CLINICAL STUDY PROTOCOL: 1802R2135

Study 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
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EudraCT Number:	2019-002120-32
Study Phase:	2
Product Code Number:	Cefiderocol (S-649266)
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* The study sponsor may be 1 or more of the above companies. Throughout the protocol, the term "sponsor" represents the various legal entities identified in the "Sponsor List of the Study Administrative Structure" in the protocol. The above companies are referred to as Shionogi.

SYNOPSIS

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

Study Number: 1802R2135

Study Phase: 2

Primary Objectives:

- 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 pharmacokinetics (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

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).

Exploratory Objectives:

- To estimate the probability of target attainment (PTA) for the 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

Study Design:

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 (including but not limited to complicated urinary tract infection [cUTI], complicated intra-abdominal infection [cIAI], hospital-acquired pneumonia [HAP]/ventilator-acquired pneumonia [VAP], and sepsis or bloodstream infections [BSI]) 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 age range (Table S-1).

Table S-1 Cohort Description

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

The single-dose phase in all 4 cohorts will confirm cefiderocol exposures in at least 6 subjects prior to conducting a multiple-dose phase (Cohorts 2, 3, and 4) in additional subjects.

Enrollment will be stopped for the applicable cohort to allow for analysis of the PK data prior to moving from single-dose to multiple-dose in Cohorts 2, 3, and 4.

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

Screening will occur within 4 days prior to Treatment Day 1 or on Treatment Day 1 in both the single- and multiple-dose phase. Prior to Screening, sites will be asked to send a Permission to Screen Form containing limited information of the potential subject to Shionogi medical monitors for evaluation and agreement. The purpose of this form is to check the eligibility of subjects being enrolled into the study.

In the single-dose phase, cefiderocol will be administered (in addition to 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. Subjects will subsequently receive cefiderocol every 8 hours (q8h) for an expected 5 to 14 days; 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 single-dose phase will include only those subjects with normal renal function or mild renal impairment. The dose of cefiderocol for the single-dose phase will be determined based on body weight only; the maximum dose to be administered is not to exceed 2000 mg. The dose for the multiple-dose phase will be determined based on both body weight and renal function; the maximum dose to be administered is not to exceed 2000 mg. 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 may 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 for the multiple-dose phase, which is analogous to a Test of Cure time point and EOS if microbiological samples are available. The EOS visit will occur 28 (+ 7) days after administration of cefiderocol in the single-dose phase or 28 (+ 7) days 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 total duration of cefiderocol administration will be determined by the investigator based on clinical assessment of each subject's infection status but should be expected (at time of enrollment) to be 5 to 14 days. Note: a minimum of 6 doses will be permissible if, in the opinion of the investigator, it is in the subject's best interest. The dose of cefiderocol administered to each subject will be determined by the investigator based on dosing recommendations.

Blood samples for determination of plasma cefiderocol concentrations will be collected from each subject at prespecified time points during and/or after the cefiderocol infusion for both the single- and multiple-dose phase. Cefiderocol PK will be determined in all 6 subjects in the single-dose phase in Cohorts 1, 2, 3, and 4; cefiderocol dose recommendations may be revised by the sponsor prior to initiating enrollment of subjects in the multiple-dose phase of each respective cohort (for Cohorts 2, 3, and 4 only).

Study Population:

Hospitalized paediatric subjects 3 months to < 18 years of age with a suspected or confirmed infection (including but not limited to cUTI, cIAI, HAP/VAP, sepsis, or BSI) caused by a suspected or confirmed aerobic Gram-negative pathogen.

If the subject's infection is confirmed to be Gram-negative only before starting treatment, monotherapy with cefiderocol may be allowed.

Criteria for Inclusion and Exclusion

General Inclusion Criteria

Subjects who fulfill the following criteria will be included in the study.

1. Subject's parent(s) or legally authorized representative (LAR) provides written informed consent in accordance with regional and country-specific laws and regulations.
2. Subject provides written informed assent, when feasible (age of assent to be determined by institutional review boards/independent ethics committees [IRB's/IEC's] or be consistent with local legal requirements).
3. Hospitalized subject is 3 months to < 18 years of age at the time written informed consent/assent is obtained for the single-dose phase. Hospitalized subject is 3 months to < 12 years of age at the time written informed consent/assent is obtained for the multiple-dose phase. Premature babies will not be restricted, but the subject must have an adjusted or postnatal age of 3 months.
4. Subject has a suspected or confirmed infection (including but not limited to cUTI, cIAI, HAP/VAP, sepsis, or BSI) that requires hospitalization for treatment with IV antibiotics.
5. If subject is a sexually active female of childbearing potential and has reached menarche or Tanner stage 3, subject agrees to use barrier contraception (including condom, diaphragm, or cervical cap) with spermicide or agrees to use a highly effective method of contraception (including contraceptive implant, injectable contraceptive, combination oral contraceptive, or an intrauterine [IUD] contraceptive device) from Screening up to 28 days after administration of the last dose of cefiderocol.

General Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Subject has a documented history of any hypersensitivity or allergic reaction to any β-lactam antibiotic (Note: for β-lactams, a history of a mild rash followed by uneventful re-exposure is not a contraindication to enrollment).
2. Multiple-dose only: Subject has an infection caused only by a confirmed Gram-positive pathogen.
3. Subject has a suspected or confirmed central nervous system (CNS) infection (eg, meningitis, brain abscess, shunt infection) or osteomyelitis (which would require prolonged antibiotic therapy).
4. Subject has cystic fibrosis.
5. Single-dose phase: Subject has moderate or severe renal impairment based on estimated glomerular filtration rate (eGFR) (based on Schwartz equation [10] if ≥ 3 months to < 1 year of age and modified Bedside Schwartz equation [11] if ≥ 1 to < 18 years of age) of < 60 mL/min/1.73 m^2 at Screening.
   Multiple-dose phase: Subject has an eGFR (based on Schwartz equation [10] if ≥ 3 months to < 1 year of age and modified Bedside Schwartz equation [11] if ≥ 1 to < 18 years of age) of < 15 mL/min/1.73 m^2 at Screening.
   See Section 7.5.3.1.2 for eGFR calculations and ranges.

6. Subject has end-stage renal disease (ESRD), is on hemodialysis (HD), or receiving continuous venovenous hemofiltration (CVVH)
7. Subject has experienced shock in the prior month or is in shock at the time of Screening.
8. Subject has severe neutropenia or is severely immunocompromised
9. Subject has multiorgan failure
10. Subject has a life expectancy of < 30 days due to severity of a concurrent illness
11. Subject is a female who has a positive pregnancy test at Screening
12. Subject is a female who is breastfeeding
13. Subject has received any other investigational medicinal product (IMP) within 30 days
14. Subject has any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the study data including acute trauma to the pelvis or urinary tract
15. Subject is receiving vasopressor therapy at Screening.

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

A cUTI is defined as a clinical syndrome characterized by pyuria and a microbial pathogen in the urine in the context of the following underlying features: recurrent urinary tract infections (2 or more in a 12-month period); obstructive uropathy; a functional or anatomical abnormality of the urinary tract, including anatomical malformations or neurogenic bladder; vesicoureteric reflux; urinary tract catheterization; an invasive urogenital procedure, such as cystoscopy or urogenital surgery; or azotemia caused by intrinsic renal disease. In addition, pediatric subjects should have at least 2 of the following signs and symptoms depending on their age:

For subjects < 2 years of age
Fever defined as body temperature ≥ 38.0°C, failure to thrive, recent weight loss, irritability, poor feeding, lack of normal level of activity, abdominal pain/tenderness on physical examination, vomiting, or jaundice

For subjects ≥ 2 to < 18 years
Fever defined as body temperature ≥ 38.0°C, chills or rigors, dysuria, urinary urgency, urinary frequency, new-onset urinary incontinence, suprapubic pain, flank pain, abdominal pain, pelvic pain, suprapubic tenderness or costovertebral angle tenderness on physical examination, nausea, or vomiting

Hospital-acquired pneumonia is defined as an acute infection of the pulmonary parenchyma associated with clinical signs and symptoms, such as fever or hypothermia, chills, rigors, cough, purulent sputum production, chest pain, or dyspnea, accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient hospitalized for more than 48 hours or developing within 7 days after discharge from a hospital. Patients with HAP may or may not require intubation and mechanical ventilation.

Ventilator-associated pneumonia is defined as an acute infection of the pulmonary parenchyma associated with clinical signs and symptoms, such as fever or hypothermia, chills, rigors, purulent respiratory secretions, and increased oxygen requirements. These signs and symptoms are in addition to laboratory abnormalities, such as leukocytosis accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient on mechanical ventilation for a minimum of 48 hours.

