recruitment***

This was a multi-centre study conducted at 24 sites, including 2 sites in Belgium, Estonia, Latvia, Russia, and Spain; 3 sites in Georgia and Hungary; and 4 sites in Thailand and Ukraine.

First patient first visit: 18 August 2020

Last patient last visit: 06 Feb 2023

Report date: 25 July 2023

The study protocol was subject to multiple revisions during the course of the study, none of which are considered to have significantly impacted on interpretation of the study.

***Baseline data***

**Table 11-2 Baseline Demographic Characteristics (Safety Population)**

| Characteristic Statistic/Category | Single-dose Phase | | | | | Multiple-dose Phase | | | |
|---|---|---|---|---|---|---|---|---|---|
| | C1 N = 6 | C2 N = 6 | C3 N = 6 | C4 N = 6 | Overall N = 24 | C2 N = 12 | C3 N = 11 | C4 N = 6 | Overall N = 29 |
| Age (months), n | 6 | 6 | 6 | 6 | 24 | 12 | 11 | 6 | 29 |
| Mean | 171.2 | 109.2 | 34.3 | 12.2 | 81.7 | 104.3 | 52.4 | 8.8 | 64.9 |
| Standard deviation | 16.1 | 20.4 | 15.6 | 6.3 | 65.9 | 22.7 | 14.3 | 5.0 | 41.0 |
| Median | 175.5 | 111.0 | 29.0 | 13.5 | 73.5 | 107.0 | 60.0 | 6.5 | 64.0 |
| Minimum, maximum | 150, 190 | 81, 131 | 25, 66 | 3, 21 | 3, 190 | 75, 143 | 28, 68 | 5, 17 | 5, 143 |
| Age (years), n | 6 | 6 | 6 | 6 | 24 | 12 | 11 | 6 | 29 |
| Mean | 14.27 | 9.10 | 2.87 | 1.05 | 6.82 | 8.72 | 4.35 | 0.73 | 5.41 |
| Standard deviation | 1.34 | 1.68 | 1.30 | 0.53 | 5.48 | 1.88 | 1.20 | 0.42 | 3.43 |
| Median | 14.65 | 9.25 | 2.40 | 1.15 | 6.15 | 8.90 | 5.00 | 0.55 | 5.30 |
| Minimum, maximum | 12.5, 15.8 | 6.8, 10.9 | 2.1, 5.5 | 0.3, 1.8 | 0.3, 15.8 | 6.3, 11.9 | 2.3, 5.7 | 0.4, 1.4 | 0.4, 11.9 |
| Sex (n, %) | | | | | | | | | |
| Male | 2 (33.3) | 2 (33.3) | 3 (50.0) | 3 (50.0) | 10 (41.7) | 3 (25.0) | 2 (18.2) | 4 (66.7) | 9 (31.0) |
| Female | 4 (66.7) | 4 (66.7) | 3 (50.0) | 3 (50.0) | 14 (58.3) | 9 (75.0) | 9 (81.8) | 2 (33.3) | 20 (69.0) |
| Race (n, %) | | | | | | | | | |
| White | 6 (100) | 6 (100) | 4 (66.7) | 2 (33.3) | 18 (75.0) | 11 (91.7) | 11 (100) | 3 (50.0) | 25 (86.2) |
| Black/African American | 0 | 0 | 1 (16.7) | 1 (16.7) | 2 (8.3) | 0 | 0 | 0 | 0 |
| Asian | 0 | 0 | 1 (16.7) | 3 (50.0) | 4 (16.7) | 1 (8.3) | 0 | 3 (50.0) | 4 (13.8) |
| Ethnicity (n, %) | | | | | | | | | |
| Not Hispanic/Latino | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 24 (100) | 12 (100) | 11 (100) | 6 (100) | 29 (100) |
| Weight (kg), n | 6 | 6 | 6 | 6 | 24 | 12 | 11 | 6 | 29 |
| Median | 63.50 | 29.15 | 13.90 | 8.80 | 19.85 | 26.50 | 16.00 | 6.85 | 19.00 |
| Minimum | 43.0 | 20.0 | 9.8 | 4.9 | 4.9 | 20.0 | 11.0 | 5.7 | 5.7 |
| Maximum | 69.0 | 44.6 | 19.7 | 11.4 | 69.0 | 35.5 | 25.0 | 7.9 | 35.5 |
| Height (cm), n | 6 | 6 | 6 | 6 | 24 | 12 | 11 | 6 | 29 |
| Median | 164.00 | 131.50 | 89.95 | 74.75 | 115.00 | 131.00 | 109.00 | 66.50 | 112.00 |
| Minimum | 141.0 | 112.0 | 80.0 | 53.5 | 53.5 | 112.0 | 90.0 | 61.0 | 61.0 |
| Maximum | 172.0 | 160.0 | 118.0 | 99.0 | 172.0 | 152.0 | 118.0 | 77.0 | 152.0 |
| BMI ($kg/m^2$), n | 6 | 6 | 6 | 6 | 24 | 12 | 11 | **6** | **29** |
| Median | 24.02 | 16.78 | 15.06 | 17.00 | 17.84 | 15.49 | 14.57 | 14.45 | 15.26 |
| Minimum | 20.3 | 14.4 | 13.3 | 9.2 | 9.2 | 13.5 | 11.0 | 13.3 | 11.0 |
| Maximum | 25.3 | 20.7 | 22.4 | 18.5 | 25.3 | 20.6 | 18.0 | 17.2 | 20.6 |
| eGFR grading group (n, %)[a] | | | | | | | | | |
| ≥ 120 mL/min/1.73 $m^2$ | 2 (33.3) | 1 (16.7) | 2 (33.3) | 4 (66.7) | 9 (37.5) | 3 (25.0) | 1 (9.1) | 4 (66.7) | 8 (27.6) |
| 90 to < 120 mL/min/1.73 $m^2$ | 4 (66.7) | 4 (66.7) | 4 (66.7) | 0 | 12 (50.0) | 7 (58.3) | 5 (45.5) | 2 (33.3) | 14 (48.3) |
| 60 to < 90 mL/min/1.73 $m^2$ | 0 | 1 (16.7) | 0 | 2 (33.3) | 3 (12.5) | 2 (16.7) | 5 (45.5) | 0 | 7 (24.1) |

BMI = body mass index; C = cohort; mos = months; eGFR = estimated glomerular filtration rate; yrs = 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.

