Pharmacokinetics, Safety, and Tolerability of Cefiderocol, a Novel Siderophore Cephalosporin for Gram-Negative Bacteria, in Healthy Subjects

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Cefiderocol is a novel parenteral siderophore cephalosporin that shows potent efficacy against various Gram-negative bacteria, including carbapenem-resistant strains, *in vitro* and in preclinical models of infection. The aim of the present study was to evaluate the pharmacokinetics (PK), safety, and tolerability of cefiderocol after both single and multiple dosing by intravenous infusion over 60 min in healthy adult subjects. A single-ascending-dose study at doses of 100, 250, 500, 1000, and 2000 mg was conducted in 40 healthy Japanese males and females (six active and two placebo per cohort). A multiple-ascending-dose study at doses of 1000 (two groups), and 2000 mg every 8 h (q8h) was conducted in 30 healthy Japanese and Caucasian males (eight active and two placebo per cohort). There were no serious or clinically significant adverse events (AEs) observed in either study. A single subject receiving 1000 mg cefiderocol q8h was withdrawn due to AEs. Dose-proportional increases in $C_{\text{max}}$, $AUC_{0-\text{last}}$, and $AUC_{0-\text{inf}}$ were observed across the dose range of 100 to 2000 mg. The mean plasma half-life of cefiderocol was 1.98 to 2.74 h. Cefiderocol was primarily excreted unchanged in the urine (61.5% to 68.4% of dose). There was little accumulation of $C_{\text{max}}$ and AUC by q8h dosing, and the PK of cefiderocol did not change with multiple dosing. This study indicates that single and multiple intravenous doses of cefiderocol at up to 2000 mg were well tolerated in healthy subjects and exhibited linear PK at up to 2000 mg.

**Key words:** cefiderocol, pharmacokinetics, Gram-negative bacterial infection, siderophore, cephalosporin
INTRODUCTION

There is an urgent need to develop new antibiotics to combat the recent worldwide increase in the incidence in multidrug-resistant Gram-negative bacterial strains (1). In particular, it is becoming more challenging to treat serious nosocomial infections caused by Gram-negative pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* as well as carbapenem-resistant Enterobacteriaceae (2). The 2017 global priority pathogens list from the World Health Organization has carbapenem-resistant *A. baumannii* and *P. aeruginosa* and carbapenem-resistant, third-generation cephalosporin-resistant Enterobacteriaceae as the three pathogens with the highest priority for the research and development of new antibiotics (3). The mechanisms responsible for Gram-negative carbapenem resistance include the spread of exogenous carbapenemases (4, 5), overexpression of efflux pumps, overexpression of chromosomal β-lactamases, and deficiency in outer membrane porins (4, 6–8).

Cefiderocol (also known as S-649266) is a novel catechol-substituted siderophore cephalosporin with potent *in vitro* and *in vivo* activity against a variety of Gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii* (9–11) (M. A. Hackel, submitted for publication). The catechol moiety, which is found at the three-position side chain, forms a chelating complex with ferric iron (12). This allows cefiderocol to function as a siderophore and enter bacterial cells through active transport via a “Trojan horse” mechanism that utilizes the bacterial iron transport system (12). In an *in vitro* study in *P. aeruginosa*, the iron-mediated uptake of cefiderocol was shown to contribute to its antibacterial activity (12).

No siderophore antibiotics have been approved for clinical use to date, although naturally occurring and synthetic siderophore-conjugated antibiotics have been under investigation for
several decades (13, 14). Cefiderocol is the first siderophore antibiotic to advance into late-stage development (15, 16). The primary objective of the present study was to evaluate the pharmacokinetics (PK), safety, and tolerability of single- and multiple-dose administration of cefiderocol by intravenous infusion in healthy Japanese and Caucasian adult subjects. A secondary objective was to evaluate the production of any cefiderocol metabolites.

RESULTS

Subjects. A total of 70 subjects were enrolled in the study (40 in the single-dose study; 30 in the multiple-dose study). Of these, 54 received cefiderocol and 16 received placebo. Table 1 shows the demographics and baseline characteristics of all dosed subjects. The data obtained from all subjects receiving cefiderocol were included in the PK analysis.

Safety and tolerability. Cefiderocol was generally well tolerated in the single-dose and multiple-dose studies (Tables 2 and 3).

In the single-dose study, nine AEs reported by six subjects in the cefiderocol groups were considered possibly or probably related to study treatment: diarrhea (two events in two subjects), rash (two events in two subjects), and one event each of abdominal pain, blood urine present, red blood cells urine positive, white blood cell count increased, and white blood cells urine positive.

In the placebo group, four AEs reported by three subjects were considered possibly related to study treatment (one event each of diarrhea, dizziness, nausea, and white blood cells urine positive).

In the multiple-dose study, 16 AEs reported by seven subjects in the cefiderocol 1000-mg 1st group were considered possibly or probably related to the study treatment: rash (five events in five subjects), blood TSH increased (three events in three subjects), pyrexia (two events in two
subjects), and one event each of alanine aminotransferase increased, aspartate aminotransferase increased, blood TSH decreased, blood urea increased, blood urine present, and headache. In the cefiderocol 1000-mg 2\textsuperscript{nd} and 2000-mg groups, 22 AEs reported by 12 subjects were considered possibly or probably related to the study treatment: alanine aminotransferase increased (four events in four subjects), aspartate aminotransferase increased (three events in three subjects), diarrhea (three events in two subjects), rash (three events in two subjects), pyrexia (two events in two subjects), white blood cell count increased (two events in two subjects), and one event each of abdominal pain, blood creatine phosphokinase increased, headache, oropharyngeal pain, and white blood cells urine positive. TSH abnormalities were reported only in the 1000-mg 1\textsuperscript{st} group.