Study Drug, Dose, and Mode of Administration

Cefiderocol will be administered IV over 3 hours (Note: 3 hours is the required duration to ensure adequate time over MIC for multidrug-resistant Gram-negative infections). Shorter infusion times may be allowed in the multiple-dose phase if agreed on by the sponsor via the Request for Shortened Infusion Duration Form and if in the best interest of the subject. Infusion time must be 3 hours in the single-dose phase. The single-dose phase will include only those subjects with normal renal function or mild renal impairment. The dose of cefiderocol for the single-dose phase will be determined based on body weight only; the maximum dose to be administered is not to exceed 2000 mg (Table S-2). The dose for the multiple-dose phase will be determined based on both body weight and renal function; the maximum dose to be administered is not to exceed 2000 mg (Table S-3). Sites will be instructed to monitor renal function as per their routine practice/guidelines and to change doses immediately if renal function changes. The dose will be modified for subjects with moderate or severe renal impairment (Table S-4). All revised dosing recommendations will be provided by the sponsor, discussed with the investigator, and documented.

Table S-2 Dosing Limits for Cefiderocol in Single-dose Phase: Subjects with Normal Renal Function or Mild Renal Impairment

Cohort	Single-dose Phase Dose		Infusion Time
	Body Weight		
	≥ 34 kg	< 34 kg	
1 (12 to < 18 years of age)	2000 mg	60 mg/kg*	3 hours
2 (6 to < 12 years of age)	2000 mg	60 mg/kg*	3 hours
3 (2 to < 6 years of age)	2000 mg	60 mg/kg*	3 hours
4 (3 months to < 2 years of age)	2000 mg	60 mg/kg*	3 hours

* **No more than 2000 mg of cefiderocol should be administered.**

The single-dose phase will include only those subjects with normal renal function (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m^2) or mild renal impairment (eGFR 60 to < 90 mL/min/1.73 m^2). See Section 7.5.3.1.2 for eGFR calculations and ranges.

Table S-3 Dosing Limits for Cefiderocol in Multiple-dose Phase: Subjects with Normal Renal Function or Mild Renal Impairment

Cohort	Multiple-dose Phase Dose		Frequency	Infusion Time
	Body Weight			
	≥ 34 kg	< 34 kg		
1 (12 to < 18 years of age)	Cohort 1 not applicable in multiple-dose phase			
2 (6 to < 12 years of age)	2000 mg	60 mg/kg*	q8h	3 hours
3 (2 to < 6 years of age)	2000 mg	60 mg/kg*	q8h	3 hours
4 (3 months to < 2 years of age)	2000 mg	60 mg/kg*	q8h	3 hours

q8h = every 8 hours

* **No more than 2000 mg of cefiderocol should be administered.**

Shorter infusion times may be allowed in the multiple-dose phase if agreed by the sponsor via the Request for Shortened Infusion Duration Form, and if in the best interest of the subject. Infusion volume adjustments by age and weight will be provided in the pharmacy manual.

See Section 7.5.3.1.2 for estimated glomerular filtration rate calculations and ranges.

Table S-4 Dosing Limits for Cefiderocol in Multiple-dose Phase: Subjects with Moderate or Severe Renal Impairment

Renal Function	Multiple-dose Phase Dose					
	Body Weight ≥ 34 kg			Body Weight < 34 kg		
	Dose (mg)	Frequency	Infusion Time	Dose (mg/kg)	Frequency	Infusion Time
Moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m^2)	1500	q8h	3 hours	45	q8h	3 hours
Severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2)	1000	q8h	3 hours	30	q8h	3 hours

eGFR = estimated glomerular filtration rate; q8h = every 8 hours

Shorter infusion times may be allowed in the multiple-dose phase if agreed by the sponsor via the Request for Shortened Infusion Duration Form, and if in the best interest of the subject. Infusion volume adjustments by age and weight will be provided in the pharmacy manual.

Expected total duration of cefiderocol administration is 5 to 14 days. A minimum of 6 doses will be permissible if, in the opinion of the investigator, it is in the subject's best interest.

Duration of Treatment:

Single-dose phase: 1 day

Multiple-dose phase: expected 5 to 4 days (a minimum of 6 doses will be permissible if, in the opinion of the investigator, it is in the subject's best interest). In special circumstances, treatment beyond 14 days may be allowed following review and approval of individual cases by the Shionogi medical monitor.

Safety Assessments: Safety assessments including physical examinations, vital sign measurements, and clinical laboratory tests will be performed at prespecified time points prior to, during, and after administration of study treatment. Additionally, safety data will be captured at various time points during the study as part of routine patient care.

Adverse events (AEs) will be collected and monitored from the time signed informed consent/assent is obtained through the end of study (EOS) visit or 28 (+ 7) days after the single dose of cefiderocol in the single-dose phase or 28 (+ 7) days after administration of the last dose of study treatment in the multiple-dose phase. Subjects with ongoing AEs will be monitored until either resolution or stabilization is achieved, the subject is referred for continued care to another health care professional, or until a determination of the cause being unrelated to the study drug or procedure is made or the subject is lost to follow-up. Investigator causality must be included with all SAEs reported to the sponsor. Serious AEs with missing investigator causality will be followed up by the CRO urgently until a response is provided to the sponsor.

Pharmacokinetic Assessments: Blood samples for determination of plasma cefiderocol concentrations will be collected from each subject at prespecified based time points during and/or after the cefiderocol infusion (after dosing of cefiderocol in the single-dose phase and during one of the dosing intervals from the 6^{th} to the 12^{th} dose of cefiderocol in the multiple-dose phase).

Efficacy Assessments (Multiple-dose Phase only):

Clinical Outcome: Clinical outcome assessments (signs and/or symptoms of infection eg, fever, irritability, pain, physical signs such as increased heart rate) will be performed at EOT (within 24 hours of administration of the last dose of study treatment or early termination), and at a Posttreatment visit 7 (± 4) days after EOT (multiple-dose phase) and at EOS (conducted on site or as a phone call). Additionally, any available clinical outcome data used for the initial diagnosis of infection and obtained at any time after initiation of study treatment (cefiderocol alone or administration with SOC) as part of routine patient care will be captured as study data.

Microbiological Outcome: If available, microbiological data (Gram stain, culture, colony forming units, or sensitivity results, and pathogen identification) for specimens collected at the initial diagnosis of infection and obtained at any time after initiation of study treatment as part of routine patient care will be captured as study data and used to assess microbiological outcome. The time points for collection of microbiological specimens are otherwise not prespecified by the protocol (EOT, Posttreatment Visit, and EOS, if applicable). In subjects where it is not possible to obtain a posttreatment culture and/or EOS culture, determination of presumed microbiological eradication may be made based on resolution of all presenting clinical sign and symptoms of the infection (clinical cure).

Statistical Methods:

Unless otherwise noted, continuous variables will be summarized by using the number of nonmissing observations (N), arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum values as summary statistics; categorical variables will be summarized by using the frequency count and the percentage of subjects in each category as summary statistics.

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

No inferential statistical testing will be performed in this study.

In general, all tables will be presented by cohort and treatment regimen (ie, single-dose or multiple-dose). Individual subject data, PK data, and any derived data will be presented by treatment group and listed by subject. All analyses and tabulations will be performed by using both the SAS Version 9.4 or higher and/or WinNonlin Version 6.2.1 or higher.

Analysis Populations

- **Safety population** includes all enrolled subjects who receive at least 1 dose of cefiderocol.
- **Pharmacokinetic Concentration population** includes all enrolled subjects who receive at least 1 dose of cefiderocol and have at least 1 PK blood sample.
- **Pharmacokinetic Concentration Summary population** includes all enrolled subjects who receive 1 dose of cefiderocol in the single-dose phase and ≥ 4 doses of cefiderocol in the multiple-dose phase of the study and those 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 the concentration-time data and the concentration data summary.
- **Intent-to-treat (ITT) population** includes all enrolled subjects who receive at least 1 dose of cefiderocol.
- **Microbiological ITT (MITT) population** includes all ITT subjects who have a baseline Gram-negative pathogen in the multiple-dose phase.

Study Duration: Screening can last up to 4 days for the single-dose and multiple-dose phases. Study duration for individual subjects is approximately 28 days in the single-dose phase and 42 days (or longer if treatment beyond 14 days is allowed by the Shionogi medical monitor) in the multiple-dose phase from the time of first drug infusion. Planned duration of the entire study is approximately 2 years and 9 months from first subject in to last subject last visit.