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)

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

Sources: Table 14.1.3.1.1; Table 14.1.3.2.1

***Baseline medical history***

In the Safety Population, 24 (100%) participants in the Single-dose Phase and 26 (89.7%) participants in the Multiple-dose Phase reported medical history at baseline. The most frequently reported (> 2 participants in either phase) preferred terms in the Single-dose and Multiple-dose Phases, respectively, were appendicitis (37.5%, 31.0%), peritonitis (0, 10.3%), pneumonia (4.2%, 10.3%), UTI (12.5%, 10.3%), hydronephrosis (0, 10.3%), and vesicoureteric reflex (12.5%, 10.3%). For the Multiple-dose Phase MITT Population, 15 (83.3%) participants reported medical history at baseline. The most frequently reported (≥ 2 participants in either phase) preferred terms were appendicitis (27.8%), peritonitis (11.1%), pneumonia (16.7%), ureteral stent insertion (11.1%), and vesicoureteric reflex (11.1%).

***Prior SOC antibiotics***

In the Safety Population of the Single-dose Phase, 20 (83.3%) participants received prior SOC treatment. Nine (37.5%) participants received ceftriaxone, 5 (20.8%) participants each received metronidazole and amikacin, 4 (16.7%) participants received cefazolin, 3 (12.5%) participants received and amikacin sulfate; 2 (8.3%) participants received meropenem, and 1 (4.2%) participant each received cefotaxime, ceftriaxone sodium, piperacillin sodium/tazobactam sodium, piperacillin/tazobactam, meropenem trihydrate, ceftazidime, ciprofloxacin, colistin, ertapenem, gentamicin, and vancomycin.

In the Safety Population of the Multiple-dose Phase, 6 (20.7%) participants received cefazolin; 5 (17.2%) participants each received metronidazole, amikacin, and amikacin sulfate; 4 (13.8%) participants received meropenem; 2 (6.9%) participants each received cefotaxime, ceftriaxone sodium, piperacillin sodium/tazobactam sodium, and piperacillin/tazobactam; and 1 (3.4%) participant each received meropenem trihydrate, amoxicillin trihydrate/clavulanate potassium, cefixime, cefotaxime sodium, sulfamethoxazole/trimethoprim, and tobramycin.

***Concomitant SOC antibiotics***

In the Safety Population of the Single-dose Phase, 100% of participants received concomitant SOC treatment. Eight (33.3%) participants received ceftriaxone; 6 (25.0%) participants received amikacin; 2 (8.3%) participants each received amikacin sulfate, meropenem, ceftriaxone sodium, cefotaxime, piperacillin/tazobactam, ceftazidime, and gentamicin; and 1 (4.2%) participant each received metronidazole, cefixime, ertapenem, meropenem trihydrate, sulfamethoxazole/trimethoprim, ampicillin/sulbactam, cefepime hydrochloride, ciprofloxacin, colistin, and vancomycin.

In the Safety Population of the Multiple-dose Phase, 100% of participants received concomitant SOC treatment. Nine (31.0%) participants received amikacin; 5 (17.2%) participants received amikacin sulfate; 4 (13.8%) participants received meropenem; 3 (10.3%) participants received ceftriaxone sodium; 2 (6.9%) participants each received cefotaxime, piperacillin/tazobactam metronidazole, and tobramycin; and 1 (3.4%) participant each received cefixime, ertapenem, meropenem trihydrate, sulfamethoxazole/trimethoprim, akritoin, amoxicillin trihydrate/clavulanate potassium, azithromycin, cefdinir, cefotaxime sodium, co-trimoxazole, nitrofurantoin, piperacillin, piperacillin sodium, piperacillin sodium/tazobactam sodium, rifampicin, and tazobactam.

***Non-antibiotic medications***

The vast majority of patients received prior and concomitant non-antibiotic medications including paracetamol, propofol, fentanyl, sodium chloride, isoflurane, ibuprofen, calcium, potassium, and atracurium.

## Table 11-3 Baseline Infection Type (Safety Population)

| Infection Type | Single-dose Phase | | | | | Multiple-dose Phase | | | |
|---|---|---|---|---|---|---|---|---|---|
| | C1 N = 6 | C2 N = 6 | C3 N = 6 | C4 N = 6 | Overall N = 24 | C2 N = 12 | C3 N = 11 | C4 N = 6 | Overall N = 29 |
| cUTI | 0 | 2 (33.3) | 2 (33.3) | 1 (16.7) | 5 (20.8) | 3 (25.0) | 4 (36.4) | 3 (50.0) | 10 (34.5) |
| cIAI | 6 (100) | 3 (50.0) | 1 (16.7) | 0 | 10 (41.7) | 9 (75.0) | 4 (36.4) | 1 (16.7) | 14 (48.3) |
| HAP/VAP | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 2 (18.2) | 0 | 2 (6.9) |
| BSI | 0 | 0 | 0 | 3 (50.0) | 3 (12.5) | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Sepsis | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Other[a] | 0 | 1 (16.7) | 1 (16.7) | 2 (33.3) | 4 (16.7) | 0 | 1 (9.1) | 0 | 1 (3.4) |

BMI = body mass index; BSI = blood stream infection; C = cohort; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; eGFR = estimated glomerular filtration rate; HAP = hospital-acquired pneumonia; mos = months; VAP = ventilator-associated pneumonia; yrs = years

a Other infection types were 2 participants with community-associated pneumonia and 1 participant with cutaneous infection

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

Source: Table 14.1.3.2.1

## Table 11-4 Baseline Infection Type (MITT Population)

| Infection Type | Multiple-dose Phase (Cefiderocol + Standard of Care) | | | |
|---|---|---|---|---|
| | C2 N = 7 | C3 N = 8 | C4 N = 3 | Overall N = 18 |
| cUTI | 2 (28.6) | 4 (50.0) | 1 (33.3) | 7 (38.9) |
| cIAI | 5 (71.4) | 2 (25.0) | 0 | 7 (38.9) |
| HAP/VAP | 0 | 2 (25.0) | 0 | 2 (11.1) |
| BSI | 0 | 0 | 0 | 1 (5.6) |
| Sepsis | 0 | 0 | 1 (33.3) | 1 (5.6) |

BMI = body mass index; BSI = blood stream infection; C = cohort; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; eGFR = estimated glomerular filtration rate; HAP = hospital-acquired pneumonia; MITT = microbiological intent-to-treat population; mos = months; VAP = ventilator-associated pneumonia; yrs = years

