Statistical Analysis Plan

Sponsor Name: Shionogi Inc.
Protocol Number: 1802R2135

Protocol Title: 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

Protocol Version and Date: Version 7, 18 Nov 2021

[redacted] **Project Code:** 7003659

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[redacted]

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[redacted]

[redacted]

I confirm that I have reviewed this document and agree with the content.

Approvals

[redacted] Approval

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Name, Title	Signature	Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation	Description
$\%fT_{>MIC}$	percentage of time of the dosing interval that is required for plasma concentrations to be above the mean inhibitory concentration
AE	adverse event
BLQ	below the lower limit of quantification
BMI	body mass index
BSI	bloodstream infection
CFU	colony forming units
CHMP	committee for medicinal products for human use
cIAI	complicated intra-abdominal infection
CLSI	Clinical and Laboratory Standards Institute
CRO	clinical research organization
cUTI	complicated urinary tract infection
CV%	coefficient of variation
DSMB	data safety monitoring board
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EUCAST	European Committee on Antimicrobial Susceptibility Testing
HAP	hospital-acquired pneumonia
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHMA	International Health Management Associates
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)

Abbreviation	Description
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MITT	microbiological intent to treat
N/A	not applicable
PDCO	paediatric committee
PK	pharmacokinetic(s)
PKC	pharmacokinetic concentration
PKCS	pharmacokinetic concentration summary
PT	Preferred Term
PTA	probability of target attainment
q8h	every 8 hours
SAE	serious adverse event
SAP	statistical Analysis Plan
SAS	Statistical Analysis System
SD	standard deviation
SOC	standard of care
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TLF	table, listing and figure
TOC	test of cure
VAP	ventilator-acquired bacterial pneumonia
WHO	World Health Organization

[redacted]

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures that will be produced and the statistical methodologies that will be used are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all tables, listings and figures (TLFs) with guidance supplied by Shionogi. The pharmacokinetic (PK) concentration analysis will be carried out by [redacted], following this SAP with guidance supplied by Shionogi & Co., Ltd. Additional PK analyses, including pooling the plasma concentration data in this study with other pediatric studies, will be carried out following a separate PK analysis plan that will be written and reported separately by the Clinical Pharmacology & Pharmacokinetics Department of Shionogi & Co., Ltd.

2.2. Timings of Analyses

The analysis of safety, efficacy, and pharmacokinetics is planned after database lock. Unless otherwise specified, the analysis will include all data collected in the database from the start of the study through database lock. Additional data collected after the database lock from the primary analysis of the study will be prepared as an addendum to the study report according to regulatory or scientific need. Data collected after the database lock will be specifically noted in the study report.

2.3. Interim Analyses

A data safety monitoring board (DSMB) will periodically review the study data. Interim analyses for the DSMB will be specified separately in the DSMB Charter.

The decision to move to the next cohort (for Cohort 4) or multiple-dose phase (for Cohorts 2, 3, and 4) will be based primarily on review of the results of the PK analysis and safety data by Shionogi. Cohort 4 (single dose) will commence after safety and PK data have been assessed from at least 6 subjects from the single-dose Cohorts 1, 2 and 3 (with a minimum of 3 subjects from Cohort 3). The multiple-dose phase (Cohorts 2, 3, and 4) will begin after safety and PK data from 6 subjects in the corresponding single-dose cohort have been assessed. Further description of the PK analysis can be found in the PK Analysis Plan.

[redacted]

3. Study Objectives

3.1. Primary Objective

- To assess the safety and tolerability of cefiderocol after single-dose administration in hospitalized paediatric subjects 3 months to < 18 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 paediatric subjects 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative bacterial infections
- To assess the safety and tolerability of cefiderocol after multiple-dose administration in hospitalized paediatric subjects 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections
- To assess the PK of cefiderocol after multiple-dose administration in hospitalized paediatric subjects 3 months to < 12 years of age with suspected or confirmed aerobic Gram-negative bacterial infections

3.2. Secondary Objective

- Multiple-dose phase only: Whenever cefiderocol is administered alone, to assess the clinical response at the Posttreatment visit (7 [±◦4] days following End of Treatment [EOT]) and at the End-of-study (EOS) visit, AND to assess the microbiological response at the Posttreatment visit (7 [±◦4] days) following EOT and EOS (if available)

3.3. Exploratory Objectives

- To estimate the Probability of Target Attainment (PTA) for percent of time that free drug concentrations in plasma exceed the Minimum Inhibitory Concentration (MIC) over the dosing interval (%$fT_{>MIC}$) of ≥ 75% with infections caused by pathogens with MICs ≤ 4 µg/mL
- Multiple-dose phase only: To describe the clinical outcome of cefiderocol when given alone or in combination with standard of care (SOC) antibiotics to treat infections caused by aerobic Gram-negative pathogens in hospitalized paediatric subjects 3 months to < 12 years of age at the Posttreatment visit, EOT, and EOS
- 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 paediatric subjects 3 months to < 12 years of age at the Posttreatment visit, EOT, and EOS

3.4. Brief Description

This is a multicenter, single-arm, open-label, single- and multiple-dose study to assess the safety, tolerability, and PK of cefiderocol in hospitalized paediatric subjects 3 months to < 18 years of age with a suspected or confirmed aerobic Gram-negative bacterial infection caused by a suspected or confirmed aerobic Gram-negative pathogen requiring systemic antibiotics for an expected 5 to 14 days.

The study will consist of 4 separate cohorts of paediatric subjects grouped according to the age range in Table 3.1.

Table 3.1 Cohort Description

[redacted]

Cohort	Age Range	Single-dose Phase (minimum per cohort)	Multiple-dose Phase (minimum per cohort)
1	12 to < 18 yrs	N = 6	Not applicable
2[a]	6 to < 12 yrs	N = 6	N = 10
3[a]	2 to < 6 yrs	N = 6	N = 10
4[a,b]	3 mos to < 2 yrs	N = 6	N = 10

mos = months; PK = pharmacokinetic; yrs = years

[a] Cohorts 1, 2, and 3 in the single-dose phase will be initiated in parallel.

[b] The multiple-dose phase (Cohorts 2, 3, and 4) will begin after safety and PK data from 6 subjects in the corresponding single-dose cohort have been assessed.

[c] Cohort 4 (single dose) will begin after safety and PK data from at least 6 subjects from the single-dose Cohorts 1, 2, and 3 (with a minimum of 3 subjects from Cohort 3) have been assessed.

Cohort 1 will consist of a minimum of 6 subjects with a single-dose phase only. Cohorts 2, 3, and 4 will have both a single-dose phase and multiple-dose phase (an expected minimum of 5 days to a maximum of 14 days).

The single-dose phase of Cohorts 1, 2, and 3 will be initiated in parallel. Within the single-dose Cohorts 2, 3, and 4, the PK of cefiderocol will be determined in all subjects prior to initiating enrollment of subjects in the multiple-dose phase of each respective cohort.