Date: XX Nov 2021

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$\%fT_{>MIC}$	percentage of time of the dosing interval that is required for plasma concentrations to be above the mean inhibitory concentration
$fT_{>MIC}$	time during which plasma concentrations are above the mean inhibitory concentration
AE	adverse event
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve extrapolated from time 0 to infinity
$AUC_{0\text{-}\tau}$	area under the concentration-time curve over the dosing interval τ
BLA	β-lactamase
BSI	bloodstream infection
CFU	colony forming units
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
cIAI	complicated intra-abdominal infection
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	carbapenem-resistant
CrCL	creatinine clearance level
CRO	clinical research organization
cUTI	complicated urinary tract infections
CV%	coefficient of variation
CVVH	continuous venovenous hemofiltration
DSMB	data safety monitoring board
ECG	electrocardiogram/electrocardiography
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ESBL	extended spectrum β-lactamase
ESRD	end-stage renal disease

EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMR	geometric least squares mean ratio
HAP	hospital-acquired pneumonia (synonymous with hospital-acquired bacterial pneumonia [HABP])
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HD	hemodialysis
HIPAA	Health Information Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IgM	immunoglobulin M
IEC	independent ethics committee
IMP	investigational medicinal product
IPM/CS	imipenem/cilastatin
IRB	institutional review board
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IV	intravenous(ly)
KPC	*Klebsiella pneumoniae* carbapenemase
LAR	legally authorized representative
Max	maximum
MDR	multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
Min	minimum
MITT	microbiological intent to treat
MRI	magnetic resonance imaging
NDM	New Delhi metallo-β-lactamase
NP	nosocomial pneumonia
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OXA	Class D oxacillinases
PBP	penicillin-binding protein

PD	pharmacodynamic
PDCO	The Paediatric Committee (EMA's scientific paediatric committee)
PER	*Pseudomonas* extended resistance
PK	pharmacokinetic(s)
PTA	probability of target attainment
q8h	every 8 hours
QA	quality assurance
QC	quality control
RR	reference range
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
SOP	standard operating procedure
$t_{1/2,z}$	apparent terminal elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TOC	test of cure
ULN	upper limit of normal
VAP	ventilator-acquired pneumonia (synonymous with ventilator-acquired bacterial pneumonia [VABP])
VIM	Verona integron-encoded metallo-β-lactamase
WHO	World Health Organization
XDR	extensively drug-resistant

GLOSSARY

Concomitant antibiotics	Any antibiotic used to treat an infection other than the qualifying Gran-negative infection
Concomitant therapy	Any therapy other than study treatment administered after the first dose of study treatment in the study
End of Study (EOS)	Defined as the last visit that occurs 28 (+ 7) days after administration of cefiderocol in the single-dose phase or 28 (+ 7) days after administration of the last dose of study treatment (cefiderocol and SOC combination, cefiderocol alone [if Gram-negative infection confirmed in multiple-dose phase], in the multiple-dose phase; this visit may be performed on-site or via phone call
End of Treatment (EOT)	Defined as within 24 hours after single dose 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.
Standard of Care (SOC) antibiotic	Any antibiotic used to treat the qualifying Gram-negative infection
Study drug	Refers to cefiderocol
Study treatment	Refers to cefiderocol and SOC combination, cefiderocol alone (if the infection is confirmed to be caused by a Gram-negative pathogen only prior to starting treatment in the multiple-dose phase)

1. INTRODUCTION

The ability to treat bacterial infections due to multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacilli, including Enterobacteriaceae and the nonfermenters, *Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* and *Acinetobacter baumannii*, is a critical and growing unmet medical need. In particular, the emergence of resistance to carbapenems in Gram-negative bacteria, including Enterobacteriaceae, *Pseudomonas,* and *Acinetobacter* species, over the last decade has become a major concern worldwide, because of its rapid spread and the lack of development of new antimicrobial drugs effective in this area [1].

Since the description of a metallo-β-lactamase (BLA), imipenemase-1, in *P. aeruginosa*, a serine carbapenemase, oxacillinase-23, in *A. baumannii*, and a serine carbapenemase, *Klebsiella pneumoniae* carbapenemase-1 (KPC-1), in *K. pneumoniae,* carbapenemase-encoding genes have spread worldwide and are now distributed throughout different species of Gram-negative MDR bacteria, which are now responsible for a large and increasing number of nosocomial infections. These carbapenemases inhibit almost all β-lactam antibiotics, including carbapenems, and are now reported mainly in Enterobacteriaceae, *A. baumannii*, and *P. aeruginosa* [1].

Although most reports of β-lactam resistance focus on hydrolyzing enzymes, 2 other mechanisms of resistance are important when considering the overall phenotype of Gram-negative resistance among the β-lactam classes and other classes of antibiotics. These include porin channel mutants (entrance channels for antibiotics and important bacterial nutrients) and efflux pumps (exit channels with active excretion mechanisms for removal of antibiotics from the bacterial cells), which are particularly prevalent among extensively drug-resistant *P. aeruginosa* [2, 3]. Not infrequently, several β-lactam resistance mechanisms exist in the same bacterial strain.

In 2011, Nordmann et al observed that carbapenemases had been reported increasingly in Enterobacteriaceae during the previous 10 years and that their spread across the world was of great concern. They concluded that society was now at the edge of 2 concomitant epidemics of carbapenemase-producers worldwide; the first to be caused mainly by carbapenemase-producing *Escherichia coli* as a source of community-acquired infections, and the second, to likely be caused mainly by nosocomial carbapenemase-producing *K. pneumoniae* of all types [4].

The outcome of a carbapenem-resistant infection can often be fatal. Falagas et al calculated that 26% to 44% of deaths in 7 studies were attributable to carbapenem resistance. A pooled analysis of 9 studies showed that the death rate was higher among those subjects infected with carbapenem-resistant Enterobacteriaceae than those infected with carbapenem-susceptible Enterobacteriaceae (reference range [RR] 2.05, 95% confidence interval [CI] 1.56 to 2.69) [5].

As with any other antibiotics of the β-lactam class, cefiderocol acts by binding to penicillin-binding proteins (PBPs), which allows the β-lactam structure to form a covalent bond with the serine residue at the catalytic active site of the PBP, thereby

irreversibly inhibiting the transpeptidase activity responsible for cross-linking peptidoglycan from lipid precursors essential for bacterial cell wall synthesis. However, the molecular structure of cefiderocol offers several unique and important characteristics that result in enhanced activity against resistant Gram-negative bacteria. The chemical structure of cefiderocol is similar to ceftazidime and cefepime, which are third- to fourth-generation cephalosporins with a feature of the good activity against Gram-negative bacteria due to their high stability to a variety of beta-lactamases including AmpC and extended-spectrum beta-lactamases (ESBL). Cefiderocol has a pyrrolidinium group in the side chain at position 3 of the cephem core similar to cefepime and a carboxypropanoxyimino group in the side chain at position 7 similar to ceftazidime. The major difference in the chemical structure of cefiderocol and these cephalosporins (ceftazidime and cefepime) is the presence of a catechol group on the side chain at position 3 of the cephem core. Importantly, in addition to passive diffusion through porin channels, the catechol moiety forms chelating complexes with trivalent (ferric) iron in plasma, resulting in the ability of cefiderocol to act as a siderophore and to be transported across the outer cell membrane of Gram-negative bacteria by the active iron transport system common to Gram-negative bacteria.

As a result, cefiderocol overcomes 2 additional mechanisms of antibiotic resistance resulting from porin channel mutations or efflux-pump overproduction. Therefore, cefiderocol is the first β-lactam antibiotic that is associated with enhanced stability to hydrolysis by all known classes of BLAs, including serine-carbapenemases (Class A [eg, KPC] and Class D oxacillinases [OXA]) and metallo-carbapenemases (Class B [New Delhi metallo-β-lactamase [NDM], verona integron-encoded metallo-β-lactamase [VIM], and imipenemase), and because of the unique mechanism of cell entry, cefiderocol is associated with enhanced antibacterial activity against Gram-negative bacteria, including carbapenem-resistant strains.

Cefiderocol is being developed to address the unmet medical need to treat carbapenem-resistant infections caused by Gram-negative bacteria, namely, the treatment of infections caused by carbapenem-resistant, Gram-negative bacteria, including Enterobacteriaceae, such as *E. coli* and *K. pneumoniae*, and nonfermenters, such as *P. aeruginosa*, *S. maltophilia*, and *A. baumannii*, independent of the underlying mechanism of carbapenem resistance.