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

Source: Table 14.1.3.2.3

**Table 11-5 Baseline Gram-negative Pathogens (MITT Population)**

| Baseline Infection Site | Baseline Pathogen | Multiple-dose Phase | | | |
|---|---|---|---|---|---|
| | | C2 N = 7 | C3 N = 8 | C4 N = 3 | Overall N = 18 |
| BSI | *Neisseria meningitidis* | 0 | 0 | 1 (33.3) | 1 (5.6) |
| HAP/VAP | *Klebsiella pneumoniae* | 0 | 2 (25.0) | 0 | 2 (11.1) |
| Sepsis | *Salmonella* | 0 | 0 | 1 (33.3) | 1 (5.6) |
| cIAI | *Escherichia coli* | 5 (71.4) | 2 (25.0) | 0 | 7 (38.9) |
| cUTI | *Enterobacter cloacae* complex | 0 | 0 | 1 (33.3) | 1 (5.6) |
| | *Escherichia coli* | 2 (28.6) | 4 (50.0) | 0 | 6 (33.3) |

BMI = body mass index; BSI = blood stream infection; C = cohort; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; eGFR = estimated glomerular filtration rate; HAP = hospital-acquired pneumonia; MITT = microbiological intent-to-treat population; mos = months; VAP = ventilator-associated pneumonia; yrs = years

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

Source: Table 14.1.3.2.4.1

For *Enterobacter cloacae* complex, 1 isolate was resistant to cefepime, ceftazidime, ceftriaxone, and ciprofloxacin. Thirteen *E. coli* isolates were sensitive to most antibiotics tested but resistant to ceftriaxone (2, 15.4%), ciprofloxacin (3, 23.1%), and piperacillin/tazobactam (1, 7.7%). All *Klebsiella pneumoniae* (2) and *Salmonella* (1) isolates were susceptible to all antibiotics tested. The interpretation of susceptibility results using EUCAST guidelines generally aligned with CLSI for majority of the antibiotics.

***Assessor's comment:***

Baseline demographics for the ITT and MITT Populations were similar to those of the Safety Population, with the exception of eGFR grading groupings. In the MITT Population, the eGFR distribution was more skewed towards severe moderate to severe renal impairment, with 11.1% with ≥ 120 mL/min/1.73m2, 50.0% with 90 to ≤ 120 mL/min/1.73m2, and 38.9% with 60 to < 90 mL/min/1.73m2.

In the Single-dose Phase, infection type at baseline was primarily cIAI (41.7%), cUTI (20.8%), BSI (12.5%), and other infection type (16.7%). In the Multiple-dose Phase, infection type at baseline was primarily cIAI (48.3%) and cUTI (34.5%). This was similar between Safety and ITT Populations. For the MITT Population of the Multiple-dose Phase, infection types at baseline were cUTI (38.9%), cIAI (38.9%), HAP/VAP (11.1%), BSI (5.6%), and sepsis (5.6%).

***Number analysed***

In the Multiple-dose Phase, all 29 participants were included in the ITT and Safety Populations. The MITT Population comprised 18 (62.1%) of these 29 participants. Eleven (37.9%) participants were excluded from the MITT population who did not have a Gram-negative pathogen at baseline (5 [41.7%] participants in Cohort 2; 3 [27.3%] in Cohort 3; and 3 [50.0%] in Cohort 4). The PKC and the PKCS Populations were identical, and each included 28 (96.6%) of the 29 enrolled participants.

**Table 11-1 Analysis Populations and Reasons for Exclusion From Analysis Populations (All Enrolled Participants)**

| | Single-dose Phase | | | | | Multiple-dose Phase | | | |
|---|---|---|---|---|---|---|---|---|---|
| Participants: | C1 N = 6 n (%) | C2 N = 6 n (%) | C3 N = 6 n (%) | C4 N = 6 n (%) | Overall N = 24 n (%) | C2 N = 12 n (%) | C3 N = 11 n (%) | C4 N = 6 n (%) | Overall N = 29 n (%) |
| Included in ITT | - | - | - | - | - | 12 (100) | 11 (100) | 6 (100) | 29 (100) |
| Included in MITT | - | - | - | - | - | 7 (58.3) | 8 (72.7) | 3 (50.0) | 18 (62.1) |
| Excluded from MITT | - | - | - | - | - | 5 (41.7) | 3 (27.3) | 3 (50.0) | 11 (37.9) |
| No baseline Gram-negative pathogen | - | - | - | - | - | 5 (41.7) | 3 (27.3) | 3 (50.0) | 11 (37.9) |
| Included in PKC | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 24 (100) | 12 (100) | 10 (90.9) | 6 (100) | 28 (96.6) |
| Excluded from PKC | 0 | 0 | 0) | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (3.4) |
| Did not have ≥ 1 PK blood sample | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (3.4) |
| Included in PKCS | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 24 (100) | 12 (100) | 10 (90.9) | 6 (100) | 28 (96.6) |
| Excluded from PKCS | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (3.4) |
| Did not have ≥ 1 PK blood sample | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (3.4) |
| Included in Safety | 6 (100) | 6 (100) | 6 (100) | 6 (100) | 24 (100) | 12 (100) | 11 (100) | 6 (100) | 29 (100) |

C = cohort; ITT = intent-to-treat population; MITT = microbiological ITT; mos = months; PKC = pharmacokinetic concentration; PKCS = pharmacokinetic concentration summary; yrs = years

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).

Percentages are based on the number of enrolled participants.

Source: Table 14.1.2.2

***Safety results***

Adverse events were classified by System Organ Class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

In the Safety Population of the Multiple-dose Phase, the median extent of exposure was 8.0 days (range: 2 to 15 days); 86.2% of participants received 5 to 14 days of treatment. The median total number of doses received was 24.0 (range: 6 to 42 doses). The longest exposure to cefiderocol was in Cohort 3 (2 to < 6 years) at a median of 27.0 doses over 9.0 days.

*Adverse events*

In the Single-dose Phase, a total of 5 (20.8%) participants experienced 12 TEAEs, including 1 participant (1 event) in Cohort 2, 3 participants (7 events) in Cohort 3, and 1 participant (4 events) in Cohort 4. No SAEs were reported.

In the Multiple-dose Phase, a total of 7 (24.1%) participants experienced 10 TEAEs, including 2 participants (2 events) in Cohort 2, 1 participant (1 event) in Cohort 3, and 4 participants (7 events) in Cohort 4.

All events were mild to moderate, with no severe adverse events reported. No deaths were reported during the study. No treatment-related TEAEs, treatment-related SAEs, or TEAEs leading to cefiderocol withdrawal were reported.