Single-dose Cohort 4 (the youngest age group) will commence after safety and PK data is evaluated from a minimum of 6 subjects from the single-dose Cohorts 1, 2, and 3 (with a minimum of 3 subjects from Cohort 3). The multiple-dose cohorts will begin after analyzing safety and PK data from 6 subjects in the corresponding single-dose cohort.

Enrollment will be stopped to allow for analysis of the PK data prior to moving from single-dose to multiple-dose in Cohorts 2 and 3 and prior to both the single- and multiple-dose phases of the youngest age group, Cohort 4. Sites that are activated for enrollment will be instructed via email or a phone call from the sponsor or [redacted] to pause enrollment in the relevant age cohort, until the available data have been processed and evaluated; additionally, Interactive Response Technology (IRT) will be de-activated to prevent enrollment until data have been evaluated.

In the single-dose phase, each of the 4 cohorts will include a minimum of 6 paediatric subjects (at least 24 subjects total).

In the multiple-dose phase (Cohorts 2, 3, and 4), each cohort will include a minimum of 10 paediatric subjects (at least 30 subjects total).

Overall, it is expected that at least 54 evaluable paediatric subjects will be enrolled in the study across all 4 cohorts.

For summary of plasma cefiderocol concentrations, evaluable subjects in the single-dose phase will include those who have received 1 dose of study drug and who have at least 1 PK blood sample above the limit of quantification. In the multiple-dose phase, evaluable subjects will include those who have received ≥ 4 doses of study drug and who have at least 1 PK blood sample above the limit of quantification.

[redacted]

Screening of subjects will occur within 4 days prior to administration of cefiderocol in the single-dose phase or administration of the first dose of study treatment in the multiple-dose phase.

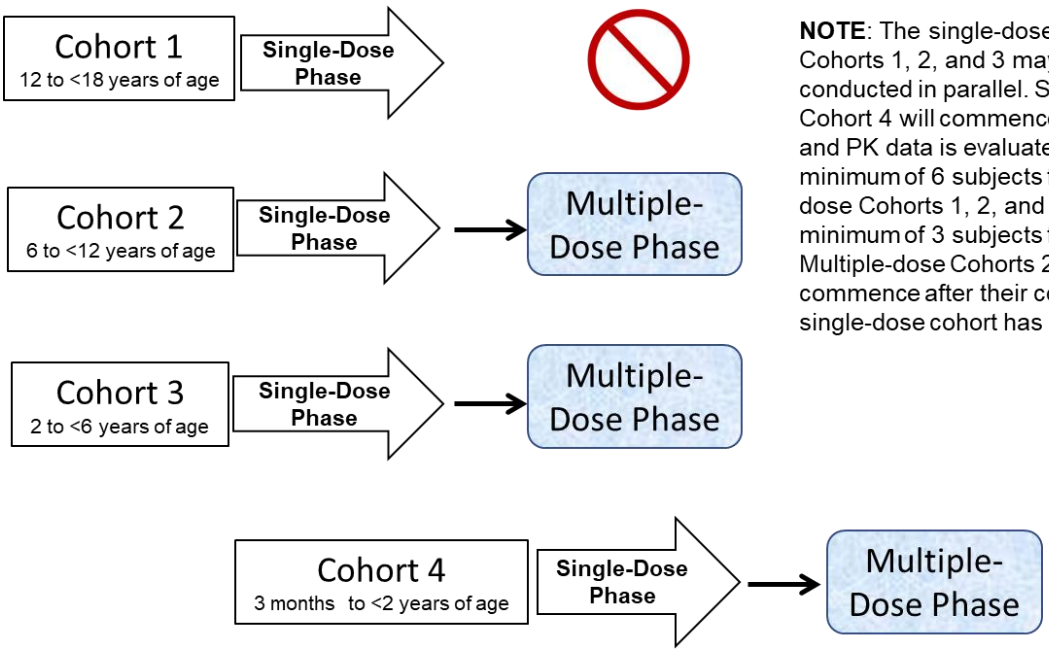
In the single-dose phase, study drug will be administered (in addition to standard of care [SOC]) at any time during the SOC treatment regimen. In the multiple-dose phase, cefiderocol will be administered on Day 1 (in addition to SOC), within 72 hours of the start of potentially effective treatment with SOC antibiotics for infection and will subsequently receive cefiderocol every 8 hours (q8h) for an expected minimum of 5 days to a maximum of 14 days total; the total duration of cefiderocol administration will be determined by the investigator based on clinical assessment of each subject's infection status. Each dose of cefiderocol will be administered intravenously (IV) over 3 hours. The infusion may be shortened if this is in the best interest of the subject and if approved by the sponsor via the Request for Shortened Infusion Duration Form. The dose of cefiderocol for both phases of the study will be determined based on body weight and renal function. The single-dose phase will include only those subjects with normal renal function or mild renal impairment. The SOC administered will be selected by the investigator based on the suspected or confirmed pathogen(s) for the infection in accordance with local standards and can be modified at any time during the subject's participation in the study at the investigator's discretion. In the multiple-dose phase, if the subject's infection is confirmed to be Gram-negative only before starting treatment, monotherapy with cefiderocol will be allowed.

End-of-treatment (EOT) assessments will occur within 24 hours after administration of cefiderocol (single-dose phase) or within 24 hours after administration of the last dose of study treatment (multiple-dose phase), or at early termination. A further clinical assessment will occur at a Posttreatment visit 7 (± 4) days after EOT (multiple-dose phase), which is analogous to a Test of Cure (TOC) and EOS time point, if microbiological samples are available. The EOS visit will occur 28 (+7) days after administration of cefiderocol in the single-dose phase or after administration of the last dose of study treatment in the multiple-dose phase; this visit may be performed on-site or via phone call. The study schematic including a schedule of assessments is provided in Figure 3-1 and Table 3-2 of Protocol.

The total duration of cefiderocol administration will be determined by the investigator based on clinical assessment of each subject's infection status, but is expected to be (at time of enrollment) within 5 to 14 days. In the single-dose phase, the maximum duration of study participation for a subject from Treatment (Day 1) to the EOS visit (28 (+7) days after administration of the single dose of cefiderocol) is 28 days. In the multiple-dose phase (expected treatment duration of 5 to 14 days), the maximum duration of study participation for a subject from Treatment (Day 1) to the EOS visit (28 (+7) days after administration of the last dose of study treatment) is 42 days.

Figure 3-1 Study Schematic

[redacted]



NOTE: The single-dose phase of Cohorts 1, 2, and 3 may be initiated and conducted in parallel. Single-dose Cohort 4 will commence after safety and PK data is evaluated from a minimum of 6 subjects from the single-dose Cohorts 1, 2, and 3 (with a minimum of 3 subjects from Cohort 3). Multiple-dose Cohorts 2, 3, and 4 will commence after their corresponding single-dose cohort has concluded.