There was a higher frequency of rash (five events in five of eight subjects [62.5%]) in the 1000-mg 1\textsuperscript{st} group in the multiple-dose study compared with the 1000-mg 2\textsuperscript{nd} (no events) and 2000-mg groups (three events in two of eight subjects [25%]). Allergy tests conducted for the two subjects with rash in the 2000-mg group showed levels almost within normal ranges, and measurement of cefiderocol-specific IgG and IgE yielded nondetectable levels.

All of the AEs were mild in intensity except for one AE that was moderate (pyrexia in the 1000-mg 1\textsuperscript{st} group). There were no deaths, serious AEs, abnormal 12-lead or continuous ECG findings, or abnormal changes in vital signs except for the subjects in the multiple-dose study with pyrexia. One subject in the cefiderocol 1000-mg 2\textsuperscript{nd} group withdrew due to pyrexia on the last day of study drug administration. There was no dose-response trend in the incidence of AEs, which was relatively evenly spread between the dose groups, including the placebo groups.

**Blood iron and total-iron binding capacity levels.** In the single-dose study, the mean value of blood iron was slightly below the lower limit of normal (LLN) (reference range, 80 to 199 μg/dl [male]; 70 to 179 μg/dl [female]) in the 500-mg group on day 5 (71.2 μg/dl) and day 8.
(68.3 μg/dl) and in the 1000-mg group on day 8 (76.8 μg/dl); no mean value below the LLN was observed in the 2000-mg group or the placebo group. In the multiple-dose study, the mean value of blood iron was slightly below the LLN in the 1000-mg 1st group on days 5, 11, and 17, and in the 1000-mg 2nd group on days 5, 11, 13, 14, and 17; no mean value below the LLN was observed in the 2000-mg group or the placebo group (Table 6).

Pharmacokinetics in plasma. Mean plasma concentration profiles of unchanged cefiderocol after the infusion of single doses ranging from 100 to 2000 mg are shown in Fig. 1. A summary of the PK parameters following single-dose administration of cefiderocol is shown in Table 4. Geometric mean values (coefficient of variation [CV%] geometric mean) ranged from 7.76 to 156 μg/ml (4.6% to 10.7%) for $C_{\text{max}}$, 17.03 to 388.9 μg·h/ml (6.3% to 22.5%) for $\text{AUC}_{0-\text{last}}$, and 17.49 to 389.7 μg·h/ml (6.3% to 22.7%) for $\text{AUC}_{0-\text{inf}}$, suggesting low to moderate inter-individual variability for plasma exposure in all dose groups. The geometric mean plasma half-life ($t_{1/2,z}$) of cefiderocol was 1.98 to 2.74 h. Estimates of the slopes (95% confidence interval [CI]) for $C_{\text{max}}$, $\text{AUC}_{0-\text{last}}$, and $\text{AUC}_{0-\text{inf}}$ of cefiderocol were 1.00 (0.965 to 1.04), 1.04 (0.983 to 1.09), and 1.03 (0.975 to 1.08), respectively, indicating dose-proportional increases in these parameters across the dose range of 100 to 2000 mg. Statistical analyses showed no dose dependency for $t_{1/2,z}$, CL, MRT, $\text{Feu}_{0-48}$, or $\text{CL}_R$. 

Fig. 2 shows mean plasma concentration profiles of cefiderocol following multiple infusions in the 1000-mg 1st, 1000-mg 2nd, and 2000-mg groups. Mean trough concentrations from 48 to 192 hours after the start of initial infusion were 5.18 to 5.60, 5.11 to 5.39, and 9.66 to 13.0 μg/mL for the 1000-mg 1st, 1000-mg 2nd, and 2000-mg groups, respectively. A summary of the PK parameters of cefiderocol after multiple-dose administration is shown in Table 5. Plasma concentration profiles and linear regression for plasma trough concentrations indicated
that steady state was achieved within 1 day after the initiation of multiple dosing (day 3). Plasma concentrations were similar in the 1000-mg 1st and 1000-mg 2nd groups. Ratios of $C_{\text{max}}$ and $AUC_{0-\tau}$ between dose groups on day 10 were close to the dose ratio (ie, 2), suggesting dose-proportional increases in $C_{\text{max}}$ and $AUC_{0-\tau}$ following multiple dosing. Accumulation ratios of $C_{\text{max}}$ and $AUC_{0-\tau}$ with q8h dosing were 1.069 and 1.053 at 1000 mg, and 1.084 and 1.164 at 2000 mg, respectively. The comparisons of AUC ($AUC_{0-\text{inf}}$ on day 1; $AUC_{0-\tau}$ on day 10), CL, and CL_R between days 1 and 10 indicated no change in PK with multiple dosing.

In the single dose groups, the plasma concentration of cefiderocol were below the lower limit of quantitation (BLQ) in most samples after 12 hours at 100 mg, 16 hours at 250 mg, 24 hours at 500 and 1000 mg, and 36 hours at 2000 mg. In the multiple dose groups, most samples had the plasma cefiderocol concentration BLQ after 24 hours in both 1000-mg groups and 36 hours in the 2000-mg group. Urinary excretion. Mean urine concentration profiles of unchanged cefiderocol after the infusion of single doses ranging from 100 to 2000 mg are shown in Fig. 3. Dose-dependent increases in the urine concentrations appeared across the dose range of 100 to 2000 mg. Geometric mean urinary excretion ratio relative to dose of cefiderocol ranged from 61.5% to 68.4% as unchanged drug product (Fig. 4). The amount of cefiderocol metabolites was estimated to be less than 10%, as described below. The urine concentration of cefiderocol was BLQ in most urine samples collected from 24 to 48 hours in any of the single dose groups. In the multiple dose groups, all urine samples at the nominal sampling time had detectable level of cefiderocol above the lower limit of quantitation.