**Table 12-3 Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)**

| | Single-dose Phase | | | | | Multiple-dose Phase | | | |
|---|---|---|---|---|---|---|---|---|---|
| | C1 N = 6 n (%) | C2 N = 6 n (%) | C3 N = 6 n (%) | C4 N = 6 n (%) | Overall N = 24 n (%) | C2 N = 12 n (%) | C3 N = 11 n (%) | C4 N = 6 n (%) | Overall N = 29 n (%) |
| Participants with any TEAEs | 0 | 1 (16.7) | 3 (50.0) | 1 (16.7) | 5 (20.8) | 2 (16.7) | 1 (9.1) | 4 (66.7) | 7 (24.1) |
| Blood and lymphatic system disorders | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Anaemia | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 0 | 0 |
| Neutropenia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Cardiac disorders | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 0 | 0 |
| Bradycardia | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 0 | 0 |
| Congenital, familial and genetic disorders | 0 | 0 | 0 | 1 (16.7) | 1 (4.2) | 0 | 0 | 0 | 0 |
| Laryngomalacia | 0 | 0 | 0 | 1 (16.7) | 1 (4.2) | 0 | 0 | 0 | 0 |
| Gastrointestinal disorders | 0 | 1 (16.7) | 2 (33.3) | 1 (16.7) | 4 (16.7) | 0 | 0 | 0 | 0 |
| Abdominal pain | 0 | 1 (16.7) | 1 (16.7) | 0 | 2 (8.3) | 0 | 0 | 0 | 0 |
| Gastrooesophageal reflux disease | 0 | 0 | 0 | 1 (16.7) | 1 (4.2) | 0 | 0 | 0 | 0 |
| Haematochezia | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 0 | 0 |
| General disorders and administration site conditions | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 0 | 0 |
| Pyrexia | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 0 | 0 |
| Infections and infestations | 0 | 0 | 0 | 1 (16.7) | 1 (4.2) | 1 (8.3) | 0 | 3 (50.0) | 4 (13.8) |
| Candida infection | 0 | 0 | 0 | 1 (16.7) | 1 (4.2) | 0 | 0 | 0 | 0 |
| Pneumocystis jirovecii infection | 0 | 0 | 0 | 1 (16.7) | 1 (4.2) | 0 | 0 | 0 | 0 |
| Urinary tract infection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (33.3) | 2 (6.9) |
| Purulent discharge | 0 | 0 | 0 | 0 | 0 | 1 (8.3) | 0 | 0 | 1 (3.4) |
| Respiratory syncytial virus infection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Staphylococcal bacteraemia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Investigations | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 1 (16.7) | 1 (3.4) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| C-reactive protein increased | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 0 | 0 |
| Alanine aminotransferase increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Product issues | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 0 | 0 |
| Device connection issue | 0 | 0 | 1 (16.7) | 0 | 1 (4.2) | 0 | 0 | 0 | 0 |
| Renal and urinary disorders | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 1 (16.7) | 2 (6.9) |
| Renal impairment | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 1 (16.7) | 2 (6.9) |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 0 | 0 | 0 | 1 (8.3) | 0 | 0 | 1 (3.4) |
| Epistaxis | 0 | 0 | 0 | 0 | 0 | 1 (8.3) | 0 | 0 | 1 (3.4) |

C = cohort; mos = months; TEAE = treatment-emergent adverse events; yrs = years

One participant in Cohort 4 (3 months to <2 years) of the Multiple-dose Phase experienced the SAEs of urinary tract infection and Staphylococcal bacteraemia.

***Assessor's comment:***

The safety database provided by this study is small. However, the TEAEs reported are consistent with the underlying condition, comorbidities and known safety profile of cefiderocol as established in adults. No new safety concerns are identified.

The narrative provided for the participant with cUTI (administered cefiderocol + piperacillin/tazobactam as SOC) who reported multiple SAEs during the multiple-dose phase describe SAEs of UTI (urinalysis positive, urine culture negative) and Staphylococcal bacteraemia reported days 34-37 and days 38-44, respectively.

Urine culture from Screening grew *Klebsiella pneumoniae*. Study drug treatment was concluded day 6. The participant was recorded as Clinical Cure at both EOT and EOS assessment timepoints.

There was a complex medical background (hydronephrosis, motor dysfunction, Noonan syndrome, thrombocytosis, recurrent urinary tract infection, vesicoureteric reflux), concurrent active pneumonia and concomitant medications of cefdinir and nitrofurantoin. Both SAEs were moderate in severity, resolved by the end of the study and considered by the investigator to be unrelated to study drug. This is agreed considering the reported events do not seem to represent a failure of study treatment/ lack of efficacy.

*Clinical laboratory tests*

**Table 12-6 Summary of Laboratory Tests Outside Prespecified Ranges in the Multiple-dose Phase (Safety Population)**

| Parameter (unit)<br>Visit<br>Category | Cohort 2<br>N = 12<br>n (%) | Cohort 3<br>N = 11<br>n (%) | Cohort 4<br>N = 6<br>n (%) | Overall<br>N = 29<br>n (%) |
|---|---|---|---|---|
| Alanine Aminotransferase (U/L) | | | | |
| Baseline Value > 5 x ULN | 1 (8.3) | 0 | 0 | 1 (3.4) |
| Day 1 Value > 5 x ULN | 1 (8.3) | 0 | 0 | 1 (3.4) |
| Posttreatment Value > 3 x ULN | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Alkaline Phosphatase (U/L) | | | | |
| EOT Increase from baseline ≥ 50% and Value > ULN | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Posttreatment increase from baseline ≥ 50% and Value > ULN | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Hemoglobin (g/L) | | | | |
| Day 3 Decrease from baseline ≥ 1.5 g/dL | 2 (16.7) | 1 (9.1) | 0 | 3 (10.3) |
| Day 4 Decrease from baseline ≥ 1.5 g/dL | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Day 9 Decrease from baseline ≥ 1.5 g/dL | 1 (8.3) | 0 | 0 | 1 (3.4) |
| EOT Decrease from baseline ≥ 1.5 g/dL | 1 (8.3) | 0 | 0 | 1 (3.4) |
| Leukocytes ($10^9$/L) | | | | |
| Day 1 Increase from baseline ≥ 20% and > ULN | 0 | 2 (18.2) | 0 | 2 (6.9) |
| Day 3 decrease from baseline ≥ 50% and < LLN | 0 | 1 (9.1) | 0 | 1 (3.4) |
| Day 3 increase from baseline ≥ 20% and > ULN | 1 (8.3) | 1 (9.1) | 1 (16.7) | 3 (10.3) |
| Day 6 increase from baseline ≥ 20% and > ULN | 1 (8.3) | 0 | 0 | 1 (3.4) |
| Platelets ($10^9$/L) | | | | |
| Day 6 increase from baseline ≥ 100% and > ULN | 1 (8.3) | 0 | 0 | 1 (3.4) |
| Day 8 increase from baseline ≥ 100% and > ULN | 0 | 2 (18.2) | 0 | 2 (6.9) |
| EOT Increase from baseline ≥ 100% and > ULN | 0 | 0 | 1 (16.7) | 1 (3.4) |
| Posttreatment Increase from baseline ≥ 100% and > ULN | 0 | 0 | 2 (33.3) | 2 (6.9) |
| Urea nitrogen (mmol/L) | | | | |
| Day 3 increase from baseline ≥ 50% and > ULN | 0 | 1 (9.1) | 0 | 1 (3.4) |
| Day 7 increase from baseline ≥ 50% and > ULN | 0 | 1 (9.1) | 0 | 1 (3.4) |
| EOT Increase from baseline ≥ 50% and > ULN | 0 | 1 (9.1) | 0 | 1 (3.4) |
| Posttreatment Increase from baseline ≥ 50% and > ULN | 0 | 1 (9.1) | 1 (16.7) | 2 (6.9) |

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; C = cohort; EOS = end of study; EOT = end of treatment; LLN = lower limit of normal; ULN = upper limit of normal

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). Percentage is calculated using the number of participants with valid baseline measurements as the denominator.