PK = pharmacokinetic

Table 3-2 Study Schedule of Assessments

Study Phase	Screening	Cefiderocol Administration	End-of-Treatment (EOT)	Post-treatment Visit	End-of-Study (EOS) Visit
Single-dose	Within 4 days prior to first dose of study treatment (cefiderocol)	1 day	Within 24 hours after last dose of study treatment (or early termination)	N/A	28 (+ 7) days after single dose of cefiderocol
Multiple-dose		5 to 14 days		7 (± 4) days after EOT	28 (+ 7) days after last dose of study treatment

3.5. Determination of Sample Size

The design and the sample size of this study have been discussed with and agreed to by the Paediatric Committee [PDCO] (the European Medicines Agency [EMA]'s scientific pediatric committee) prior to study initiation. This study's primary purpose is to assess the PK and safety of cefiderocol in paediatric subjects 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative infections. Efficacy is not a primary endpoint; therefore, the sample size calculations do not take into account efficacy endpoints.

[redacted]

The design of the paediatric study and the number of subjects included in each cohort and overall was discussed, agreed upon, and approved by PDCO and is in line with the Committee for Medicinal Products for Human Use (CHMP)/PDCO scientific advice Shionogi received in 2016 (Procedure No.: EMEA/H/SA/3435/1/2016/PED/III). It also reflects the requirements in the current draft Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements.

3.6. Treatment Assignment and Blinding

This study has a single-dose phase and a multiple-dose phase and will include 4 separate age-specific cohorts of pediatric subjects, grouped according to age range (Table 3-1, in SAP Section 3.1).

The single-dose phase (in all 4 cohorts) will enroll subjects with Gram-negative bacterial infections and will confirm cefiderocol exposures in a minimum of 6 subjects prior to conducting a multiple-dose phase (in Cohorts 2, 3, and 4) in additional subjects.

This is a single-arm and open-label study.

3.7. Study Procedures and Flowchart

The study procedures and the times to be performed are summarized in the Time and Events Schedule, which is provided in the protocol Appendix 1.

4. Endpoints

4.1. Safety Endpoints

The following safety and tolerability endpoints will be evaluated:

- Adverse Events
  - Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), treatment-related TEAEs and TEAEs leading to discontinuation of study drug
  - Special Situations – Abuse, Misuse, Overdose and Medication Error
- Vital signs (blood pressure, pulse rate, respiratory rate, body temperature)
  - observed and change from baseline values
- Clinical laboratory assessments
  - Routine lab tests (hematology, blood chemistry, urinalysis)
    - observed and change from baseline values
  - Estimated glomerular filtration rate (eGFR)
  - Urine pregnancy test
  - Microbiologic cultures
- Physical examination findings

4.2. Efficacy Endpoints

The following efficacy endpoints will be analyzed in the multiple-dose phase only at the EOT, the Posttreatment visit, and the EOS with cefiderocol alone:

- Clinical outcome (Clinical Cure, Clinical Failure, Indeterminate)
- Microbiological outcome per pathogen and per subject (Eradication, Persistence, Indeterminate)

4.3. Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be evaluated for subjects in the multiple-dose phase at EOT, the Post-treatment visit, and EOS when treated with cefiderocol alone or in combination with SOC:

- Clinical outcome (Clinical Cure, Clinical Failure, Indeterminate)
- Microbiological outcome per pathogen and per subject (Eradication, Persistence, Indeterminate)

4.4. Pharmacokinetic Endpoints

The following pharmacokinetic endpoints will be evaluated:

- Plasma cefiderocol concentrations

4.5. Pharmacokinetic/Pharmacodynamic Endpoints

The pharmacokinetic/pharmacodynamic endpoints (parameters) will be specified in a PK Analysis Plan.

[redacted]

5. Analysis Sets

5.1. Safety Population

The Safety Population will be defined as all enrolled subjects who received at least 1 dose of cefiderocol. The Safety Population will be used for all safety analyses.

5.2. Pharmacokinetic Concentration Population

The Pharmacokinetic Concentration (PKC) Population will include all enrolled subjects who received at least 1 dose of cefiderocol and have at least 1 PK blood sample. This population will be used for the PK concentration listing.

5.3. Pharmacokinetic Concentration Summary Population

The Pharmacokinetic Concentration Summary (PKCS) Population will include all enrolled subjects who received 1 dose of cefiderocol in the single-dose phase and ≥ 4 doses of cefiderocol in the multiple-dose phase and those subjects who have at least 1 PK blood sample above the limit of quantification. This population will be used for the concentration summary, as well as for plotting of the concentration-time data and concentration data summary.

5.4. Intent-to-Treat Population (Multiple-dose Phase Only)

The Intent-to-treat (ITT) Population will be defined as all enrolled subjects who received at least 1 dose of cefiderocol.

5.5. Microbiological Intent-to-Treat Population (Multiple-dose Phase Only)

The Microbiological Intent-to-treat (MITT) Population will include all ITT subjects who have a baseline Gram-negative pathogen from any specimen from a baseline infection site.

5.6. Protocol Deviations

Major protocol deviations will be summarised, listed, and specified in the “Protocol Deviation Specifications Document” separately. A final list of major protocol deviations will be determined based on the data review prior to database lock.

[redacted]

6. General Aspects for Statistical Analysis

6.1. General Methods

All analyses and summaries will be produced using Statistical Analysis System (SAS®) version 9.4 or higher. All SAS programs used to generate analytical results will be developed and validated according to [redacted] programming standards and SAS validation procedures. Summaries will be presented by dose phase (single dose or multiple dose), cohort, and overall for each dose phase, unless otherwise specified.

Unless otherwise noted, continuous variables will be summarized using the number of nonmissing observations (N), arithmetic mean (Mean), standard deviation (SD), median, minimum, and maximum values as summary statistics.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The total number of subjects with a nonmissing value for the given variable will be used as the denominator for percent calculations, unless stated otherwise. All percentages will be presented with 1 decimal, unless otherwise specified. Percentages equal to 100 will be presented as 100, and percentages will not be presented for zero frequencies.

All subject study data, including data not appearing in tables, will be presented in subject data listings. Individual subject data, PK data, and any derived data will be listed by subject. All pre- and postdose assessments including repeat and unscheduled assessments will be included in the data listings.

No inferential statistical hypothesis testing will be performed in this study.

Summary statistics calculated for PK data are described in SAP Section 9 – Analysis of Pharmacokinetics.

6.2. Key Definitions

6.2.1. Baseline Definition

Baseline for weight, height: Baseline is the last available data within 4 days prior to Treatment Day 1 or on Treatment Day 1.

Baseline for other vital sign parameter: Baseline is the last available data prior to Treatment Day 1 pre dosing.

Baseline for Laboratory Evaluations: Baseline is the last available data within 4 days prior to Treatment Day 1 or on Treatment Day 1 for single dose phase, and are within 4 days prior to Treatment Day 1 or at Screening visit (excluding before 4 days prior to Treatment Day 1) in multiple dose phase.

Baseline for Gram-Negative Pathogen: Baseline pathogens wil be determined from appropriate specimens from the baseline infection site collected within the 4 days prior to the first dose of cefiderocol in the multiple-dose phase of this study. If specimens are collected on multiple dates before the first infusion, the specimens collected on the latest date for each pathogen will be used to determine baseline pathogens. If there are more than one appropriate clinical specimens on the latest date, appropriate clinical specimens for the baseline will be selected following below priority.