Exploratory study of human metabolites in plasma and urine. In plasma and urine, the most prominent peak identified by mass spectrometry (MS) was unchanged cefiderocol. Two types of methylated cefiderocol with low MS response were detected, along with an additional
nine metabolites. These metabolites had been identified previously in animal studies; there were no human-specific metabolites identified in plasma or urine. All urine metabolites were at trace levels, and the total amount was 10% or less of the administered dose. Plasma metabolites showed no notable differences between single and multiple dosing, suggesting that accumulation of metabolites is unlikely with multiple dosing.
Cefiderocol is a novel parenteral siderophore cephalosporin with in vitro and in vivo efficacy against Gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii* (9–11). In the present study, cefiderocol was well tolerated at doses of up to 2000 mg q8h in healthy volunteers. There were no serious or clinically significant AEs, and only one subject withdrew due to an AE (fever). The PK analysis showed dose-proportional increases in exposure at doses ranging from 100 to 2000 mg, with little accumulation with multiple dosing. The majority of cefiderocol was excreted unchanged in the urine. The results from this study and a phase 1 single-dose study in subjects with renal impairment (17) were used to develop a population PK model for adjusting the dose of cefiderocol based on renal function (18).

Because the proposed mechanism of action of cefiderocol involves iron chelation, the present study included laboratory tests to evaluate the effect of cefiderocol on iron homeostasis. Several multiple-dose cefiderocol groups had blood iron levels slightly below the lower limit of normal, which the investigator attributed to bone marrow iron uptake due to hematopoiesis from the frequent blood samplings. In our opinion, the fluctuation of iron concentration in the blood was neither clinically significant nor related to the study drug. Further supporting our hypothesis, the total iron-binding capacity in the cefiderocol groups did not show significant change compared with the placebo group (Supplemental Table 1).

With 60% to 70% of the administered dose of cefiderocol excreted in the urine as unchanged parent drug and <10% as metabolites, the excretory fate of the remaining ~20% is not known. Further study, such as a mass-balance trial, is needed to characterize the metabolism and excretion of cefiderocol.
Due to iodide contamination in the initial drug supply, additional safety measures were added to the multiple-dose study. The high frequency of rash and the TSH abnormalities in the 1000-mg 1st group in the multiple-dose study were likely attributed to iodide exposure (19). As the formulation no longer contains iodide, these safety concerns are not relevant to the ongoing clinical development of cefiderocol.

In conclusion, this study indicates that single and multiple intravenous doses of cefiderocol were well tolerated in healthy subjects and dose proportionality for PK was observed.

MATERIALS AND METHODS

Subjects. Eligible subjects were healthy Japanese and Caucasian males or Japanese females not of childbearing potential (ie, permanently sterilized, postmenopausal) aged 20 to 60 years with body weight of 50.0 to 80.0 kg (40.0 to 80.0 kg for Japanese females; ≥50.0 kg for Caucasian males) and body mass index of ≥18.5 and <25.0 kg/m² (≥18.5 and <30.0 kg/m² for Caucasian males). Subjects with impaired heart, liver, renal, lung, endocrine, central nerve, blood, or metabolic function were excluded. All subjects provided written informed consent prior to the start of the study. The patients enrolled in the multiple-dose study were provided written informed consent that included additional literature-based safety information about iodide ingestion. The study was performed at the CPC Clinical Trial Hospital (Kagoshima, Japan) with the approval of the institutional ethics committee and in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Study design. This was a phase 1, single-center, randomized, double-blind, placebo-controlled study conducted in two parts: a single-ascending-dose study and a multiple-ascending-dose study. The single-dose study was planned to include up to six single doses of cefiderocol in
six cohorts (100, 250, 500, 1000, 2000, and 4000 mg), but dose escalation to the highest dose
(4000 mg) was not performed because a lower dose achieved the prespecified stopping criteria
(>10-fold lower exposure than the rat no-observed-adverse-event level ($C_0=1660 \mu g/ml$). A total
of 40 healthy Japanese males and females (six active and two placebo per cohort) participated in
the single-dose study, with three, one, and one postmenopausal females in the 500-mg, 1000-mg,
and 2000-mg cohorts, respectively. Eligible subjects were admitted to the study center one day
prior to administration, were confined to the study center until day 3, and returned to the study
center on days 4, 5, and 8±1 for follow-up.