Source: Table 14.3.4.1.4

No clinically significant changes in clinical laboratory test values were identified in this study, with the exception of the liver events described below.

One participant in Cohort 4 of the Multiple-dose Phase (cefiderocol + SOC) experienced liver events that were not considered to be related to cefiderocol by the investigator. The participant was a 5.0-month-old Asian male with a history of choledochal cyst. At baseline (Day -1), prior to cefiderocol administration, ALT was 80 U/L (normal range: 5 to 33 U/L); ALP was 243 U/L (normal range: 134 to 518 U/L); AST was 56 U/L (normal range: 20 to 67 U/L); and bilirubin was 0.35 mg/dL (range: 0.05 to 0.68 mg/dL) (Listing 16.2.8.1.8.2). On Day 3, ALP was 526 U/L. On Day 34, ALT was 233 U/L and AST

was 50 U/L. At EOS, ALT was 233 U/L with no abnormal symptoms. The participant was referred to a follow-up hepatologist, and at the last visit a further decline in AST (51 U/L) and ALT (50 U/L) levels was reported.

***Assessor's comment:***

The narrative provided for the participant who experienced significant liver events during the multiple-dose phase of the study indicates a complex medical history (including and not limited to anomalous pulmonary venous connection, bacterial urinary tract infection, choledochal cyst, hydronephrosis, patent ductus arteriosus, pneumonia, vesicoureteric reflux) and confounding concomitant medicants including ertapenem and sulfamethoxazole/trimethoprim. The adverse event of elevated ALT occurred on day 34, whereas study drug treatment had concluded on day 3. The investigator considered the AE of increased ALT as mild and not related to study drug. There are no factors identified from the narrative to suggest a causative relationship to cefiderocol.

*Other*

No abnormal findings in vital signs (blood pressure, pulse rate, respiratory rate, and temperature) or physical examinations were observed in the Single-dose or Multiple-dose Phases.

***PK results***

Plasma cefiderocol concentrations from the single-dose phase and multiple-dose phase, respectively, are summarised below. Pharmacokinetic parameters including maximum observed plasma concentration ($C_{max}$), area under the concentration-time curve (AUC), and half-life ($t_{1/2}$) will be estimated in the planned population PK analysis and reported separately.

*Single-dose Phase*

All 24 (100%) enrolled participants in the Single-dose Phase were included in the PKC and PKCS Populations (Table 11-1). Plasma cefiderocol concentrations are summarised in Table 11-10. Mean plasma concentration-time profiles for the PKCS Population are shown in Figure 11-1 on linear and semi-logarithmic scales.

The plasma cefiderocol concentration profiles after the single dose 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 were 72.7 to 97.1 and 7.86 to 10.8 µg/mL, respectively, in the 4 cohorts.

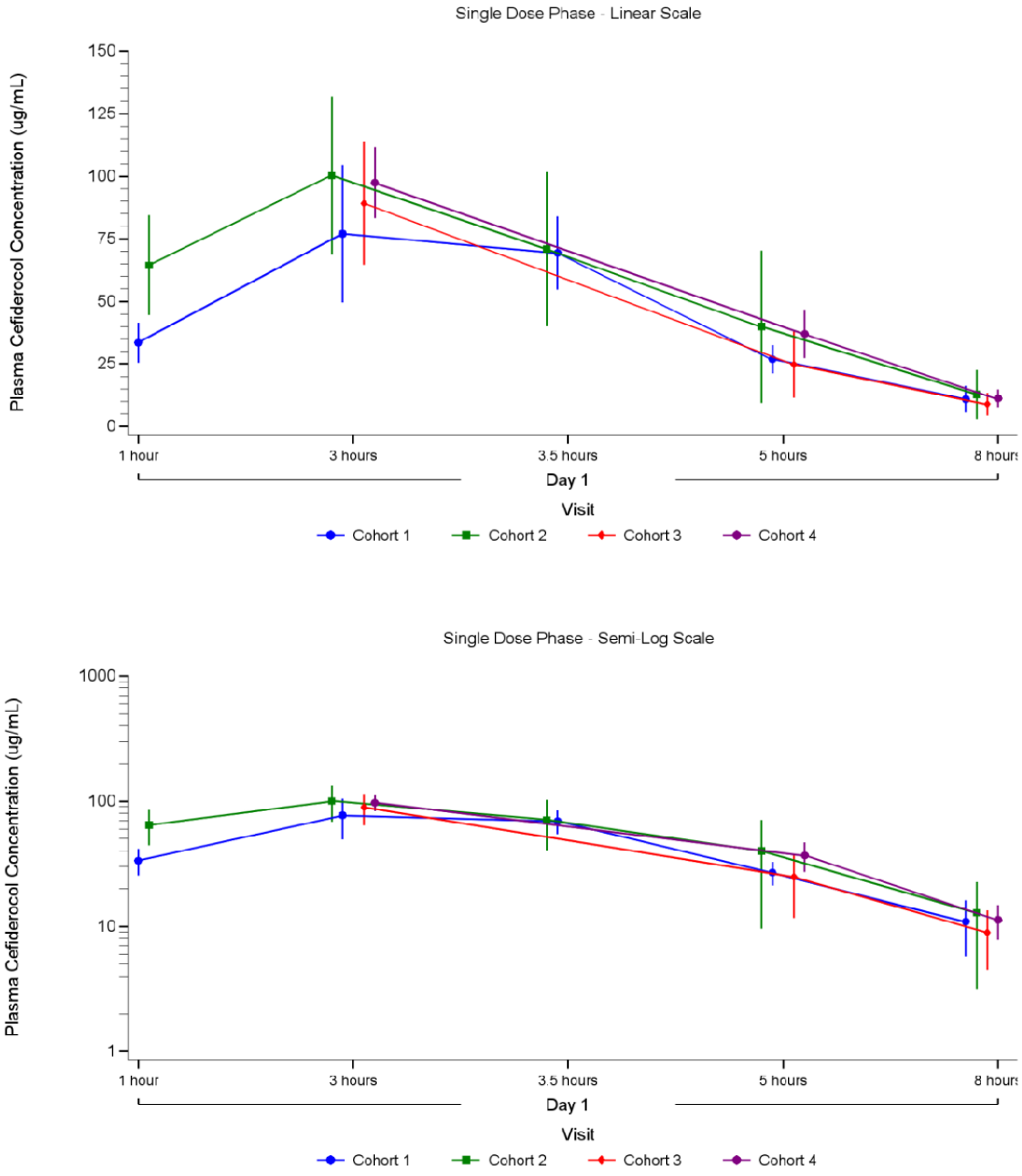
**Table 11-10 Plasma Cefiderocol Concentrations – Single-dose Phase (PKCS Population)**