[redacted]

1. When pathogens are identified as resent samples for the same subject, the larger req num ending with S02 wil be used for analysis
2. When multiple records identified from same pathogen, same date, pathogen with the highest quantitative value will be considered
3. When mutiple records identified from same pathogen, same date, pathogen with any valid minimum inhibitory concentration (MIC) for cefiderocol will be considered.

In case different Gram-negative pathogens are obtained from specimens from the baseline infection site, all of them will be considered as baseline pathogens.

Baseline for Microbiology Susceptibility: Microbiology Susceptibility tested for pathogens identified from IHMA. Baseline followed the baseline Gram-Negative Pathogen.

6.2.2. Post baseline Gram-Negative pathogen

If multiple records from the same parameter on the same date, the record with the highest quantitative for urine sample will be used.

6.2.3. Appropriate clinical specimens

Appropriate clinical specimens are defined as sputum, tracheal aspirate, bronchoalveolar lavage (BAL) fluid, protected specimen brush, pleural fluid, lung biopsy for HAP/VAP, blood for BSI/sepsis/cIAI, or urine for cUTI. Specimens that were collected from other sites may be considered as appropriate specimen. This will be determined by the medical monitor. If the infection site is “other”, it will be determined whether the specimen is an appropriate clinical specimen or not by medical monitor. The time window of the 4 days prior to the first dose of cefiderocol will be determined based on time unit, ie within 5760 min from the first infusion.

Eligibility of subjects into the MITT Analysis Population will be based on local lab results of baseline pathogens if the microbiological culture results are not sent to a central lab for confirmation or if central lab results are missing. In addition, in such a case, the local lab result will be used for analysis.

6.2.4. Day 1

Day 1 will be defined as the day of the first dose of cefiderocol.

6.2.5. Study Day

For events that occur before the first dose of study drug, study day = date of the event – first dose date; for events that occur on or after the first dose of study drug, study day = date of the event – first dose date + 1. There will be no Day 0.

6.2.6. Nominal time

Nominal time will be defined as the scheduled measurement time relative to time 0. Time 0 will be the time of dosing for the treatment period of interest.

[redacted]

6.3. Handling of Microbiologic Data

If a pathogen is identified from local laboratory data but it is not sent to a central laboratory, the name reported by local laboratory will be used for analysis. In this case, the minimum inhibitory concentration (MIC) will be treated as unknown.

If a pathogen name is different between the local and central laboratory, the name assigned by the central laboratory will be used for the analysis. However, if the sample sent to International Health Management Associates Inc. (IHMA) was reported as “unknown” or the sample was not sent to IHMA, pathogen will be considered as no growth and used for analysis.

6.4. Missing Data

In general, missing data will not be imputed. All analyses will be based on observed cases. Sections 6.4.1 and 6.4.2 note the situations where missing data will be imputed.

6.4.1. Handling of Missing Dates/Months/Years for Prior/Concomitant Therapies

If the medication cannot be classified into concomitant medications or prior medications due to incomplete date, the rules below will be applied for the classification.

For start date,

- If the year and month are observed but the day is missing, the first day of the month will be used unless the month and year are the same as the month and year of first dose date, then the day of first dose date will be imputed.
- If the year is observed but the month and day are missing, the first day of the year, 01 Jan, will be used unless year is the same as first dose date, then the first dose date will be used
- If the start date is completely missing, the medication will be considered concomitant unless the stop date is before study drug administration.
- If the start and stop dates are both completely missing, a therapy will be considered concomitant.
- If the year is observed but the time is missing, the first time of the day, 00:00 AM will be used.
- If the end date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

For end date,

- If the year and month are observed but the day is missing, the last day of the month will be used unless the month and year are the same as the month and year of last dose date, then the last dose date will be imputed.
- If the year is observed but the month and day are missing, the last day of the year, 31 Dec, will be unless the year is the same as the last dose date, then the last dose date will be used.
- If the end date is completely missing and the medication is still ongoing, then the missing end date will not be imputed. If the medication is not ongoing and the start date is prior to the first dose date, the end date will be imputed using the first dose date.
- If both start and end dates are completely missing, medication will be considered concomitant.
- If the year is observed but the time is missing, the end time of the day, 23:59 PM will be used.
- If the imputed end date is before the start date (imputed or non-imputed start date), then the stop date will be imputed using the start date.

The original partial or missing date will be shown in listings for all prior and concomitant medications.

[redacted]

6.4.2. Missing Microbiological or Clinical Outcome

For clinical and microbiological outcomes, subjects who are lost to follow-up or have missing or "indeterminate" outcomes will be included in the denominator as indeterminate for cure/eradication rate, ie, considered as nonresponders.

6.5. Visit Windows

Visits specified in the electronic case report form (eCRF) will be used for this study. Measurements will be performed according to the Time and Events Schedule in protocol Appendix 1. The acceptable time deviations relative to the time points specified in protocol Appendix 1 are shown in Table 6-1. Every effort will be made to adhere as closely as possible to the procedure time points specified.

Table 6-1 Acceptable Time Windows

Study Activity	Time Points		Acceptable Time Window
Screening	Can be Treatment Day 1		Within 4 days prior to Treatment Day 1
Enrollment	Treatment Day 1		---
Drug infusion	See Appendix 1		± 15 minutes
Dosing interval	See Appendix 1		± 15 minutes
Pharmacokinetic blood sampling	**Cohorts 1 and 2**	1 hour after start of infusion	± 15 minutes
		3 hours after start of infusion	Within 15 minutes prior to the end of infusion using a separate line or immediately after the end of infusion using the same line and with proper flushing
		3.5 hours after start of infusion	± 15 minutes
		5 and 8 hours after start of infusion	± 30 minutes
	Cohorts 3 and 4	3 hours after start of infusion	Within 15 minutes prior to end of infusion using a separate line or immediately after the end of infusion using the same line and with proper flushing
		5 and 8 hours after start of infusion	± 30 minutes
EOT	Within 24 hours after last day of study treatment		As soon as possible after last dose (same calendar day)
Posttreatment	7 days after EOT		± 4 days
EOS	28 days after last dose of study treatment		+ 7 days

EOS = End of Study; EOT = End of Treatment

EOS = End of Study; EOT = End of Treatment.

[redacted]

All the data, including unscheduled visits, will be included in the listings. If multiple records exist at the same visit/time point, the closest record to target day will be used for the purpose of summary tables. If these are some records that have the same difference from the target day, the latest record will be used.

[redacted]

7. Demographic, Other Baseline Characteristics, and Medication

7.1. Subject Disposition and Withdrawals

The number of subjects screened, screen failed, and enrolled will be summarized.

A summary table will be produced detailing the number and percentages of all subjects who are enrolled, subjects in each analysis populations, subjects who received study drug (cefiderocol), subjects who completed study drug, subjects who discontinued study drug, subjects who completed the study and subjects who prematurely discontinued the study. In addition, reasons leading to discontinuation from study and study drug discontinuation will be summarized for each cohort and overall. A listing of subject disposition, and a separate listing of subjects that discontinued or withdraw early will also be provided.