1.1 Nonclinical Summary

See the current Investigator's Brochure (IB) for a summary of nonclinical studies.

1.2 Clinical Pharmacology Studies

To date, a total of 212 healthy adult subjects or subjects with impaired renal function who participated in 6 completed clinical pharmacology studies (a single-and multiple-ascending dose study [Study 1203R2111], an intrapulmonary pharmacokinetic (PK) study [Study 1214R2112], a renal impairment study [Study 1222R2113], a mass balance study [Study 1516R2114], a thorough QT/QTc study [Study 1603R2116], and a 3-part drug interaction study [Study 1521R2115]) have received single doses of cefiderocol ranging

from 100 to 4000 mg (4 g) or multiple doses of up to 2000 mg (2 g) for up to 10 days, infused intravenously (IV) over 1 or 3 hours.

In general, cefiderocol was safe and well tolerated in clinical pharmacology studies. There were no treatment-related or dose-dependent trends in vital sign measurements, electrocardiogram (ECG) parameters, or clinical laboratory test results. There were no deaths or serious adverse events (SAEs) reported in any study. Adverse events (AEs) occurred relatively infrequently and were mostly mild in severity, and almost all resolved spontaneously without intervention. There were no dose-dependent trends in the frequency or type of AEs reported.

Cefiderocol is associated with linear PK, has a relatively short apparent terminal half-life ($t_{1/2,z}$), and is primarily excreted unchanged in the urine. A summary of the PK profile for cefiderocol is provided; additional details are provided in the current version of the IB.

- After administration of a single 2000-mg dose of cefiderocol infused over 3 hours, the geometric mean and coefficient of variation (CV% of geometric mean) of cefiderocol maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) extrapolated to infinity (AUC_{0-inf}) were 89.7 µg/mL (20.5%) and 386.1 µg·hr/mL (17.2%), respectively. The C_{max} and AUC increased in a dose-proportional manner within the dose range from 100 to 2000 mg and 2000 to 4000 mg.
- After administration of 1000- and 2000-mg doses of cefiderocol every 8 hours (q8h), no accumulation for the C_{max} (ratio of C_{max} [Day 10/Day 1]: 1.07 to 1.08-fold) or AUC over the dosing interval τ ($AUC_{0-\tau}$) (ratio of $AUC_{0-\tau}$ [Day 10/Day 1]: 1.05 to 1.16-fold) was observed. Steady state was attained within 1 day after the start of multiple dose administration.
- After administration of a single 1000-mg dose of [^{14}C]-cefiderocol infused over 1 hour, the majority of total radioactivity in plasma was accounted for intact drug. Additionally, 98.6% and 2.8% of the administered dose was excreted in urine and feces, respectively, with an overall recovery of total radioactivity (urine and feces combined) of 101.4% of the administered dose. More than 90% of the dose was excreted as unchanged cefiderocol in urine.
- After administration of a single 2000-mg dose of cefiderocol infused over 3 hours, the apparent terminal elimination half-life ($t_{1/2,z}$) of cefiderocol was 2.4 hours. A similar $t_{1/2,z}$ of 2.74 hours was estimated after administration of a single 2000-mg dose of cefiderocol infused over 1 hour (Study 1203R2111).
- Cefiderocol did not increase the C_{max} or AUC of furosemide (for OAT1 and OAT3) and metformin (for OCT1, OCT2, and MATE2-K). Cefiderocol increased the C_{max} and AUC of rosuvastatin (for OATP1B3) by 1.28-fold (90% CI, 1.12 to 1.46) and 1.21-fold (1.08 to 1.35), respectively (Study 1521R2115). These results suggest no clinically significant drug-drug interaction potential via these transporters.

- There was no clinically meaningful effect of age, sex, race, or body weight on the PK of cefiderocol based on a population PK analysis. No dose adjustment of cefiderocol based on demographic characteristics is considered to be necessary.
- A dedicated study to assess the potential effect of hepatic impairment on the PK of cefiderocol was not conducted. However, the need for a dose adjustment in subjects with hepatic impairment is not expected considering the primary route of elimination for cefiderocol is renal excretion.
- After administration of a single 1000-mg dose of cefiderocol infused over 1 hour, the geometric least squares mean ratios (GMRs) [renal impairment/normal renal function] and their 90% CIs for the $AUC_{0\text{-}inf}$ of cefiderocol for subjects with mild, moderate, severe and end-stage renal disease (ESRD) requiring hemodialysis (HD) were 1.0 (0.8 to 1.3), 1.5 (1.2 to 1.9), 2.5 (2.0 to 3.3), and 4.1 (3.3 to 5.2), respectively. Dose adjustment of cefiderocol in subjects with renal impairment or augmented renal clearance is recommended.
- The 3- to 4-hour HD removed approximately 60% of cefiderocol dose. A supplemental dose immediately following HD is therefore recommended.
- In a thorough QT/QTc study (Study 1603R2116), after administration of single 2-g (therapeutic) and 4-g (supra-therapeutic) doses, cefiderocol did not prolong the QT interval to a level of regulatory concern and met the criteria stipulated in the FDA E14 Guidance for Industry [6] associated with a negative thorough QT/QTc study.

Phase 2 and 3 Studies

A Phase 2 study (Study 1409R2121) in patients with complicated urinary tract infections (cUTI), with or without pyelonephritis or acute uncomplicated pyelonephritis, to assess the composite outcome of clinical response and microbiologic eradication of cefiderocol compared with IPM/CS in subjects at risk for MDR Gram-negative pathogens has been conducted. Subjects with infections due to known carbapenem-resistant (CR) pathogens were excluded from participation in the study. The study was a multicenter, randomized, double-blind, active-controlled, parallel-group study in which a total of 452 hospitalized subjects were randomized (2:1) to receive IV cefiderocol 2000 mg or IPM/CS 1000 mg administered over 1 hour, 3 times daily at 8-hour intervals for 7 to 14 days. Subjects were evaluated daily for clinical response and safety during hospitalization and periodically during follow-up for up to approximately 42 days from the time of randomization. The recommended duration of treatment with IV study antibiotics was 7 to 14 days. If in the opinion of the investigator it became in the subject's best interest, then treatment could have been stopped after a minimum of 5 days. Safety assessments included AE monitoring, clinical laboratory safety tests (hematology, chemistry, endocrinology, and urinalysis), vital sign measurements, physical examinations, and 12-lead ECG recordings. The safety population consisted of all randomized subjects who received at least 1 actual dose of the study drug (448 subjects; 300 in the cefiderocol treatment group and 148 in the IPM/CS group).

The response rate for the primary endpoint of the composite of microbiological eradication and clinical response at Test of Cure (TOC) for cefiderocol was not only

noninferior to IPM/CS (72.6% versus 54.6% of subjects in the cefiderocol and IPM/CS groups, respectively, with an adjusted treatment difference [cefiderocol - IPM/CS] of 18.58% [95% CI; 8.23%, 28.92%], based on the prespecified noninferiority margins of -20% and −15%), but also was consistent with superiority.

The most frequently observed AE was diarrhea, which was reported by 4.3% (13/300 subjects) in the cefiderocol treatment group and 6.1% (9/148 subjects) in the IPM/CS group. Serious AEs were reported in 4.7% (14/300 subjects) in the cefiderocol group compared with 8.1% (12/148 subjects) in the IPM/CS group. One death (cardiorespiratory arrest, considered unrelated to study drug) was reported in a subject treated with cefiderocol. The ECG analysis did not demonstrate a significant effect of study drug on QTcF duration or other ECG parameters.

Cefiderocol was generally well tolerated, with more than 90% of subjects completing treatment (similar to those in the IPM/CS group). Overall AE rates were generally similar between the 2 treatment groups (40.7% [122/300] of subjects in the cefiderocol group compared with 51.4% [76/148] of subjects in the IPM/CS group. The observed safety profile of cefiderocol is as expected for a β-lactam antibiotic, and no unexpected safety concerns were identified.

A pathogen-based Phase 3 study in subjects with evidence of CR, Gram-negative infections at various infection sites (CREDIBLE-CR, Study 1424R2131) and a Phase 3 study in subjects with nosocomial pneumonia (NP; APEK-NP, Study 1615R2132) were completed. In the CREDIBLE study, the primary endpoints of the study showed that clinical and microbiological outcomes were comparable between the cefiderocol and best available therapy treatment groups. In the APEKS-NP study, cefiderocol was noninferior to high-dose extended infusion meropenem in the treatment of subjects with documented nosocomial pneumonia caused by Gram-negative bacteria for all-cause mortality at Day 14. Please refer to the current IB for a summary of the results.