The multiple-dose study was planned to include up to two doses of cefiderocol (1000 and
2000 mg) in two groups. It was discovered that the study drug was contaminated with 0.36%
iodide (which is lower than the detection limit by traditional elemental analysis) before the start
of the multiple-dose study. Consequently, a second 1000-mg group with purified study drug was
added to the multiple-dose study after the 1000-mg 1st group finished. The 1000-mg 2nd group
was conducted with the study drug that was free of iodide, which was removed by additional
purification. The study therefore included 55 groups that received study drug once: 100, 250,
500, 1000, 2000 mg (which received iodide-contaminated study drug) and three groups that
received study drug every 8 h (q8h) for 10 days: 1000-mg 1st group (which received iodide-
contaminated study drug), 1000-mg 2nd group (which received iodide-free study drug), and 2000-
mg group (which received iodide-free study drug). A total of 30 healthy males (eight active and
two placebo per group) participated in the multiple-dose study, with two Caucasians in each of
the 1000-mg groups and three Caucasians in the 2000-mg groups. Eligible subjects were
admitted to the study center one day prior to administration, were confined to the study center
until day 12, and returned to the study center on days 13, 14, and 17±1 for follow-up visits.
Safety evaluation. Safety was assessed through adverse events (AEs), physical examinations, vital signs, 12-lead and continuous electrocardiogram (ECG) recordings, and laboratory tests (hematology, blood chemistry including iron and total iron binding capacity, and urinalysis). Thyroid function tests (thyroid-stimulating hormone [TSH], free thyroxine, and free triiodothyronine) and allergy tests (blood tryptase level, serum complement activity, and plasma histamine level) were added for the multiple-dose study in response to the iodide contamination in the initial drug supply, and additional immunological tests (cefiderocol-specific immunoglobulin G [IgG] and immunoglobulin E [IgE]) were conducted for two subjects in the 2000-mg cohort in the multiple-dose study who experienced rash during the study. All safety data collected were assessed for severity and relationship to study treatment. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0.

Sample collection and analysis. For the single-dose study, plasma samples were collected prior to infusion (0 h) and at 0.5 (during infusion), 1.0 (just before completion of infusion), 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10, 12, 16, 24, 36, and 48 h after the start of infusion. Urine samples were collected at 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 24, and 24 to 48 h from the start of the infusion.

For the multiple-dose study, plasma samples were collected as follows: at 0, 0.5, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10, 12, and 16 h from the start of the first (morning) infusion on day 1; prior to morning infusion (0 h) on days 2, 3, 5, 8, 9; and at 0, 0.5, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10, 12, 16, 24, 36, and 48 h from the start of the final (morning) infusion on day 10. Urine samples were collected at 0 to 8 and 8 to 24 h from the start of the first (morning) infusion on day 1, and at 0 to 8 and 8 to 24 h from the start of the final (morning) infusion on day 10.
Concentrations of cefiderocol in human plasma and urine were determined by a liquid chromatography with mass spectrometry (LC/MS/MS) method (17). The lower limit of quantification of cefiderocol was 0.1 µg/ml in plasma and 1 µg/ml in urine. Partial validation for changing instrumentation was performed using QTRAP 5500 and Triple Quad 5500. The assay was linear from 0.1 to 100 and 1 to 1000 µg/mL for plasma and urine, respectively. The precision of the assay was 4.3% to 11.2% and 1.0% to 8.8% for plasma and urine, respectively. The accuracy of the assay was -7.0% to 7.0% and -6.4% to 9.0% for plasma and urine, respectively.

Pharmacokinetic and statistical analyses. The following PK parameters were calculated by noncompartmental methods using WinNonlin (Version 6.2.1, Certara L.P., Princeton, NJ) based on plasma and urine concentration data: maximum plasma concentration (C\text{max}), time to maximum plasma concentration (T\text{max}), area under the concentration-time curve from time zero to the time of the last quantifiable concentration after dosing (AUC\text{0-\text{last}}), area under the concentration-time curve extrapolated from time zero to infinity (AUC\text{0-\infty}), area under the concentration-time curve over the dosing interval τ (AUC\text{0-τ}), terminal elimination half-life (t\text{1/2,z}), mean residence time (MRT), total clearance (CL), urinary excretion ratio relative to dose over 48 h (Fe\text{u0-48}), and renal clearance (CL\text{R}).

Dose proportionality of PK parameters was examined by using a power model. Dose proportionality, dose independency, effect of multiple doses, and accumulation ratio of PK parameters were examined by analysis of variance. Achievement of steady state was assessed by visual inspection of plots and by linear regression for plasma trough concentrations. SAS (Version 9.1, SAS Institute Inc., Cary, NC) was used for statistical analyses.
Exploratory study of human metabolites in plasma and urine. Analysis and identification of cefiderocol and its metabolites were determined by an LC (Agilent 1100 series [Agilent Technologies]) -MS/MS (LTQ Orbitrap Velos [Thermo Fisher Scientific]) system. Exploratory investigations of major or human-specific minor metabolites were performed using pooled plasma samples (single-dose study, 2000-mg group: 1, 2, 4, 12, and 24 h after dose; multiple-dose study, 1000-mg 1st and 2nd groups: 1, 2, 4, 8, and 12 h after day 1 morning dose and 0, 1, 2, 4, and 8 h after day 10 morning dose) and pooled urine (single-dose study, 2000-mg group: 0 to 8, 8 to 12, 12 to 24, and 24 to 48 h after dose).