The number and proportion of subjects included in each analysis population and the reasons for exclusion will also be presented. A listing of subjects excluded from each analysis population will also be produced.

7.2. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics, including date of birth, age (in months as collected on the Demographics eCRF), age in years, sex, race, ethnicity, height (cm), weight (kg), body mass index (kg/m^2), and eGFR ($mL/min/1.73\ m^2$), will be summarized by cohort using standard descriptive statistics for the Safety, ITT, and MITT Populations. Infection type (complicated urinary tract infection [cUTI], pneumonia, complicated intra-abdominal infection [cIAI], hospital-acquired pneumonia [HAP]/ventilator-acquired pneumonia [VAP], sepsis or bloodstream infections [BSI], other) will be summarized by single and multiple dose phases. In addition, for subjects in multiple dose phase, these parameters will be summarized by treatment regimen (cefiderocol alone or cefiderocol + SOC) for ITT and MITT Population.

The baseline Gram-negative pathogen will be summarized by cohort groups and baseline infection site for the MITT Population. In addition, baseline Gram-negative pathogen will be summarized by cohort groups and treatment regimen (cefiderocol alone or cefiderocol + SOC) for ITT and MITT Population.

The baseline pathogen will also be summarized for the MIC values, and susceptibility will be defined by Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) of the baseline pathogen. For this analysis, the MIC for cefiderocol, amikacin, aztreonam, ceftazidime-avibactam, imipenem, ceftolozanetazobactam, ciprofloxacin, meropenem, cefepime, colistin, and tigecycline will be used, and the number of subjects, MIC_{50}, MIC_{90}, and range will be calculated for summary statistics of MIC. MIC_{50} and MIC_{90} will be defined as the smallest value no less than 50% and 90% of the data, respectively; MIC_{50} and MIC_{90} will be calculated only when the number of subjects with a particular bacterium is 10 or more.

Body mass index (BMI) is calculated as follows:

$BMI\ (kg/m^2) = Weight(kg)/[Height(m)^2]$

Age in years is calculated as follows:

Age (years) = (Age in months collected in eCRF)/12 and rounded up to one decimal place.

Demographics and informed consent data will be listed by subject for all the subjects.

[redacted]

7.3. Inclusion/Exclusion Criteria

All inclusion/exclusion criteria definitions will be listed. Inclusion/exclusion criteria deviations will be listed by subject.

7.4. Medical History

Medical history will be summarized for the MITT and Safety Populations by MedDRA System Organ Class (SOC) and Preferred Term (PT). The reported medical history terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher.

Medical history findings will be listed by subject using the Safety and MITT Populations.

7.5. Prior and Concomitant Therapies

The original verbatim terms of the prior and concomitant therapies collected in the eCRF will be coded using the World Health Organization (WHO) Drug Dictionary, Version Sep. 2019.

In the event of a missing start date or time associated with a therapy, prior/concomitant therapy will be determined by imputation using the algorithm described in Section 6.4.1.

Prior and concomitant therapies will be listed and summarized for the Safety Population. Prior and concomitant therapy data will be listed chronologically by subject and will include the data collected in the eCRF, along with the coded variables. For the summary tables, the number and percentage of subjects under each preferred drug or procedure name will be summarized by cohort. If a subject has taken 1 or more prior or concomitant medications more than once, the subject will be counted only once during any given drug class. Prior and Concomitant Therapies will be summarized by antibiotic therapy, standard of care treatment for disease and non-antibiotix therapy using the Safety Population.

7.5.1. Prior Therapy

Prior antibiotic therapy is defined as any antibiotic administered for current infection. Prior therapy (Prior antibiotic therapy, Prior Standard of Care Treatment for Disease, Prior Non-Antibiotic theraphy) is defined as any therapy administered within 14 days prior to administration of the first dose of cefiderocol.

7.5.2. Concomitant Therapy

Concomitant therapy (Concomitant antibiotic therapy, Concomitant Standard of Care Treatment for Disease, Concomitant Non-Antibiotic theraphy)is defined as any therapy administered after study drug is administered in the study.

[redacted]

8. Efficacy

Efficacy endpoints will be evaluated for subjects in the multiple-dose phase of the study for the ITT and MITT analysis Populations.

The efficacy endpoints are as follows:

- Clinical outcome, defined as the categories below:

  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 drug 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 cannot be made.

  cUTI:

  - 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 is 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 drug therapy; or death due to cUTI.
  - Indeterminate: Lost to follow-up such that a determination of clinical cure/failure cannot be made.

  BSI/Sepsis:

  - Clinical Cure: Resolution or substantial improvement of baseline signs and symptoms. Subjects with bacteremia must have eradication of bacteremia 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 drug therapy; or death due to BSI/sepsis.
  - Indeterminate: Lost to follow-up such that a determination of clinical cure/failure cannot be made.

[redacted]

- Microbiological outcome per pathogen defined as the categories below:

  HAP/VAP/cIAI and BSI/Sepsis:

  - 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 for reasons other than a successful clinical outcome.
  - Eradication: Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen. If it is not possible to obtain an appropriate clinical culture and the subject has a successful clinical outcome, the response will be presumed to be eradication.

  cUTI:

  - Persistence: A urine culture shows that the baseline Gram-negative uropathogen found at entry at ≥ 10^5 CFU/mL grows to ≥ 10^3 CFU/mL.
  - Indeterminate: No urine culture obtained or additional antibiotic therapy for the treatment of the current infection including missed sampling.
  - Eradication: A urine culture shows that the baseline Gram-negative uropathogen found at entry at ≥ 10^5 colony forming units (CFU)/mL is reduced to < 10^3 CFU/mL.

Clinical response will be characterized based on an evaluation of clinical signs and symptoms by the investigator or designee. Clinical outcomes will be characterized at EOT, Posttreatment, and EOS if available.

The microbiological outcomes per subject determined by investigator will be entered in the eCRF. When the investigator confirms:

- that the subject experiences eradication of all baseline Gram negative pathogens then “Eradication” will entered. For subjects with baseline infection other than cUTI who achieved clinical cure at corresponding visit, the response will be considered as Eradicated.

- that the subject experiences persistence of any baseline Gram-negative pathogen then “Persistence” will be entered

- that the subject experiences anything other than above then “Indeterminate” will be entered.

Emergent (ie, nonbaseline) pathogens will be considered separately, and will not affect the per-subject microbiological outcome.

[redacted]

8.1. Efficacy Endpoints and Analyses

8.1.1. Clinical Outcomes

For subjects treated with cefiderocol alone, the number and proportion of subjects in each category will be calculated for each time point (EOT and Posttreatment visit and at EOS). Subjects will be presented by cohort and overall, for the ITT and MITT Populations. Note that the study is not designed to collect outcome data at EOS on all subjects, and summaries for Clinical Outcomes will be underestimated due to indeterminate caused by missing data.