On 14 Nov 2019, Shionogi received FDA approval of cefiderocol, for the treatment of subjects 18 years of age or older with cUTI including kidney infections caused by susceptible Gram-negative microorganisms, who have limited or no alternative treatment options. On 28 Apr 2020, Shionogi received European Commission marketing authorization for cefiderocol for the treatment of infections due to aerobic Gram-negative bacteria in adult patients with limited treatment options. On 28 Sep 2020, Shionogi received FDA approval of cefiderocol for the treatment of patients 18 years of age or older with hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) caused by susceptible Gram-negative microorganisms.

1.3 Rationale for Study

The primary purpose of the proposed study is to provide safety data commensurate with the intended duration of treatment clinically and to obtain PK data that will be used to confirm dosing recommendations to support the safe and effective use of cefiderocol in paediatric subjects 3 months to < 18 years of age with suspected or confirmed aerobic Gram-negative infections. The PK for cefiderocol from this study will be used for

modeling and simulations performed to estimate the probability of target attainment (PTA) for a percentage of time that free drug concentrations in plasma exceed the minimum inhibitory concentration (MIC) over the dosing interval (%$fT_{>MIC}$) of ≥ 75%, which has been identified as the pharmacodynamic (PD) parameter associated with efficacy for cefiderocol. Using this approach, a potentially efficacious dose (and dosing regimen) of cefiderocol can be estimated and will therefore confirm the dosing recommendations for the age range included in the proposed study.

The PD parameter of %$fT_{>MIC}$ is considered to be a reliable estimate of efficacy considering that the effectiveness of β-lactam antibiotics, including cephalosporins such as cefiderocol, is directly linked to the duration of time above the MIC of the bacterial pathogen being treated, and therefore plasma drug exposures drive clinical efficacy for most infection types. Specifically, β-lactam antibiotics, as a result of their relatively slow bactericidal action, exhibit time-dependent bactericidal activity with minimal increases in bactericidal activity with concentrations greater than the point of maximal killing (or 4 times the MIC) [7]. Therefore, clinical efficacy of β-lactam antibiotics is dependent on the duration of time that free drug concentrations are above the MIC (or $fT_{>MIC}$), which is used, along with the drug half-life, to develop dosing recommendations (dose and frequency of administration) such that the $fT_{>MIC}$ is optimized. It is generally accepted that clinically effective dosing regimens provide drug concentrations that exceed the MIC of the causative pathogen for a minimum of 40% to 50% of the dosing interval [7]. The $fT_{>MIC}$ for β-lactam antibiotics is a well-established PD parameter and has been incorporated into the PK/PD model for cefiderocol using a target value derived from nonclinical models of infection. Hence, PK/PD modeling and simulations based on predictive PK and human exposure data, a well-established PD parameter associated with clinical efficacy for β-lactam antibiotics, and nonclinical data supporting the target value for %$fT_{>MIC}$ provide a reliable approach to support dosing recommendations for cefiderocol in the paediatric population.

1.4 Overall Paediatric Program

Three months to < 18 years

Due to the different indications being pursued globally and the different health authority requirements for the conditions to be studied, the evaluation of paediatric subjects is being assessed in more than 1 study in subjects 3 months to < 18 years of age. This study will enroll subjects with aerobic Gram-negative pathogens (including but not limited to cUTI, complicated intra-abdominal infections [cIAI], hospital-acquired pneumonia [HAP]/ventilator-acquired pneumonia [VAP], and sepsis or bloodstream infections [BSI]) in the single-dose and multiple-dose phase. Another paediatric study will investigate cefiderocol in paediatric subjects with a variety of infections including but not limited to cUTI, cIAI, HAP/VAP, BSI, and sepsis in the single-dose phase, with the multiple-dose phase specific to subjects with cUTI and HAP/VAP.

< 3 months

A third study to investigate cefiderocol in subjects < 3 months is also planned.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• 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	• Adverse events • Vital signs • Physical examinations • Clinical laboratory assessments • C_{max}, $AUC_{0\text{-}inf}$, and $t_{1/2}$ after single dose • C_{max}, $AUC_{0\text{-}\tau}$, and $t_{1/2}$ after a minimum of 4 doses
Secondary	
• 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)	• Clinical outcome • Microbiological outcome
Exploratory	
• To estimate the PTA for percent of time that free drug concentrations in plasma exceed the MIC over the dosing interval (%$fT_{>MIC}$) of ≥ 75% with infections caused by pathogens with MICs ≤ 4 µg/mL • 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	• Clinical outcome • Microbiological outcome • %$fT_{>MIC}$ for causative pathogens • PTA for 75% $fT_{>MIC}$

aerobic Gram-negative pathogens in hospitalized paediatric subjects 3 months to < 12 years of age at the Posttreatment visit, EOT, and EOS.	

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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 (including but not limited to cUTI, cIAI, HAP/VAP, and sepsis or BSI) 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 age range (Table 3-1).

Table 3-1 Cohort Description

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

mos = months; PK = pharmacokinetic; yrs = years

a Cohorts 1, 2, and 3 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 single-dose Cohorts 1, 2, and 3 (with a minimum of 3 subjects from Cohort 3) have been assessed.

The single-dose phase (in all 4 cohorts) will enroll subjects with Gram-negative bacterial infection 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.

Cohort 1 will consist of a single-dose phase only.

Cohorts 2, 3, and 4 will each consist of both a single-dose phase and a multiple-dose phase (an expected 5 to 14 days). Note: a minimum of 6 doses will be permissible if, in the opinion of the investigator, it is in the subject's best interest.

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 begin 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 will begin after analyzing safety and PK data from 6 subjects in the corresponding single-dose cohort.

Enrollment will be stopped for the applicable cohort to allow for analysis of the PK data prior to moving from single-dose to multiple-dose in Cohorts 2, 3, and 4. Sites that are activated for enrollment will be instructed via email or a phone call from the sponsor or clinical research organization (CRO) 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. The phone call will be followed by written notification via "Dear Dr. Letter".

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 cefiderocol 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 cefiderocol and who have at least 1 PK blood sample above the limit of quantification.

Screening will occur within 4 days prior to Treatment Day 1 or on Treatment Day 1 in both the single- and multiple-dose phase. Prior to Screening, sites will be asked to send a Permission to Screen Form to Shionogi's medical monitor for evaluation and agreement. The purpose of the form is to check the eligibility of potential subjects being enrolled into the study.

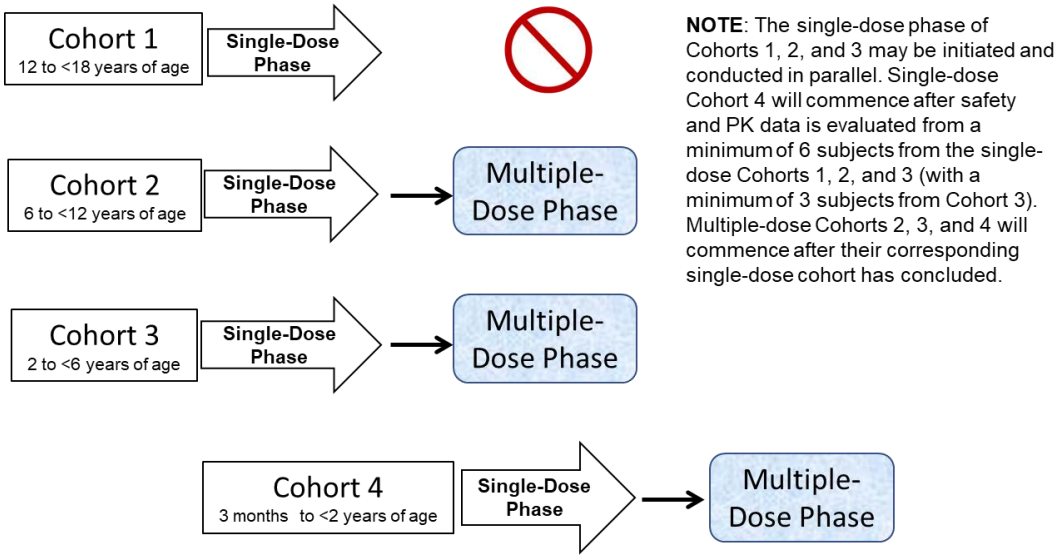
In the single-dose phase, cefiderocol will be administered (in addition to SOC) at any time during the SOC treatment regimen. In the multiple-dose phase, cefiderocol will be administered on Day 1 (in addition to SOC), within 72 hours of the start of potentially effective treatment with SOC antibiotics for infection. Subjects will subsequently receive cefiderocol every 8 hours (q8h) for an expected 5 to 14 days; 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 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 single-dose phase will include only those subjects with normal renal function or mild renal impairment. The dose of cefiderocol for the single-dose phase will be determined based on body weight only; the maximum dose to be administered is not to exceed 2000 mg. The dose for the multiple-dose phase will be determined based on both body weight and renal function; the maximum dose to be administered is not to exceed 2000 mg. 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 may 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 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 28 (+ 7) days 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.