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## Table 1. Subject demographics and baseline characteristics

|                | Single-Dose | Multiple-Dose |                |
|----------------|-------------|---------------|----------------|
|                | Cefiderocol |               | Cefiderocol    |
|                | 100 mg (n=6)| 250 mg (n=6)  | 500 mg (n=6)   |
|                | 100 mg (n=6)| 1000 mg (n=6) | 2000 mg (n=6)  |
|                | Placebo (n=10) | Placebo (n=10) | Placebo (n=10) |
| Age, yr        | 23.3        | 26.7          | 38.8           | 28.8 | 30.5 | 34.5 | 32.6 | 29.6 | 34.1 | 31.8 |
| Mean           | 26.7        | 16.5          | 4.1            | 14.7 | 14.1 | 8.1  | 6.0  | 10.1 | 8.0  |
| SD             | 2.5         | 3.7           | 16.5           | 25.36 | 21.60 | 21.59 | 21.46 | 22.38 | 21.49 | 24.47 |
| Range          | 20–27       | 23–32         | 26–60          | 25–36 | 21–60 | 21–59 | 21–46 | 22–38 | 21–49 | 24–47 |
| Male, n (%)    | 6 (100)     | 6 (100)       | 4 (66.7)       | 6 (100) | 5 (83.3) | 8 (80.0) | 8 (100) | 8 (100) | 8 (100) | 6 (100) |
| Race, n (%)    | Japanese    | 6 (100)       | 6 (100)        | 6 (100) | 6 (100) | 10 (100) | 6 (75.0) | 7 (87.5) | 6 (75.0) | 4 (66.7) |
| Caucasian      | 0           | 0             | 0              | 0      | 0      | 0      | 2 (25.0) | 1 (12.5) | 2 (25.0) | 2 (33.3) |
| Height, cm     | Mean        | 167.93        | 170.73         | 159.13 | 169.85 | 166.12 | 168.30 | 174.30 | 170.35 | 176.24 | 175.33 |
|                | SD          | 6.51          | 2.55           | 5.01   | 6.42   | 4.44   | 6.21   | 4.83   | 4.39   | 7.26   | 6.41   |
| Range          | 156.4–157.3 | 153.1–160.3   | 158.0–158.6    | 156.7–160.7 | 167.8–180.1 | 164.9–177.4 | 166.8–185.6 | 169.8–184.6 |
| Weight, kg     | Mean        | 60.43         | 64.28          | 54.88  | 65.47  | 59.08  | 63.95  | 69.81  | 63.44  | 60.70  | 70.72  |
|                | SD          | 5.70          | 4.48           | 5.10   | 5.81   | 4.26   | 8.33   | 10.30  | 4.72   | 11.03  | 8.55   |
| Range          | 54.5–71.0   | 57.3–69.3     | 45.1–59.4      | 58.1–73.2 | 52.1–62.9 | 55.0–77.0 | 59.9–90.4 | 55.5–87.9 | 57.3–91.0 | 59.3–83.1 |
| BMI, kg/m²     | Mean        | 21.47         | 22.63          | 21.63  | 22.70  | 21.42  | 22.54  | 22.89  | 21.90  | 22.39  | 23.00  |
|        | SD        | Range     | CCr, m l/min | Mean | SD      | Range     | eGFR, m l/min/1.73 m² | Mean | SD      | Range     |
|--------|-----------|-----------|--------------|------|---------|-----------|------------------------|------|---------|-----------|
|        | 2.25      | 18.9–24.6 |              | 140.0| 16.2    | 121.4–168 |                       | 116.5| 7.5     | 108.1–127 |
|        | 1.48      | 20.0–23.7 |              | 168.2| 13.2    | 131.6–185 |                       | 123.5| 8.7     | 113.5–151 |
|        | 1.99      | 19.2–22.8 |              | 116.3| 28.6    | 75.1–135  |                       | 104.5| 4.7     | 76.4–113  |
|        | 2.33      | 19.2–24.8 |              | 293.5| 24.6    | 120.7–191 |                       | 148.4| 15.3    | 114.2–171 |
|        | 1.41      | 19.1–22.9 |              | 113.3| 294     | 96.4–127  |                       | 104.6| 9.6     | 86.4–114  |
|        | 2.28      | 18.7–24.9 |              | 111.3| 294     | 86.3–114  |                       | 104.6| 9.6     | 86.3–114  |
|        | 2.68      | 19.1–22.9 |              | 148.6| 22.6    | 90.3–116  |                       | 104.6| 9.6     | 86.3–114  |
|        | 2.99      | 19.3–27.6 |              | 190.6| 17.1    | 110.9–160 |                       | 104.6| 9.6     | 86.3–114  |
|        | 2.57      | 19.1–22.9 |              | 180.6| 17.1    | 110.9–160 |                       | 104.6| 9.6     | 86.3–114  |
|        | 2.68      | 19.1–22.9 |              | 183.5| 17.1    | 110.9–160 |                       | 104.6| 9.6     | 86.3–114  |
|        | 2.68      | 19.1–22.9 |              | 131.5| 17.1    | 110.9–160 |                       | 104.6| 9.6     | 86.3–114  |
|        | 2.68      | 19.1–22.9 |              | 121.5| 17.1    | 110.9–160 |                       | 104.6| 9.6     | 86.3–114  |

BMI, body mass index; CCR, creatinine clearance; eGFR, estimate glomerular filtration rate; SD, standard deviation.
Table 2. Incidence of adverse events in the single-dose study