For subjects treated with cefiderocol alone, the number and proportion of subjects in each category and each baseline Gram-negative pathogen will be calculated for each time point (EOT, and Posttreatment visit and at EOS). Subjects will be presented by cohort and overall, for the MITT Population.

In addition, the proportion of clinical cure rate at Post treatment visit by each baseline pathogen and MIC will be calculated.

8.1.2. Microbiological Outcomes

For subjects treated with cefiderocol alone, the number and proportion of subjects in each category will be calculated for each time point (EOT, and Posttreatment visit and at EOS). Subjects will be presented by cohort and overall, for the MITT Populations. Note that the study is not designed to collect outcome data at EOS on all subjects, and summaries for microbiological outcomes will be underestimated due to indeterminate caused by missing data

For subjects treated with cefiderocol alone, the number and proportion of each category by each baseline Gram-negative pathogen will be calculated for each time point (EOT and Posttreatment visit and at EOS if available). Subjects will be presented by cohort and overall, for the MITT Population.

In addition, the proportion of eradication rate at Post treatment visit by each baseline pathogen and MIC will be calculated.

8.2. Exploratory Efficacy Endpoints and Analyses

8.2.1. Clinical Outcomes

For subjects treated with cefiderocol in combination with SOC, the number and proportion of subjects in each category will be calculated for each time point (EOT, Posttreatment and EOS). Subjects will be presented by cohort and overall, for the ITT and MITT Populations. The same analysis will be performed for subjects with cefiderocol + SOC and all subjects treated with cefiderocol.

8.2.2. Microbiological Outcomes

For subjects treated with cefiderocol in combination with SOC, the number and proportion of subjects in each category will be calculated for each time point (EOT, Posttreatment and EOS). Subjects will be presented by cohort and overall, for the MITT Population. The same analysis will be performed for subjects with cefiderocol + SOC and all subjects treated with cefiderocol.

[redacted]

9. Pharmacokinetic Analyses

The PK concentration data will be analyzed using SAS® version 9.4 or higher. The PK concentration listings will be performed on the PK Concentration Population, and PK concentration tables will be performed on the PK Concentration Summary Population.

Additional PK analyses, including using the pooled plasma concentration data in this study and other pediatric studies and population PK analyses, will be will be performed using nonlinear mixed effects model approach and will be planned and reported separately by the Clinical Pharmacology & Pharmacokinetics of Shionogi & Co., Ltd. NONMEM Version 7.3 or higher will be used for the analyses.

9.1. PK Sampling Schedule

At each PK sampling time point, up to 0.4 mL of blood (but no less than 180 µL, ie, 0.18 mL) will be obtained adding up to the maximum blood sample volumes shown in Table 9-1::

Table 9-1 Total PK Blood Sample Volumes

Cohorts	**Cohort 1**	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Cohorts 1 and 2 Flexible Sampling**	
Age	12 years to < 18 years	6 years to < 12 years	2 years to < 6 years	3 months to < 2 years	3 point-design	4 point-design
Number of samples	5 samples	5 samples	3 samples	3 samples	3 samples	4 samples
Total PK blood volume	2.0 mL	2.0 mL	1.2 mL	1.2 mL	1.2 mL	1.6 mL

Cohorts 1 and 2: total of 5 blood samples for determination of plasma cefiderocol concentrations will be collected from each subject as specified in Table 9-2 in the multiple-dose phase during 1 of the dosing intervals from the 6th to the 12th dose of cefiderocol. In the multiple-dose phase of the study in Cohort 2, if individual blood draws are needed (versus using a central line), it will be acceptable to adjust the sampling time points to a minimum of 3 or 4 samples (versus ideally 5 samples).

Cohorts 3 and 4: A total of 3 blood samples for determination of plasma cefiderocol concentrations will be collected from each subject as specified in Table 9-2 in the multiple-dose phase during 1 of the dosing intervals from the 6th to the 12th dose of cefiderocol.

The option to use an indwelling catheter to facilitate blood sampling or application of a topical anesthetic cream prior to venipuncture will be allowed.

Table 9-2 Blood Sampling Times After Start of Infusion

Cohort	**Sampling Time Points (hours) After Start of Infusion**				
	1	**3***	**3.5**	**5**	**8**
Single-dose Phase					
Cohort 1	X	X	X	X	X

[redacted]

Cohort 2	X	X	X	X	X
Cohort 3		X		X	X
Cohort 4		X		X	X
Multiple-dose Phase					
Cohort 1	NA	NA	NA	NA	NA
Cohort 2	X	X	X	X	X
Cohort 3		X		X	X
Cohort 4		X		X	X

NA = not applicable

* Within 15 minutes prior to the end-of-infusion using a separate line or immediately after the end of infusion using the same line and with proper flushing.

If using a 3-point design, sampling times after the start of infusion are: 3, 5, and 8 hours. If using a 4-point design, sampling times after the start of infusion are: 3, 5, and 8 hours, and 1 or 3.5 hours.

For each blood sample collected, the actual sampling time will be recorded in the eCRF.

Acceptable visit windows for PK sampling time points are detailed in Section 6.4.

9.2. Plasma Pharmacokinetic Endpoint

The following PK endpoints will be evaluated:

- Plasma cefiderocol concentrations

Plasma cefiderocol concentrations will be listed and summarized by phase.

9.3. Presentation of Concentration Data

9.3.1. Handling of Missing Data or Data Below the Lower Limit of Quantification (BLQ)

Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis at the discretion of the PK scientist. Any such exclusion will be clearly listed in the CSR along with justification for exclusion.

Missing concentration data for all subjects who are administered scheduled study treatments will be considered as noninformative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For summary of plasma concentration, the concentration BLQ will be treated as zero (0) for calculations of mean, SD, CV%, minimum, median, and maximum and treated as missing for calculations of the Geometric mean value and CV% Geometric mean.

Samples taken far outside the sampling windows may be excluded from by-time point summary statistics; this will be determined prior to database lock.

[redacted]

For individual concentration-time profiles, BLQ values will be replaced with:

- Zero for time-points prior to the first non-zero concentration in a linear plot.
- Zero for time-points after the first non-zero concentration in a linear plot.
- "Missing" for all BLQ values in a semi-logarithmic plot.

9.3.2. Listing and Presentation of Individual Pharmacokinetic Data

The PKC Population will be used for all individual plasma sampling collection time and concentration listings, while all summaries and graphics will be conducted using the PKCS Population. Individual plasma concentrations of cefiderocol will be presented by cohort, phase (single-dose and multiple-dose phases), infusion time (1, 2, and 3 hours), and nominal sampling time.

The following individual plots will be produced:

- Spaghetti plot linear and semi-logarithmic plasma concentration versus time plots using actual sample times (a line to connect all time points of plasma concentration) - all Individual subjects combined (1 line per subject).

9.3.3. Summary of PK Concentrations

Table summaries and graphics will be conducted using the PKCS Population. Descriptive statistics, including N, mean, SD, CV% (calculated by SD/mean × 100), Geometric mean and CV% Geometric mean, median, minimum, and maximum values will be presented for plasma concentrations by cohort, phase (single-dose and multiple dose phases), infusion time (1, 2, and 3 hours), and nominal sampling time; BLQ values will be handled according to the rules described in Section 9.3.1.