The total duration of cefiderocol administration will be determined by the investigator based on clinical assessment of each subject's infection status but should be expected (at time of enrollment) to be 5 to 14 days. Note: a minimum of 6 doses will be permissible if, in the opinion of the investigator, it is in the subject's best interest. In special circumstances, treatment beyond 14 days may be allowed following review and approval of individual cases by the Shionogi medical monitor via the Treatment Extension Form. The dose of cefiderocol administered to each subject will be determined by the investigator based on dosing recommendations (Section 5.2).

Figure 3-1 Study Schematic



PK = pharmacokinetic

Cohort 1 is not applicable in the multiple-dose phase.

Multiple-dose Cohorts 2, 3, and 4 will begin after PK analyses are complete.

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 Treatment Day 1 or on Treatment Day 1	1 day	Within 24 hours after last dose of study treatment (or early termination)	NA	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

NA = not applicable

Safety assessments including physical examinations, vital sign measurements, and clinical laboratory tests will be performed at prespecified time points during Screening, during study treatment, and after administration of study treatment within 24 hours. In addition, safety data will be captured at various time points during the study from safety assessments performed as part of routine patient care (Section 7.5). Adverse events will be collected and monitored from the time signed informed consent/assent is obtained through the end of study (EOS) visit or 28 (+ 7) days after administration of cefiderocol in the single-dose phase or 28 (+ 7) days after administration of the last dose of study treatment in the multiple-dose phase.

Blood samples for determination of plasma cefiderocol concentrations will be collected from each subject at prespecified time points during and/or after the cefiderocol infusion (Section 7.4). Cefiderocol PK will be determined in the single-dose phase in each of the cohorts; cefiderocol dose recommendations may be revised by the sponsor prior to initiating enrollment of subjects in the multiple-dose phase of each respective cohort.

In the multiple-dose phase only, clinical outcome data and microbiological outcome data will be obtained. Clinical and microbiological outcome assessments will be performed at EOT, at the Posttreatment visit (7 ± 4 days after EOT), and EOS if available. Data from assessments performed prior to, during, and after treatment with SOC antibiotics as part of routine patient care will be captured as study data. The time points for collection of microbiological specimens are otherwise not prespecified by the protocol (Posttreatment Visit, EOT, and EOS, if available; Section 7.6). In subjects where it is not possible to obtain a posttreatment culture and/or EOS culture, determination of presumed microbiological eradication may be made based on resolution of all presenting clinical sign and symptoms of the infection (clinical cure).

3.2 Rationale for Study Design and Control Group

The proposed study is a nonrandomized, open-label study and will consist of 4 separate cohorts grouped by age (Section 3.1).

The doses used in this study have been selected from estimates based on modeling and simulation of adult population PK data. Because these doses have not yet been studied in children, the single-dose phase of cefiderocol will be used to confirm the exposure prior

to initiating multiple dosing. Once the safety and PK data have been confirmed in subjects in the single-dose cohorts, the corresponding multiple-dose cohort will begin. If the exposures in the single-dose arms are not as predicted, adjustments to the dosing regimen will be made by the sponsor prior to initiating the multiple-dose phase of the respective cohorts. Dose adjustments at a subject level should be made by the investigator reflecting the current creatinine clearance level (CrCL) as described in Table 5-1, Table 5-2, and Table 5-3.

The single-dose phase for Cohorts 1, 2, and 3 will initiate at the same time because renal maturation has occurred in these subjects and clearance is expected to be predictable. Cohort 4 single-dose phase will only occur after exposures have been analyzed and confirmed in at least 6 subjects total from the single-dose Cohorts 1, 2, and 3 (with a minimum of 3 subjects from Cohort 3), as the subjects in Cohort 4 have not achieved renal maturation and their clearance is less predictable. If the exposures in Cohorts 1, 2, and 3 are as expected, then Cohort 4 single-dose will commence; otherwise, the dosing regimen may be adjusted by the sponsor for Cohort 4.

Multiple dosing is being investigated in Cohorts 2, 3, and 4 to confirm safety, since these subjects may respond differently from adults. As discussed and agreed with the European Medicines Agency's (EMA's) Paediatric Committee (PDCO), Cohort 1 (adolescents) will not participate in the multiple-dose phase because it is considered appropriate to extrapolate adolescent PK data from available and adequate adult PK data. Nevertheless, it should be noted that in the overall paediatric development program for cefiderocol, adolescents' PK information from multiple dose regimens using the same dose recommendation as in the current protocol will be available from another parallel paediatric study agreed with the FDA for the paediatric development in the US.

Cefiderocol will be added to SOC in both the single- and multiple-dose phase of this study (however, monotherapy with cefiderocol may be allowed in the multiple-dose phase if the subject's infection is confirmed to be aerobic Gram-negative only before starting treatment). This is considered appropriate in the single-dose phase because a single dose of cefiderocol will not be effective in treating the underlying infection, whereas addition to SOC allows assessment of cefiderocol PK and safety while maintaining effective therapy in the subject and not restricting entry criteria to a particular baseline regimen. The use of SOC regimen is considered appropriate as each institution will likely have a different preferred antibiotic regimen and subjects will have different susceptibility profiles. It is well established that enrollment in paediatric studies is difficult when treatment options exist. By allowing any baseline treatment option (ie, SOC), enrollment will not be hindered and safety of cefiderocol can be assessed.

An open-label design is considered appropriate because placebo fluids would need to be administered for a blinded design and this would not be recommended nor ethical in a paediatric population. A double-blind design requires placebo administration of all possible formulation types, which practically and operationally would be impossible.

3.3 Study Duration

3.3.1 Study Duration for Individual Subjects

Screening can last up to 4 days for the single-dose and multiple-dose phases.

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 (administration for 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 (assuming 14 days of treatment). Note: a minimum of 6 doses will be permissible if, in the opinion of the investigator, it is in the subject's best interest.

3.3.2 Study End

The end of the study is defined as the last visit of the last subject. The estimated time for study completion, from first subject in to last subject last visit is approximately 2 years and 9 months.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1 Study Population

Male and female paediatric subjects who fulfill the following eligibility criteria will be enrolled in the study.

4.2 General Inclusion Criteria

Subjects who fulfill the following criteria will be included in the study.

1. Subject's parent(s) or legally authorized representative (LAR) provides written informed consent in accordance with regional and country-specific laws and regulations.
2. Subject provides written informed assent, when feasible (age of assent to be determined by institutional review boards/independent ethics committees [IRB's/IEC's] or be consistent with local legal requirements).
3. Hospitalized subject is 3 months to < 18 years of age at the time written informed consent/assent is obtained for the single-dose phase. Hospitalized subject is 3 months to < 12 years of age at the time written informed consent/assent is obtained for the multiple-dose phase. Premature babies will not be restricted, but the subject must have an adjusted or postnatal age of 3 months.
4. Subject has a suspected or confirmed infection (including but not limited to cUTI, cIAI, HAP/VAP, sepsis, or BSI) that requires hospitalization for treatment with IV antibiotics.
5. If subject is a sexually active female of childbearing potential and has reached menarche or Tanner stage 3, subject agrees to use barrier contraception (including condom, diaphragm, or cervical cap) with spermicide or agrees to use a highly effective method of contraception (including contraceptive implant, injectable contraceptive, combination oral contraceptive, or an intrauterine [IUD] contraceptive device) from Screening up to 28 days after administration of the last dose of cefiderocol.

4.3 General Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Subject has a documented history of any hypersensitivity or allergic reaction to any β-lactam antibiotic (Note: for β-lactams, a history of a mild rash followed by uneventful re-exposure is not a contraindication to enrollment).
2. Multiple-dose only: Subject has an infection caused only by a confirmed Gram-positive pathogen.
3. Subject has a suspected or confirmed central nervous system (CNS) infection (eg, meningitis, brain abscess, shunt infection) or osteomyelitis (which would require prolonged antibiotic therapy).
4. Subject has cystic fibrosis.