| Preferred Term                        | 100 mg (n=6) | 250 mg (n=6) | 500 mg (n=6) | 1000 mg (n=6) | 2000 mg (n=6) | Total (n=30) | Placebo (n=10) |
|---------------------------------------|--------------|--------------|--------------|---------------|---------------|--------------|----------------|
| Subjects with any adverse events     | 1 (1) 16.7%  | 0            | 1 (2) 16.7%  | 2 (4) 33.3%   | 2 (3) 33.3%   | 6 (10) 20.0%| 4 (5) 40.0%   |
| Gastrointestinal disorders           | 0            | 0            | 1 (2) 16.7%  | 0             | 1 (1) 16.7%   | 2 (3) 6.7%  | 2 (2) 20.0%   |
| Diarrhea                              | 0            | 0            | 1 (1) 16.7%  | 0             | 1 (1) 16.7%   | 2 (2) 6.7%  | 1 (1) 10.0%   |
| Abdominal pain                        | 0            | 0            | 1 (1) 16.7%  | 0             | 0             | 1 (1) 3.3%  | 0              |
| Nausea                                | 0            | 0            | 0            | 0             | 0             | 1 (1) 10.0%| 0              |
| Investigations                        | 1 (1) 16.7%  | 0            | 0            | 1 (3) 16.7%   | 1 (1) 16.7%   | 3 (5) 10.0%| 2 (2) 20.0%   |
| White blood cells urine positive      | 0            | 0            | 0            | 1 (1) 16.7%   | 0             | 1 (1) 3.3%  | 1 (1) 10.0%   |
| Blood creatine phosphokinase increased| 0            | 0            | 0            | 1 (1) 16.7%   | 0             | 1 (1) 3.3%  | 0              |
| Blood urine present                   | 0            | 0            | 0            | 1 (1) 16.7%   | 0             | 1 (1) 3.3%  | 0              |
| Red blood cells urine positive        | 1 (1) 16.7%  | 0            | 0            | 0             | 0             | 1 (1) 3.3%  | 0              |
| White blood cell count increased      | 0            | 0            | 0            | 0             | 1 (1) 16.7%   | 1 (1) 3.3%  | 0              |
| Blood glucose increased               | 0            | 0            | 0            | 0             | 0             | 1 (1) 10.0%| 0              |
| Nervous system disorders              | 0            | 0            | 0            | 0             | 0             | 1 (1) 10.0%| 0              |
| Dizziness                             | 0            | 0            | 0            | 0             | 0             | 1 (1) 10.0%| 0              |
| Skin and subcutaneous tissue disorders| 0            | 0            | 0            | 1 (1) 16.7%   | 1 (1) 16.7%   | 2 (2) 6.7%  | 0              |
| Rash   | 0  | 0  | 0  | 1 (1) 16.7% | 1 (1) 16.7% | 2 (2) 6.7% | 0  |

Data shown are the number of subjects (number of events) and percentage of subjects with adverse events. Denominators for the percentages are the numbers of subjects in the safety population in each treatment group.
Table 3. Incidence of adverse events in the multiple-dose study

| System Organ Class                        | Preferred Term | Multiple-Dose | 1000 mg | 2000 mg | Total | Placebo |
|-------------------------------------------|----------------|---------------|---------|---------|-------|---------|
|                                            |                | 1st (n=8)     | 2nd (n=8) | (n=16)  |       | (n=10) |
| Subjects with any adverse events          |                | 7 (17) 87.5%  | 6 (15) 75.0% | 6 (13) 75.0% | 12 (28) | 75.0%  |
| Gastrointestinal disorders                |                | 0             | 2 (3) 25.0% | 1 (1) 12.5% | 3 (4) 18.8% | 0 |
| Diarrhea                                  |                | 0             | 2 (3) 25.0% | 0         | 2 (3) 12.5% | 0 |
| Abdominal pain                            |                | 0             | 0         | 1 (1) 12.5% | 1 (1) 6.3% | 0 |
| General disorders and administration      |                | 2 (2) 25.0%   | 1 (1) 12.5% | 1 (1) 12.5% | 2 (2) 12.5% | 0 |
| Pyrexia                                   |                | 2 (2) 25.0%   | 1 (1) 12.5% | 1 (1) 12.5% | 2 (2) 12.5% | 0 |
| Infections and infestations               |                | 0             | 1 (1) 12.5% | 0         | 1 (1) 6.3% | 0 |
| Upper respiratory tract infection         |                | 0             | 1 (1) 12.5% | 0         | 1 (1) 6.3% | 0 |
| Investigations                            |                | 5 (9) 62.5%   | 4 (9) 50.0% | 4 (7) 50.0% | 8 (16) 50.0% | 4 (6) 66.7% |
| Alanine aminotransferase increased        |                | 1 (1) 12.5%   | 3 (3) 37.5% | 1 (1) 12.5% | 4 (4) 25.0% | 3 (3) 50.0% |
| Aspartate aminotransferase increased      |                | 1 (1) 12.5%   | 3 (3) 37.5% | 1 (1) 12.5% | 4 (4) 25.0% | 1 (1) 16.7% |
| Blood creatine phosphokinase increased    |                | 0             | 1 (2) 12.5% | 2 (2) 25.0% | 3 (4) 18.8% | 1 (1) 16.7% |
| White blood cell count increased           |                | 0             | 0         | 2 (2) 25.0% | 2 (2) 12.5% | 0 |
| Blood thyroid stimulating hormone increased|            | 3 (3) 37.5%   | 0         | 0         | 0         | 0 |
| Blood lactate dehydrogenase increased     |                | 0             | 1 (1) 12.5% | 0         | 1 (1) 6.3% | 0 |
| Adverse Event                                      | Number of Subjects | Percentage | Number of Events | Percentage |
|---------------------------------------------------|--------------------|------------|------------------|------------|
| Blood urea increased                              | 1 (1) 12.5%        | 0          | 0                | 0          |
| White blood cells urine positive                   | 0                  | 0          | 1 (1) 12.5%      | 1 (1) 6.3% |
| Blood thyroid stimulating hormone decreased        | 1 (2) 12.5%        | 0          | 0                | 0          |
| Blood urine present                                | 1 (1) 12.5%        | 0          | 0                | 0          |
| Nervous system disorders                           | 1 (1) 12.5%        | 0          | 1 (1) 12.5%      | 1 (1) 6.3% |
| Headache                                           | 1 (1) 12.5%        | 0          | 1 (1) 12.5%      | 1 (1) 6.3% |
| Respiratory, thoracic and mediastinal disorders    | 0                  | 1 (1) 12.5%| 0                | 1 (1) 6.3% |
| Oropharyngeal pain                                 | 0                  | 1 (1) 12.5%| 0                | 1 (1) 6.3% |
| Skin and subcutaneous tissue disorders             | 5 (5) 62.5%        | 0          | 2 (3) 25.0%      | 2 (3) 12.5%|
| Rash                                               | 5 (5) 62.5%        | 0          | 2 (3) 25.0%      | 2 (3) 12.5%|