The CV% Geometric mean will be calculated according to a formula:

$$\text{CV\% Geometric mean} = [\exp(sd^2) - 1]^{1/2} \times 100$$

where sd is the standard deviation for natural log (ln)-transformed data.

The following mean plots will be produced:

- The arithmetic mean plasma concentration with SD versus time profiles will be plotted by cohort, phase (single-dose and multiple-dose phases), and infusion time (1, 2, and 3 hours) within the same figure on linear scale and semi-logarithmic scales using nominal sampling times.

10. Pharmacokinetic/Pharmacodynamics Analyses

The pharmacokinetic/pharmacodynamic analyses will be planned in a PK Analysis Plan by Shionogi.

[redacted]

11. Safety

The population used for safety analyses will be the Safety Population. Safety will be assessed on the basis of adverse event (AE) reports, clinical laboratory data, physical examinations, and vital signs. By-subject listings of the safety assessments will be provided for all subjects. Summaries will be presented by dose phase (single dose or multiple dose), cohort, and overall for each dose phase, unless otherwise specified.

11.1. Extent of Exposure

Cefiderocol and SOC administration records will be listed chronologically by subject and study days.

Exposure duration and study drug regimen will be tabulated for the Safety Population. In addition, the total number of doses received for cefiderocol will be summarized.

The total number of doses will be calculated as the sum of each unique recorded infusion per subject.

Exposure duration in days will be calculated as (round up to an integer of (the stop date of the last dose/time (HH:MM) – the start date of the first dose/time (HH:MM) / (60*60*24))).

11.2. Adverse Events

Adverse events reported after the initial dose of cefiderocol will be considered treatment- emergent adverse events (TEAEs).

Adverse events will be collected from the time signed informed consent is obtained through the EOS visit or 28 (+ 7) days after administration of the last dose of the study drug. If a subject withdraws early from the study or is prematurely discontinued from study drug by the investigator, the investigator will make an effort to collect AEs for 28 days after the last dose of the study drug.

Treatment emergence will be determined by comparing the onset date with the actual date of dosing.

Adverse events will be classified by System Organ Class and PT using MedDRA Version 19.1 or higher.

All AEs will be listed by subject and chronologically by date and time of AE onset. This listing will include all data collected in the eCRF and the coded variables. Additional listings of treatment-emergent SAEs, study-drug related TEAEs, TEAEs leading to study drug withdrawal, and deaths will be provided.

11.2.1. Summaries of Adverse Events

Unless otherwise noted, TEAEs will be used for the safety analysis summaries. The following tables will be provided:

- An overall summary of the number and percentage of subjects who experience at least 1 TEAE, treatment-emergent SAE, TEAE leading to study drug withdrawal, and TEAE leading to death will be presented. The number of TEAEs, which will be counted by cases reported, will also be presented.
- TEAEs overall and by System Organ Class and PT, presenting the number and percentage of subjects with TEAEs by System Organ Class and PT. In the summary table, System Organ Class and PT within System Organ Class will be sorted by decreasing frequency. Subjects will be

[redacted]

counted only once in the number of subjects for this PT and only once for the number of subjects for the System Organ class to which this PT belongs (if multiple occurrences of the same System Organ Class or PT are recorded).

- Serious TEAEs, Treatment-related TEAEs, treatment-related serious TEAEs, nonserious TEAEs, TEAEs leading to study treatment withdrawal, and TEAEs leading to death will be summarized in similar way.
- TEAEs by maximum severity, overall, and by System Organ Class and PT, presenting the number and percentage of subjects with TEAEs by System Organ Class, PT, and maximum severity. If multiple TEAEs of the same PT occur within a subject, only the maximum severity observed for this PT with a System Organ Class will be used in summary of TEAEs by maximum severity, missing severity will be assumed as “severe”.. Severity will be classified into 3 categories: mild, moderate, and severe.

11.3. Laboratory Evaluations

Clinical laboratory tests will be performed at prespecified time points per the Time and Events Schedule in Appendix 1 of the protocol.

Routine hematology, blood chemistry, and urinalysis parameters that will be assessed are presented in Table 11-1.

[redacted]

Table 11-1 Routine Laboratory Tests

Category	Evaluation Parameters	
Hematology tests	Hematocrit Hemoglobin Platelet count	White blood cell count Differential white blood cell count
Blood chemistry tests	Aspartate aminotransferase Alanine aminotransferase Gamma glutamyltransferase Alkaline phosphatase Direct* and total bilirubin Indirect bilirubin* Total protein Albumin	C-reactive protein Blood urea nitrogen Serum creatinine Blood glucose Uric acid Electrolytes (sodium, potassium, chloride, calcium, magnesium, and bicarbonate)
Urinalysis	Microscopic analysis Protein Glucose Bilirubin	Urobilinogen Occult blood Leukocyte esterase

* If clinically indicated

Estimated GFR (eGFR) will be measured as noted below at Screening and predose if more than 24 hours after Screening) for subjects in the single-dose phase. In the multiple-dose phase, eGFR will be estimated at Screening and daily during treatment, if clinically indicated. Dose adjustments will be made following the recommendations in Table 3-4.

Estimated GFR

For ages ≥ 3 months to < 1 year, the eGFR will be based on the Schwartz equation (1984)[2]:

$$eGFR = 0.45 \times (height/Scr), \text{ if height is expressed in centimeters}$$

For ages ≥ 1 year to < 18 years, the eGFR will be based on the modified Bedside

Schwartz equation (2009)

$$eGFR = 0.413 \times (height/Scr), \text{ if height is expressed in centimeters}$$

OR

$$41.3 \times (height/Scr), \text{ if height is expressed in meters}$$

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2

[redacted]

Scr (standardized serum creatinine) = mg/dL

A list of the reference ranges for all clinical laboratory tests conducted will be provided by the study site prior to initiation of the study and updated by the study site if changes to the reference ranges are implemented during the study conduct.

The investigator or subinvestigator will assess whether any abnormal changes from Screening (within 48 hours prior to the administration of the first dose of cefiderocol) are clinically significant.

Laboratory test results will be assigned a Low/Normal/High (LNH) classification according to whether the value is below (L: low), within (N: normal), or above (H: high) the laboratory parameter's normal range; categorical laboratory test results will be classified as normal (N) or abnormal (A).

Summary statistics for laboratory test data (hematology, blood chemistry, and other specialized tests) will be presented for each scheduled time point measured after the first infusion and for the change from baseline to each time point. All clinical laboratory summaries other than specialized tests will be based on the local laboratory measurements, and only the data that can be converted into standard units will be included in analysis. The number and percentage of subjects with the following prespecified outlier category listed in Table 11-2 below at each postbaseline visit, including unscheduled visits, will be presented by cohort.