5. Single-dose phase: Subject has moderate or severe renal impairment based on estimated glomerular filtration rate (eGFR) (based on the Schwartz equation [10] if ≥ 3 months to < 1 year of age and modified Bedside Schwartz equation [11] if ≥ 1 to < 18 years of age) of < 60 mL/min/1.73 m^2 at Screening.
   Multiple-dose phase: Subject has an eGFR (based on the Schwartz equation [10] if ≥ 3 months to < 1 year of age and modified Bedside Schwartz equation [11] if ≥ 1 to < 18 years of age)) of < 15 mL/min/1.73 m^2 at Screening.
   See Section 7.5.3.1.2 for eGFR calculations and ranges.
6. Subject has ESRD, is on hemodialysis (HD), or receiving continuous venovenous hemofiltration (CVVH).
7. Subject has experienced shock in the prior month or is in shock at the time of Screening.
8. Subject has severe neutropenia or is severely immunocompromised.
9. Subject has multiorgan failure.
10. Subject has a life expectancy of < 30 days due to severity of a concurrent illness.
11. Subject is a female who has a positive pregnancy test at Screening.
12. Subject is a female who is breastfeeding.
13. Subject has received any other investigational medicinal product (IMP) within 30 days.
14. Subject has any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the study data, including acute trauma to the pelvis or urinary tract.
15. Subject is receiving vasopressor therapy at Screening.

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

A cUTI is defined as a clinical syndrome characterized by pyuria and a microbial pathogen in the urine in the context of the following underlying features: recurrent urinary tract infections (2 or more in a 12-month period); obstructive uropathy; a functional or anatomical abnormality of the urinary tract, including anatomical malformations or neurogenic bladder; vesicoureteric reflux; urinary tract catheterization; an invasive urogenital procedure, such as cystoscopy or urogenital surgery; or azotemia caused by intrinsic renal disease. In addition, pediatric subjects should have at least 2 of the following signs and symptoms depending on their age:

For subjects < 2 years of age
Fever defined as body temperature ≥ 38.0°C, failure to thrive, recent weight loss, irritability, poor feeding, lack of normal level of activity, abdominal pain/tenderness on physical examination, vomiting, or jaundice

For subjects ≥ 2 to < 18 years
Fever defined as body temperature ≥ 38.0°C, chills or rigors, dysuria, urinary urgency, urinary frequency, new-onset urinary incontinence, suprapubic pain, flank pain, abdominal pain, pelvic pain, suprapubic tenderness or costovertebral angle tenderness on physical examination, nausea, or vomiting

Hospital-acquired pneumonia is defined as an acute infection of the pulmonary parenchyma associated with clinical signs and symptoms, such as fever or hypothermia, chills, rigors, cough, purulent sputum production, chest pain, or dyspnea, accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient hospitalized for more than 48 hours or developing within 7 days after discharge from a hospital. Patients with HAP may or may not require intubation and mechanical ventilation.

Ventilator-associated pneumonia is defined as an acute infection of the pulmonary parenchyma associated with clinical signs and symptoms, such as fever or hypothermia, chills, rigors, purulent respiratory secretions, and increased oxygen requirements. These signs and symptoms are in addition to laboratory abnormalities, such as leukocytosis accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient on mechanical ventilation for a minimum of 48 hours.

4.4 Screen Failures

Screen failures are defined as subjects who provide assent and/or whose parent(s)/LAR(s) provide consent to participate in the study but the subject participating in the study did not meet the inclusion/exclusion criteria. Minimal information will be collected on subjects who fail screening requirements: informed consent/assent date, baseline subject characteristics, all of eligibility criteria not met, reasons for screen failure, any AEs that lead to discontinuations during screening, and any SAEs. This information will be entered in the eCRF.

Subjects who do not meet the criteria for participation in the study may be rescreened, after discussion with the sponsor/medical monitor. Rescreened subjects will be assigned a new screening number.

4.5 Withdrawal of Subjects from the Study or Discontinuation from Study Treatment

Withdrawal or discontinuation is defined as subjects who provide assent and/or whose parent(s)/LAR(s) provide consent to participate in the study but, the subject or parent/LAR wish to stop their participation in the study, or in the investigator's opinion, the safety of the subject is at risk.

The investigator will make every reasonable attempt to complete the study for each study subject. A subject may withdraw assent to participate in the study or a subject's parent(s)/LAR may withdraw consent for the subject's participation in the study at any time, for any reason.

The investigator or subinvestigator may discontinue a subject from study treatment at any time for any of the following reasons:

- A serious or intolerable AE occurs and the investigator or subinvestigator considers that the subject should discontinue study treatment
- Progression of the study-qualifying infection (poor or no response, aggravation, or relapse of current infection) for which the investigator considers that the subject should discontinue study treatment
- The subject recovers from the infection and antibiotic treatment is no longer required
- The subject is proven to be ineligible for the study after dosing/entry into the study
- The investigator or subinvestigator determines that the subject should be discontinued from the study treatment based on the management and discontinuation criteria for abnormal liver function tests (Appendix 2)
- The study is prematurely terminated
- The investigator or subinvestigator determines that the subject should be discontinued from study treatment for any other reasons

In the event a subject withdraws assent, and/or a subject's parent(s)/LAR withdraws consent, the subject will be discontinued from the study and no further assessments will be done. However, in the event a subject is prematurely discontinued from study treatment by the investigator or subinvestigator but assent and consent from the study have not been withdrawn, EOT (or early termination) procedures including physical examination, vital sign measurements, and clinical laboratory tests will be performed and the reporting of AEs will be obtained until the EOS visit (28 [+ 7] days after administration of the last dose of study treatment).

Subjects with ongoing AEs will be monitored until either resolution or stabilization is achieved, the subject is referred for continued care to another health care professional, or until a determination of the cause being unrelated to the study treatment or procedure is made or the subject is lost to follow-up. Investigator causality must be included with all SAEs reported to the sponsor. Serious AEs with missing investigator causality will be followed up by the CRO urgently until a response is provided to the sponsor.

The date of withdrawal or discontinuation and reason for withdrawal or discontinuation will be entered in the eCRF.

5. STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Test Drug

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

Each dose of cefiderocol will be prepared by the study pharmacist or qualified designee and labeled with appropriate information per local standards. A detailed procedure for preparation of the IV infusion solution will be provided in a separate pharmacy manual. For reconstitution and dilution instructions, follow the directions in the pharmacy manual.

5.1.2 Standard of Care

The SOC antibiotics 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.

5.2 Treatments to be Administered

The single-dose phase will include only those subjects with normal renal function or mild renal impairment. The dose of cefiderocol for the single-dose phase will be determined based on body weight only; the maximum dose to be administered is not to exceed 2000 mg. The dose for the multiple-dose phase will be determined based on both body weight and renal function; the maximum dose to be administered is not to exceed 2000 mg. Sites will be instructed to monitor renal function as per their routine practice/guidelines and to change doses immediately if renal function changes. Dosing recommendations for subjects with normal renal function or mild renal impairment and subjects with moderate or severe renal impairment (multiple-dose phase only) are provided in Table 5-1, Table 5-2, and Table 5-3, respectively. Shorter infusion times may be allowed in the multiple-dose phase if agreed by the sponsor via the Request for Shortened Infusion Duration Form, and if in the best interest of the subject. If shorter infusion times are needed, refer to the Pharmacy Manual for adjusted PK scheduling. Infusion time must be 3 hours in the single-dose phase. For all subjects enrolled in the multiple-dose phase of the study, cefiderocol doses may be adjusted based on changes in renal function as assessed (using the Schwartz equation [10] if ≥ 3 months to < 1 year of age and modified Bedside Schwartz Equation [11] if ≥ 1 to < 18 years of age) and according to the dosing recommendations for subjects with moderate or severe renal impairment (Table 5-3). See Section 7.5.3.1.2 for eGFR calculations and ranges.

After review of data from administration of cefiderocol in the single-dose phase, dosing recommendations for cefiderocol may be adjusted by the sponsor prior to administration in the multiple-dose phase or for the next subsequent cohort based on ongoing assessment of PK data. All revised dosing recommendations will be provided by the sponsor, discussed with the investigator, and documented.

Single-dose Phase (Cohorts 1, 2, 3, and 4): On Day 1 of the single-dose phase, subjects will be administered a single dose of cefiderocol infused IV over 3 hours. Cefiderocol will be administered at any time during the SOC treatment. The dose of cefiderocol administered to each subject will be based on body weight (Table 5-1). No more than 2000 mg of cefiderocol should be administered.