Data shown are the number of subjects (number of events) and percentage of subjects with adverse events.

Denominators for the percentages are the numbers of subjects in the safety population in each treatment group.

The study drug (cefiderocol) was contaminated with iodide.

The study drug (cefiderocol) was not contaminated with iodide.
Table 4. Pharmacokinetic parameters of cefiderocol following single intravenous infusions of 100 to 2000 mg

| PK parameter  | 100 mg (n=6) | 250 mg (n=6) | 500 mg (n=6) | 1000 mg (n=6) | 2000 mg (n=6) |
|---------------|-------------|-------------|--------------|--------------|--------------|
| C<sub>max</sub> (μg/ml) | 7.76 (7.8) | 18.9 (4.9) | 46.6 (10.7) | 76.4 (4.6) | 156 (7.9) |
| T<sub>max</sub> (h) | 1.0 (1.0–1.0) | 1.0 (1.0–1.0) | 1.0 (1.0–1.0) | 1.0 (1.0–1.0) | 1.0 (1.0–1.0) |
| AUC<sub>0-48</sub> (μg∙h/ml) | 17.03 (8.5) | 41.41 (6.3) | 108.0 (22.5) | 167.3 (6.9) | 388.9 (9.0) |
| AUC<sub>0-inf</sub> (μg∙h/ml) | 17.49 (8.5) | 41.94 (6.3) | 108.6 (22.7) | 168.1 (7.0) | 389.7 (9.0) |
| t<sub>1/2,z</sub> (h) | 2.00 (4.4) | 1.98 (5.5) | 2.12 (15.5) | 2.26 (5.8) | 2.74 (10.2) |
| CL (L/h) | 5.72 (8.5) | 5.96 (6.3) | 4.60 (22.7) | 5.95 (7.0) | 5.13 (9.0) |
| MRT (h) | 2.23 (3.9) | 2.18 (6.2) | 2.34 (15.2) | 2.24 (4.4) | 2.51 (4.7) |
| Feu<sub>0-48</sub> (%) | 68.4 (3.2) | 64.0 (5.4) | 65.8 (16.2) | 68.3 (6.0) | 61.5 (10.6) |
| CL<sub>R</sub> (L/h) | 3.91 (8.8) | 3.81 (10.7) | 3.03 (38.3) | 4.06 (11.2) | 31.6 (16.8) |

Geometric mean (CV% geometric mean) is shown except for T<sub>max</sub> where median and range are shown.
Table 5. Pharmacokinetic parameters of cefiderocol following multiple intravenous infusions of 1000 and 2000 mg

| PK parameter | 1000 mg 1st (n=8) | 1000 mg 2nd (n=8) | 2000 mg (n=8) |
|--------------|------------------|------------------|---------------|
| C<sub>max</sub> (μg/ml) Day 1 | 72.2 (12.0) | 69.8 (13.3) | 68.1 (16.2) |
| | 68.1 (11.5)<sup>a</sup> | 141 (22.7) | 153 (12.9) |
| T<sub>max</sub> (h) Day 1 | 1.0 (1.0–1.0) | 1.0 (1.0–1.0) | 1.00 (1.00– |
| | | | 1.25)<sup>a</sup> |
| AUC<sub>0-8</sub> (μg h/ml) | 165.5 (10.7) | NE | 160.9 (10.5) |
| AUC<sub>0-last</sub> (μg h/ml) | 176.4 (11.0) | NE | 171.0 (10.6) |
| AUC<sub>0-inf</sub> (μg h/ml) | 177.4 (10.9) | NE | 172.0 (10.6) |
| AUC<sub>0-tau</sub> (μg h/ml) | NE | 160.5 (13.5) | NE |
| t<sub>1/2,z</sub> (h) | 2.37 (11.4) | 2.35 (18.5) | 2.25 (8.8) |
| | | 2.19 (4.3)<sup>a</sup> | 2.40 (13.2) |
| CL (L/h) | 5.64 (10.9) | 6.23 (13.5) | 5.81 (10.6) |
| | | 5.93 (11.0)<sup>a</sup> | 5.91 (15.5) |
| MRT (h) | 2.49 (12.1) | NE | 2.50 (6.8) |
| | | 2.53 (13.5) | NE |
| Feu<sup>c</sup>(%) | 70.9 (6.7) | 70.0 (6.1) | 63.8 (12.3) |
| | | 64.7 (12.8)<sup>b</sup> | 67.7 (4.7) |
| CL<sub>R</sub> (L/h) | 4.02 (14.8) | 4.36 (12.8) | 3.73 (14.9) |
| | | 3.85 (17.8)<sup>b</sup> | 4.02 (17.2) |

Geometric mean (coefficient of variation [CV%] geometric mean) is shown except for T<sub>max</sub> where median and range are shown.