Table 11-2 The Outlier for Each Parameter in Laboratory Test

Parameter (Unit)	**Outlier Category**
Hemoglobin (g/dL)	Decrease from baseline ≥ 1.5 g/dL
Platelet count (10^3/μL)	Decrease from baseline ≥ 25% and value < LLN
	Increase from baseline ≥ 100% and value > ULN
White blood cell count (10^3/μL)	Decrease from baseline ≥ 50% and value < LLN
	Increase from baseline ≥ 20% and value > ULN
ALT (U/L)	Value > 3 × ULN
	Value > 5 × ULN
	Value > 10 × ULN
	Value > 20 × ULN
AST (U/L)	Value > 3 × ULN
	Value > 5 × ULN
	Value > 10 × ULN
	Value > 20 × ULN
AST (U/L) or ALT (U/L)	Value > 3 × ULN
	Value > 5 × ULN
	Value > 10 × ULN
	Value > 20 × ULN
Total bilirubin (mg/dL)	Value > 2 × ULN
	Increase from baseline ≥ 50% and value > ULN
Blood urea nitrogen (mg/dL)	Increase from baseline ≥ 50% and value > ULN
Serum creatinine (mg/dL)	Increase from baseline ≥ 0.3 mg/dL
ALP (U/L)	Increase from baseline ≥ 50% and value > ULN
AST (U/L) or ALT (U/L) + total bilirubin (mg/dL)	(AST > 3 × ULN or ALT > 3 × ULN) and (total bilirubin > 2 × ULN)

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; LLN = lower limit of normal; UN = upper limit of normal

[redacted]

Baseline will be the last value obtained prior to study drug administration within each respective phase of the study.

The eGFR and microbiology data (urine and blood collection of microbiological cultures) will be listed.

The urine pregnancy test will be performed for sexually active females of childbearing potential only. The pregnancy test results will be listed.

All serum chemistry, hematology, and urinalysis results in international standard units will be presented in data listings, with any abnormal findings appropriately flagged.

11.4. Vital Signs

Vital sign measurements will include blood pressure (systolic and diastolic), pulse rate, respiratory rate, and body temperature.

Summary statistics for vital sign measurements will be presented for each scheduled time point and for the change from baseline to each time point. Baseline will be the last value obtained prior to study drug administration within each respective study part.

Vital signs data will be listed chronologically by subject and time points.

11.5. Physical Examinations

All physical examination data will be listed by subject and summarized by cohort.

[redacted]

12. Changes from Analyses Planned in Protocol

There were no changes from the analyses planned in the protocol.

[redacted]

13. Programming Considerations

All statistical computations and construction of TLFs will be performed using SAS® for Windows Release 9.4 (SAS® Institute Inc., Cary, NC, USA).

The format of the table shells will be followed as closely as possible; however, in the course of programming and familiarization with the database, some changes may become necessary. All changes will be documented. Major changes will be documented through a formal amendment to this document.

The below programming considerations will be followed unless already specified in the above text.

13.1. General Considerations

- One SAS program can create several outputs.
- One output file can contain several outputs.
- Output files will be delivered in Word format. TLFs will be bundled separately with a table of contents for each.
- Numbering of TLFs will follow International Conference on Harmonisation (ICH) E3 guidance

13.2. Table, Listing, and Figure Format

13.2.1. General

- All TLFs will be produced in landscape format on American letter size, unless otherwise specified.
- All TLFs will be produced using the Times New Roman, size 9, which is the smallest acceptable point size for the regulatory authorities.
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides
- Headers and footers for figures will be in Times New Roman font, size 9.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as nonprintable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (eg, μ). Certain subscripts and superscripts (eg, cm2) will be employed on a case-by-case basis.

[redacted]

- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- No headers will be used.

13.2.3. Display Titles

- All output will have the following study name at the top left of each page:
- All output will have Page n of N at the top right corner of each page. TLFs will be internally paginated in relation to the total length (the page number will appear sequentially as page n of N, where N is the total number of pages in the table).
- Each TLF will be identified by the designation and a numeral. (ie, Table 14.1.1). A decimal system (x.y and x.y.z) will be used to identify TLFs with related contents. The title will be left justified. The analysis set will be identified on the line immediately following the title. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Shionogi, Protocol 1802R2135 XX of XX
Table x.y.z Line of Title
ITT Analysis Set

13.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable).
- For numeric variables, “unit” will be included in the column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N = xx) (or in the row headings, if applicable). This will be distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be cefiderocol first and then SOC followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. *General Conventions*

Data in columns of a table or listing will be formatted as follows:

- Alphanumeric values will be left justified.

[redacted]

- Whole numbers (eg, counts) will be right justified.
- Numbers containing fractional portions will be decimal aligned.

13.2.5.2. *Table Conventions*

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category will be presented in the table, even if n = 0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity will appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented, so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (eg, Medical History, Reasons for Discontinuation from the Study, etc), then only those categories for which there is at least 1 subject represented in 1 or more groups will be included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original value, and standard deviations will be printed out to 1 more significant digit than the original value. The minimum and maximum should report the same significant digits as the original values. For PK analysis, 3 significant digits will be used. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.X
Median	XXX.X
Minimum	XXX
Maximum	XXX

- Percentage values will be printed to 1 decimal place, in parentheses with no spaces, 1 space after the count, eg, 7 (12.8%), 13 (5.4%). This will also apply to confidence intervals. Values that round down to 0.0 will be displayed as “< 0.1”, or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment

[redacted]

group who have an observation will be the denominator. Percentages after zero counts will not be displayed, and percentages equating to 100% will be presented as 100%, without decimal places.

- Tabular displays of data for medical history, prior/concomitant medications, and adverse events will be presented by body system, treatment class, or System Organ Class with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and System Organ Class, medical history (by PT), drugs, and adverse events (by PT) will be displayed in decreasing order. If the incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values that cannot be estimated will be reported as "-".

- The percentage of subjects will normally be calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, the denominator will be selected after careful consideration of the appropriate number of subjects exposed. The details of this will be described in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than 1 category, a footnote or programming note will describe if the subject is included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as System Organ Class) has to be split over more than 1 page, the subheading will be followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading will only be output on the first relevant page.

13.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data will be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates will be printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as "N/A", unless otherwise specified.

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (eg, 11:26:45, or 11:26).

- Units will be included where available.

13.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (eg, treatment mean change from Baseline) values will be displayed on the Y-axis.

[redacted]

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with informational footnotes, and then reference footnotes listed as a, b, c, etc, if a reference footnote. Each new footnote will start on a new line, where possible.
- Subject-specific footnotes will be avoided, where possible.
- Footnotes will be used sparingly and to add value to the TLFs. If more than 6 lines of footnotes are needed, then a cover page will be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (ie, 'Program : myprogram.sas Listing source: 16.x.y.z').

[redacted]

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, and statistical analyses. An overview of the development of program is detailed in [redacted] Standard Operating Procedure (SOP) Developing Statistical Programs (3907) .

[redacted] SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic and efficiency and by review of the produced output.

[redacted]

15. Index of Tables

[redacted]

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Shionogi 1802R2135 SAP v1.5

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