| Visit - Blood Sampling Time Statistics | Cohort 1 N = 6 | Cohort 2 N = 6 | Cohort 3 N = 6 | Cohort 4 N = 6 | Overall N = 24 |
|---|---|---|---|---|---|
| Day 1: 1 h after start of inf., n | 6 | 6 | 0 | 0 | 12 |
| Mean (SD) | 33.5 (7.92) | 64.5 (19.8) | NA | NA | 49.0 (21.6) |
| CV (%) | 23.6 | 30.8 | | | 44.2 |
| Median (min, max) | 34.7 (24.3, 45.1) | 66.8 (38.6, 92.7) | | | 41.9 (24.3, 92.7) |
| Geometric Mean | 32.7 | 61.8 | | | 44.9 |
| Geometric SD | 1.27 | 1.38 | | | 1.54 |
| Geometric CV (%) | 24.5 | 33.2 | | | 45.0 |
| | | | | | |
| Day 1: 3 h after start of inf., n | 5 | 6 | 6 | 4 | 21 |
| Mean (SD) | 77.0 (27.5) | 100 (31.5) | 89.2 (24.4) | 97.4 (14.0) | 91.0 (25.7) |
| CV (%) | 35.7 | 31.4 | 27.4 | 14.4 | 28.3 |
| Median (min, max) | 89.0 (47.6, 106) | 86.0 (83.6, 164) | 81.5 (64.1, 130) | 100 (79.5, 109) | 87.7 (47.6, 164) |
| Geometric Mean | 72.7 | 97.1 | 86.6 | 96.5 | 87.6 |
| Geometric SD | 1.48 | 1.30 | 1.30 | 1.16 | 1.33 |
| Geometric CV (%) | 40.5 | 26.8 | 26.4 | 15.0 | 29.2 |
| | | | | | |
| Day 1: 3.5 h after start of inf., n | 5 | 6 | 0 | 0 | 11 |
| Mean (SD) | 69.4 (14.5) | 70.9 (30.6) | NA | NA | 70.2 (23.5) |
| CV (%) | 20.9 | 43.1 | | | 33.5 |
| Median (min, max) | 69.7 (51.3, 91.1) | 67.4 (44.0, 127) | | | 69.7 (44.0, 127) |
| Geometric Mean | 68.1 | 66.2 | | | 67.1 |
| Geometric SD | 1.23 | 1.48 | | | 1.36 |
| Geometric CV (%) | 21.1 | 40.9 | | | 31.5 |
| Day 1: 5 h after start of inf., n | 6 | 6 | 6 | 6 | 24 |
| Mean (SD) | 26.9 (5.51) | 39.9 (30.3) | 24.8 (13.0) | 37.0 (9.53) | 32.1 (17.5) |
| CV (%) | 20.5 | 76.0 | 52.7 | 25.7 | 54.5 |
| Median | 27.5 (18.3, 34.5) | 29.7 (12.2, 85.2) | 27.6 (3.96, 38.1) | 33.0 (28.3, 53.8) | 29.9 (3.96, 85.2) |
| Geometric Mean | 26.3 | 30.8 | 19.9 | 36.0 | 27.6 |
| Geometric SD | 1.24 | 2.24 | 2.36 | 1.27 | 1.84 |
| Geometric CV (%) | 22.0 | 95.6 | 104.0 | 24.1 | 67.3 |
| Day 1: 8 h after start of inf., n | 6 | 6 | 6 | 6 | 24 |
| Mean (SD) | 10.9 (5.16) | 12.8 (9.63) | 8.94 (4.43) | 11.3 (3.41) | 11.0 (5.89) |
| CV (%) | 47.2 | 75.2 | 49.5 | 30.2 | 53.6 |
| Median | 9.91 (4.99, 17.3) | 10.3 (3.72, 29.2) | 8.91 (3.01, 14.4) | 10.2 (7.40, 17.0) | 10.0 (3.01, 29.2) |
| Geometric Mean | 9.89 | 10.0 | 7.86 | 10.8 | 9.59 |
| Geometric SD | 1.65 | 2.19 | 1.81 | 1.34 | 1.72 |
| Geometric CV (%) | 53.1 | 92.2 | 64.6 | 29.6 | 58.8 |

C = cohort; CV = coefficient of variation; h = hour; inf. = infusion; mos = months; NA = not applicable; 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.

**Figure 11-1 Mean and SD Plasma Cefiderocol Concentration Over Time for the Single-dose Phase by Cohort, Phase, and Infusion Time (PKCS Population)**




PKCS = pharmacokinetic concentration summary; SD = standard deviation

Mean and standard deviation for plasma cefiderocol concentration present starting or greater than 0 µg/mL for this plot even though the lower range for standard deviation could be lower than 0.

*Multiple-dose Phase*

In the Multiple-dose Phase, the PKC and the PKCS Populations included 28 (100%) participants (Table 11-1). Plasma cefiderocol concentrations are summarised in Table 11-11. Mean plasma concentration-time profiles for the PKCS Population are shown in Figure 11-2 on linear and semi-logarithmic scales.

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 88.8 to 106 and 9.64 to 18.1 µg/mL, respectively, in the 4 cohorts.