AUC<sub>0-8</sub>, area under the concentration-time curve from time zero to 8 h; AUC<sub>0-last</sub>, area under the concentration-time curve from time zero to the time of the last quantifiable concentration after dosing; AUC<sub>0-inf</sub>, area under the concentration-time curve extrapolated from time zero to infinity; AUC<sub>0-tau</sub>, area under the concentration-time curve over the dosing interval τ; C<sub>max</sub>, maximum plasma concentration; CL, total clearance; CL<sub>R</sub>, renal clearance; Feu,
urinary excretion ratio relative to dose; MRT, mean residence time; NE, not evaluated; \( t_{1/2} \), terminal elimination half-life; \( T_{max} \), time to maximum plasma concentration.

\( n=7. \)

\( n=6. \)

\( Feu_{0-24} \) for day 1; \( Feu_{0-8} \) for day 10.
Table 6. Iron levels (μg/dl) in the multiple-dose study

| Time point (baseline) | Statistic | Multiple-Dose Cefiderocol | Placebo |
|-----------------------|-----------|--------------------------|---------|
|                       |           | 1000 mg 1<sup>a</sup> | 1000 mg 2<sup>b</sup> | 2000 mg | (n=8) | (n=8) | (n=8) | (n=6) |
| Day 1                 | Mean (change from baseline) | 91.6 (0) | 96.5 (0) | 132.3 (0) | 118.7 (0) |
|                       | SD        | 17.2 | 23.3 | 49.9 | 32.2 |
|                       | Median    | 90.5 | 101.5 | 127.5 | 103.0 |
|                       | Range     | 59–115 | 50–129 | 60–230 | 102–183 |
| Day 2                 | Mean (change from baseline) | 82.5 (-9.1) | 113.1 (+16.6) | 123.6 (-8.6) | 125.5 (+6.8) |
|                       | SD        | 22.3 | 17.1 | 35.6 | 21.9 |
|                       | Median    | 86.5 | 113.5 | 126.0 | 119.5 |
|                       | Range     | 52–116 | 80–135 | 81–196 | 100–164 |
| Day 3                 | Mean (change from baseline) | 95.5 (+3.9) | 92.1 (-4.4) | 111.6 (-20.6) | 115.8 (-2.8) |
|                       | SD        | 17.8 | 15.7 | 35.5 | 29.8 |
|                       | Median    | 91.5 | 93.0 | 103.0 | 115.5 |
|                       | Range     | 72–119 | 69–114 | 60–182 | 84–161 |
| Day 5                 | Mean (change from baseline) | 74.5 (-17.1) | 72.0 (-24.5) | 109.1 (-23.1) | 98.8 (-19.8) |
|                       | SD        | 13.1 | 18.4 | 24.8 | 16.0 |
|                       | Median    | 72.5 | 68.0 | 104.5 | 106.5 |
|                       | Range     | 55–94 | 53–104 | 86–166 | 77–113 |
| Day 8                 | Mean (change from baseline) | 96.9 (+5.3) | 97.9 (+1.4) | 103.4 (-28.9) | 121.0 (+2.3) |
|                       | SD        | 19.1 | 12.6 | 21.2 | 23.5 |
|                       | Median    | 95.5 | 103.0 | 106.5 | 113.5 |
|                       | Range     | 64–130 | 81–110 | 74–143 | 95–156 |
| Day 10                | Mean (change from baseline) | 80.5 (-11.1) | 89.3 (-9.3) | 89.3 (-43.0) | 116.3 (-2.3) |
|                       | SD        | 25.7 | 18.0 | 33.4 | 27.3 |
| Day     | Mean (change from baseline) | SD     | Median | Range            |
|---------|-----------------------------|--------|--------|------------------|
| Day 11  | 65.0 (-26.6) 66.9 (-31.7) 95.8 (-36.5) 121.5 (+2.8) | 26.6   | 77.5   | 14–87 35–116 46–141 82–138 |
| Day 12  | 86.6 (-5.0) 83.4 (-15.1) 109.1 (-23.1) 121.0 (+2.3) | 30.6   | 98.0   | 18–111 55–111 51–168 91–156 |
| Day 13  | 87.1 (-4.5) 71.1 (-27.4) 90.4 (-41.9) 82.0 (-36.7) | 41.6   | 77.5   | 50–178 36–107 75–116 39–167 |
| Day 14  | 95.6 (+4.0) 64.6 (-34.0) 85.4 (-46.9) 85.8 (-32.8) | 32.9   | 93.5   | 56–154 29–109 57–136 51–137 |
| Day 17  | 60.6 (-31.0) 64.3 (-34.3) 100.9 (-31.4) 87.2 (-31.5) | 33.3   | 48.5   | 33–139 37–82 59–168 49–128 |

*Reference range: 80–199 μg/dl for males; 70–179 μg/dl for females.

\(^{b}\)n=7 for days 10, 11, 12, 14, and 17.
Figure 1. Mean (SD) plasma concentrations of cefiderocol following single-dose administration.

SD, standard deviation.
Figure 2. Mean (SD) plasma concentrations of cefiderocol following multiple-dose administration. (A) 0 to 24 hours and (B) 216 to 240 hours after the start of initial infusion. SD, standard deviation.
Figure 3. Mean (SD) urine concentrations of cefiderocol following single-dose administration.

SD, standard deviation.
Figure 4. Mean (SD) fraction of cefiderocol dose excreted in urine following single-dose administration. SD, standard deviation.