**Table 11-11 Plasma Cefiderocol Concentrations – Multiple-dose Phase (PKCS Population)**

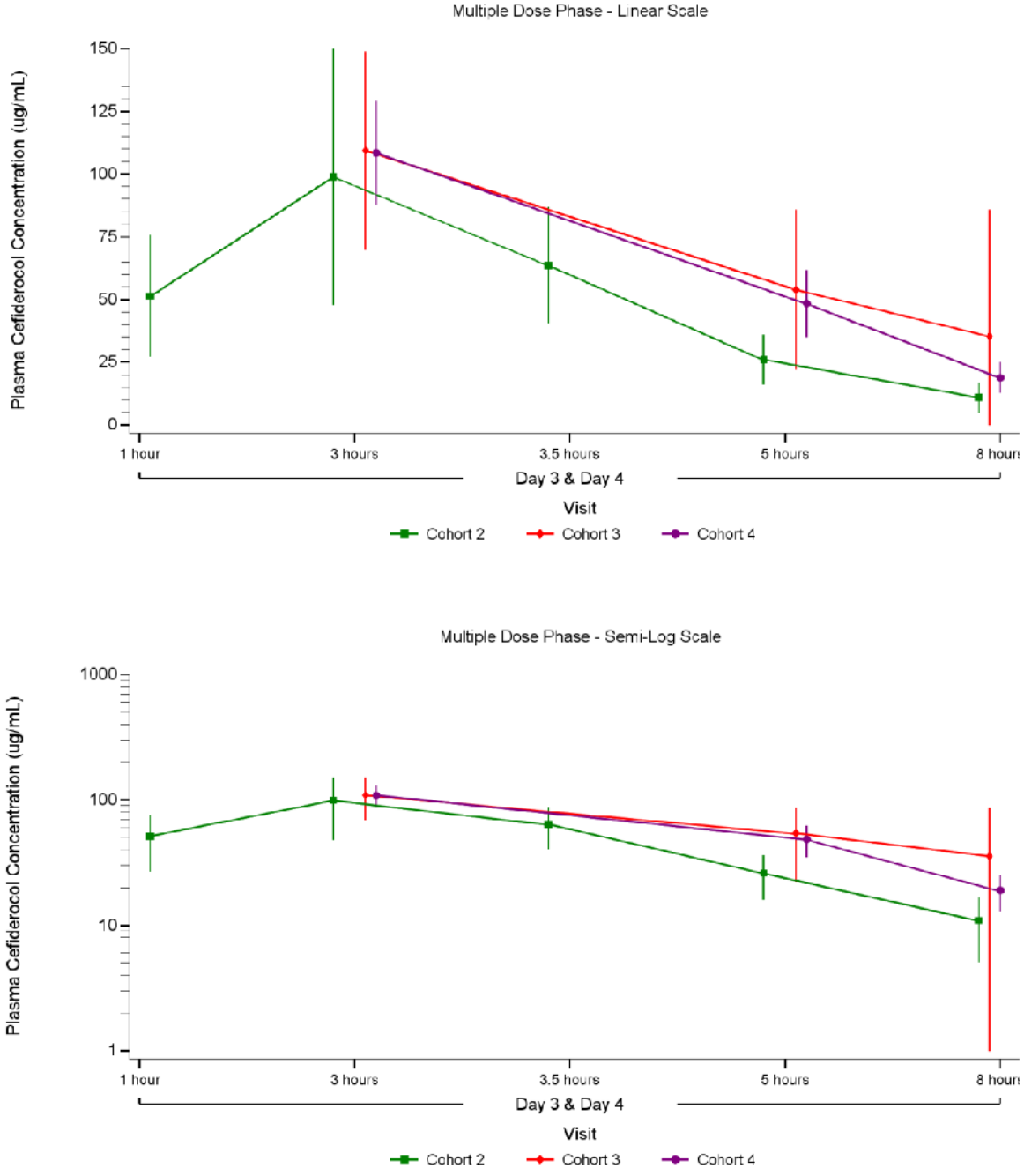
| Visit - Blood Sampling Time Statistics | Cohort 2 N = 12 | Cohort 3 N = 10 | Cohort 4 N = 6 | Overall N = 28 |
|---|---|---|---|---|
| Day 3 & Day 4 - 1 hour after the start of infusion | | | | |
| N | 12 | 0 | 0 | 12 |
| Mean (SD) | 51.4 (24.2) | NA | NA | 51.4 (24.2) |
| CV (%) | 47.2 | | | 47.2 |
| Median (min, max) | 52.5 (4.94, 90.8) | | | 52.5 (4.94, 90.8) |
| Geometric Mean (SD) | 43.0 (2.14) | | | 43.0 (2.14) |
| Geometric CV (%) | 88.8 | | | 88.8 |
| Day 3 & Day 4 - 3 hours after the start of infusion | | | | |
| N | 10 | 5 | 4 | 19 |
| Mean (SD) | 98.9 (50.8) | 109 (39.6) | 108 (20.5) | 104 (41.7) |
| CV (%) | 51.4 | 36.2 | 18.9 | 40.2 |
| Median (min, max) | 80.5 (46.0, 213) | 86.9 (72.2, 166) | 115 (79.7, 124) | 93.0 (46.0, 213) |
| Geometric Mean (SD) | 88.8 (1.61) | 103 (1.42) | 106 (1.23) | 96.2 (1.48) |
| Geometric CV (%) | 50.6 | 36.0 | 20.8 | 41.0 |
| Day 3 & Day 4 - 3.5 hours after the start of infusion | | | | |
| N | 12 | 0 | 0 | 12 |
| Mean (SD) | 63.6 (23.1) | NA | NA | 63.6 (23.1) |
| CV (%) | 36.3 | | | 36.3 |
| Median (min, max) | 57.7 (34.8, 116) | | | 57.7 (34.8, 116) |
| Geometric Mean (SD) | 60.1 (1.41) | | | 60.1 (1.41) |
| Geometric CV (%) | 35.4 | | | 35.4 |
| Day 3 & Day 4 - 5 hours after the start of infusion | | | | |
| N | 12 | 10 | 6 | 28 |
| Mean (SD) | 26.0 (9.94) | 54.0 (31.8) | 48.3 (13.4) | 40.8 (24.2) |
| CV (%) | 38.2 | 58.9 | 27.6 | 59.3 |
| Median, (min, max) | 25.1 (8.40, 42.6) | 46.3 (20.2, 95.6) | 43.0 (33.5, 67.1) | 33.2 (8.40, 95.6) |
| Geometric Mean (SD) | 24.0 (1.55) | 45.0 (1.92) | 46.8 (1.31) | 34.7 (1.79) |
| Geometric CV (%) | 46.0 | 72.8 | 27.3 | 63.4 |
| Day 3 & Day 4 - 8 hours after the start of infusion | | | | |
| N | 11 | 10 | 5 | 26 |
| Mean (SD) | 10.9 (5.87) | 35.4 (50.4) | 18.9 (6.00) | 21.9 (32.5) |
| CV (%) | 53.6 | 142.4 | 31.7 | 148.8 |
| Median, (min, max) | 7.99 (3.91, 23.5) | 12.1 (5.60, 165) | 18.8 (12.3, 26.8) | 13.1 (3.91, 165) |
| Geometric Mean (SD) | 9.64 (1.70) | 17.9 (3.14) | 18.1 (1.38) | 13.8 (2.31) |
| Geometric CV (%) | 56.9 | 165.0 | 33.3 | 101.0 |

C = cohort; CV = coefficient of variation; mos = months; NA = not applicable; PKCS = pharmacokinetic concentration summary; SD = standard deviation; years = 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.

**Figure 11-2** **Mean and SD Plasma Cefiderocol Concentration Over Time for the Multiple-dose Phase by Cohort, Phase, and Infusion Time (PKCS Population)**




PKCS = pharmacokinetic concentration summary; SD = standard deviation

Mean and standard deviation for plasma cefiderocol concentration present starting or greater than 0 µg/mL for this plot even though the lower range for standard deviation could be lower than 0.

***Assessor's comment:***

The cefiderocol pharmacokinetics has been studied across the age range of 3 months to 18 years. The summarised plasma concentrations display fairly similar concentrations across the 4 age cohorts. It is noted that in the multiple-dosing phase cohort 2 (6 to <12 years) seem to have slightly lower concentrations than cohort 3 and 4.

The primary PK endpoints, $C_{max}$, AUC, and $t_{1/2}$, will be reported separately in a population PK analysis report. This is accepted. However, 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 results***

*Clinical outcome*

All participants in the ITT and MITT Populations were treated with cefiderocol + SOC (i.e. no participant received cefiderocol alone).

At EOT, Posttreatment, and EOS, respectively, clinical cure was achieved by 29 (100%), 25 (86.2%), and 27 (93.1%) participants in the ITT Population and 18 (100%), 16 (88.9%), and 18 (100%) of the MITT Population.

All participants with infections due to *Enterobacter cloacae* complex (1 participant), *K. pneumoniae* (2 participants), *N. meningitidis* (1 participant), and *Salmonella* (1 participant) at baseline achieved clinical cure at EOT, Posttreatment, and EOS. For the 13 participants with *E. coli* at baseline, clinical cure was achieved by all 13 (100%) participants at EOT, 11 participants (84.6%) Posttreatment (with 2 participants indeterminate or missing), and all 13 participants (100%) at EOS.

*Microbiological outcome*

At EOT, Posttreatment, and EOS, respectively, eradication was achieved by 12 (66.7%), 13 (72.2%), and 14 (77.8%) of the MITT Population. All participants with infections due to *K. pneumoniae*, *N. meningitidis*, and *Salmonella* at baseline achieved eradication at EOT and Posttreatment. For participants with *E. coli* at baseline, eradication was achieved by 69.2% at EOT and 61.5% Posttreatment. For the participant with *Enterobacter cloacae* complex at baseline, the outcome was indeterminate at EOT and eradication at Posttreatment.

***Assessor's comment:***

This small safety and PK study was not designed to conclude on clinical efficacy in the paediatric population, which is derived from the PK/PD data package rather than from clinical efficacy outcomes. As such, the data are purely descriptive. Furthermore, all patients received other concomitant antibiotics according to local standard of care, making it impossible to isolate the clinical effect of cefiderocol. Rates of clinical and microbiological cure seen in this study were comparable with those seen in the pivotal/ registration study for cefiderocol.

## 2.3.3. Discussion on clinical aspects

Study 1802R2135 was a PK and safety study and as such was not designed to permit efficacy analyses beyond summary statistics. Rates of clinical and microbiological cure seen in this study were comparable with those seen in the pivotal/ registration study for cefiderocol, but it should be noted

that all participants received concomitant antibiotics according to local standard of care, this the effect of cefiderocol cannot be isolated.

The required number of patients for PK characterisation have been included in all age groups. The summarised cefiderocol plasma concentration data indicate that the plasma concentrations are in general similar across age groups and similar to the concentrations in adults with normal or mild renal function (CREDIBLE-CR study). The primary PK endpoints, $C_{max}$, AUC, and $t_{1/2}$, have not been reported. Thus, a full report is expected at the application for a paediatric indication.

The Safety Population was small, comprising just 24 patients enrolled to the single-dose phase and 29 patients enrolled to the multiple-dose phase. Cefiderocol was generally well-tolerated when administered alone and in combination with SOC to treat a suspected or confirmed aerobic Gram-negative bacterial infection in hospitalised paediatric participants 3 months to < 18 years of age, with reported adverse events consistent with the known safety profile in adults, and with the underlying condition and comorbidities. No new safety concerns are identified. However, the study was not large enough to detect rare adverse events.

# 3. CHMP overall conclusion and recommendation

Study 1802R2135, a safety and PK study, forms part of an agreed Paediatric Investigation Plan (EMEA-002133-PIP01-17-M02, Decision number EMA/PDCO/8222/2022) for cefiderocol and was conducted to support extension of the authorised indication to the paediatric population.

Not all measures as described in the agreed PIP (EMEA-002133-PIP01-17-M02, Decision number EMA/PDCO/8222/2022) are complete. The agreed PIP completion date is May 2025.

The study was not designed to conclude on clinical efficacy. Safety data were limited but consistent with the known safety profile of cefiderocol in adults, and with the underlying condition and comorbidities. The summarised plasma concentrations indicate in general similar concentrations across all age groups.

An application to extend the authorised adult indication to the paediatric population is expected to be submitted following completion of the necessary modelling and extrapolation studies, as specified in the agreed Paediatric Investigation Plan (EMEA-002133-PIP01-17-M02, Decision number EMA/PDCO/8222/2022).

There are no issues arising from assessment of this completed study that otherwise require regulatory action at this time.

☒ **Fulfilled:**

No regulatory action required.

# Annex 1 - Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

## Non-clinical studies

Product Name: Fetcroja Active substance: cefiderocol

| Study title | Study number | Date of completion | Date of submission of final study report |
|---|---|---|---|
| 3-week subcutaneous and intravenous toxicity study of cefiderocol in juvenile rats. | S-649266-TF-274-L | March 2018 | |

## Clinical studies

Product Name: Fetcroja Active substance: cefiderocol

| Study title | Study number | Date of completion | Date of submission of final study report |
|---|---|---|---|
| Open-label, single-arm, uncontrolled trial to evaluate safety, tolerability and pharmacokinetics of single and multiple doses of cefiderocol in hospitalised paediatric patients from 3 months to less than 18 years of age with suspected or confirmed infections due to aerobic Gram-negative bacteria. | 1802R2135 | 25 July 2023 | 11 August 2023 |
| Open-label, single-arm, uncontrolled trial to evaluate safety, tolerability and pharmacokinetics of single and multiple doses of cefiderocol in hospitalised paediatric patients from birth to less than 3 months of age with suspected or confirmed infections due to aerobic Gram-negative bacteria. | | | |