Multiple-dose Phase (Cohorts 2, 3, and 4): In the multiple-dose phase, subjects will be administered doses of cefiderocol infused IV over 3 hours, q8h, beginning on Day 1 and continuing for an expected 5 to 14 days (in addition to SOC), within 72 hours of the start of potentially effective treatment with SOC antibiotics for infection. The total duration of treatment with cefiderocol will be determined by the investigator based on clinical assessment of each subject's infection status. The dose of cefiderocol administered to each subject will be based on both body weight and renal function (Table 5-2). No more than 2000 mg of cefiderocol should be administered. After initiation of cefiderocol administration, cefiderocol doses may be adjusted based on changes in renal function as assessed by eGFR (using the Schwartz equation [10] if ≥ 3 months to < 1 year of age and modified Bedside Schwartz equation [11] if ≥ 1 to < 18 years of age) and according to the dosing recommendations for subjects with moderate or severe renal impairment (Table 5-3). See Section 7.5.3.1.2 for eGFR calculations and ranges.

Shorter infusion times may be allowed in the multiple-dose phase if agreed on by the sponsor via the Request for Shortened Infusion Duration Form, and if in the best interest of the subject. Infusion volume adjustments by age will be provided in the pharmacy manual.

In special circumstances, treatment beyond 14 days may be allowed following review and approval of individual cases by the Shionogi medical monitor. To apply for this, a Treatment Extension Form should be completed and submitted to the Shionogi medical monitor on Day 12 or earlier (if over the weekend) to ensure continuity of treatment.

In the multiple-dose phase, if the subject's infection is confirmed to be Gram-negative only before starting treatment, monotherapy with cefiderocol may be allowed.

Table 5-1 Dosing Limits for Cefiderocol in Single-dose Phase: Subjects with Normal Renal Function or Mild Renal Impairment

Cohort	Single-dose Phase Dose		Infusion Time
	Body Weight		
	≥ 34 kg	< 34 kg	
1 (12 to < 18 years of age)	2000 mg	60 mg/kg*	3 hours
2 (6 to < 12 years of age)	2000 mg	60 mg/kg*	3 hours
3 (2 to < 6 years of age)	2000 mg	60 mg/kg*	3 hours
4 (3 months to < 2 years of age)	2000 mg	60 mg/kg*	3 hours

* **No more than 2000 mg of cefiderocol should be administered.**

The single-dose phase will include only those subjects with normal renal function (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m^2) or mild renal impairment (eGFR 60 to < 90 mL/min/1.73 m^2). See Section 7.5.3.1.2 for eGFR calculations and ranges.

Table 5-2 Dosing Limits for Cefiderocol in Multiple-dose Phase: Subjects with Normal Renal Function or Mild Renal Impairment

Cohort	Multiple-dose Phase Dose		Frequency	Infusion Time
	Body Weight			
	≥ 34 kg	< 34 kg		
1 (12 to < 18 years of age)	Cohort 1 not applicable in multiple-dose phase			
2 (6 to < 12 years of age)	2000 mg	60 mg/kg*	q8h	3 hours
3 (2 to < 6 years of age)	2000 mg	60 mg/kg*	q8h	3 hours
4 (3 months to < 2 years of age)	2000 mg	60 mg/kg*	q8h	3 hours

q8h = every 8 hours

* **No more than 2000 mg of cefiderocol should be administered.**

Shorter infusion times may be allowed in the multiple-dose phase if agreed by the sponsor via the Request for Shortened Infusion Duration Form and if in the best interest of the subject. Infusion volume adjustments by age and weight will be provided in the pharmacy manual.

See Section 7.5.3.1.2 for estimated glomerular filtration rate calculations and ranges.

Table 5-3 Dosing Limits for Cefiderocol in Multiple-dose Phase: Subjects with Moderate or Severe Renal Impairment

Renal Function	Multiple-dose Phase Dose					
	Body Weight ≥ 34 kg			Body Weight < 34 kg		
	Dose (mg)	Frequency	Infusion Time	Dose (mg/kg)	Frequency	Infusion Time
Moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m^2)	1500	q8h	3 hours	45	q8h	3 hours
Severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2)	1000	q8h	3 hours	30	q8h	3 hours

eGFR = estimated glomerular filtration rate; q8h = every 8 hours

Shorter infusion times may be allowed in the multiple-dose phase if agreed by the sponsor via the Request for Shortened Infusion Duration Form and if in the best interest of the subject. Infusion volume adjustments by age and weight will be provided in the pharmacy manual.

Expected total duration of cefiderocol administration is 5 to 14 days. A minimum of 6 doses will be permissible if, in the opinion of the investigator, it is in the subject's best interest.

5.3 Selection and Timing of Dose for Each Subject

Dosing instructions were developed based on age-specific PK parameters estimated for paediatric subjects from a population PK model using PK data from adult subjects to target equivalent systemic exposure (AUC) to in paediatric subjects to those in adults. Specifically, a population PK model was developed based on the data obtained from adult subjects and has been modified for predicting PK in paediatric subjects. Total clearance and volume of distribution at steady state in paediatric subjects were scaled using allometric relationships developed for 15 parenteral β-lactam antibiotics including 13 cephems (12 cephalosporins) and 2 carbapenems reported by Shimamura et al [7]. The maturation factor of the elimination-relevant organ (kidney) is also incorporated into the model to simulate PK in very young children whose glomeruli are immature (ie, neonates and infants). Plasma cefiderocol concentrations were simulated to calculate C_{max} and AUC for paediatric subjects of all age groups. The dose for each age group was adjusted to provide exposure (AUC) comparable to that in adult subjects. The PTA for the fraction of time for which free plasma drug concentrations exceeds the MIC over the 8-hour dosing interval ($fT_{>MIC}$) of 75% was calculated at the adjusted doses for a MIC range from 0.25 to 16 μg/mL. The results of the calculations suggest that similar drug concentration and efficacy observed in adults can be achieved in paediatric subjects.

In the proposed study, ongoing assessment of PK parameters after single-dose administration in Cohorts 1, 2, 3, and 4 will be used to adjust the initial model-based PK parameter estimates to refine dosing recommendations, as necessary, before proceeding with multiple-dose administration in each respective cohort. The data used for this assessment will come from paediatric subjects receiving cefiderocol from this and/or other paediatric studies.

5.4 Method of Assigning Subjects to Treatment Groups

This study has a single-dose phase and a multiple-dose phase and will include 4 separate age-specific cohorts.

In the single-dose phase, cefiderocol will be administered (in addition to SOC) at any time during the SOC treatment regimen.

Subjects in the multiple-dose phase will receive cefiderocol and SOC combination or cefiderocol alone (if the subject's infection is confirmed to be Gram-negative only before starting treatment).

An IRT will be used to assign subjects to identification numbers for use in the study. When the centralized IRT has accepted and enrolled the subject, the dispensing study pharmacist or qualified designee will prepare the study drug according to the pharmacy manual.

The process for subject number assignment is described in the IRT procedure documents.

5.5 Blinding

This is an open-label study.

5.6 Packaging and Labeling

Cefiderocol powder for solution for infusion will be provided in vials containing the equivalent of 1 g cefiderocol per vial. Each vial will be labeled with information including the name of the active ingredient, protocol number, dosage form, strength, storage conditions, sponsor's name and address, and cautionary statements according to the required country regulations.

5.7 Storage and Accountability

Cefiderocol powder for solution for infusion vials must be stored according to the product label at 2ºC to 8ºC (36ºF to 46ºF) protected from light.

The investigator will ensure that the cefiderocol drug supply is stored and dispensed in accordance with the pharmacy manual. All cefiderocol supplies must be kept in a secure locked area with access limited to those authorized by the investigator.

The study pharmacist or qualified designee will maintain accurate records on the following information: receipt and condition of the cefiderocol drug supply, date of the receipt, when and how much cefiderocol is dispensed and used by each subject in the study, and any reasons for departure from the protocol-specified dispensing regimen. The drug accountability records will be available for verification by the monitor or designee at each monitoring visit. At study completion, a final reconciliation of cefiderocol will be performed. Cefiderocol must not be used for any purpose other than the present study.

5.8 Investigational Product Retention at Study Site

At the completion of the study, all the unused cefiderocol must be returned to the sponsor (or designee) as per the sponsor's written instructions or destroyed as per the CRO's standard operating procedures (SOPs) and a destruction certificate will be provided as needed.

5.9 Treatment Compliance

The IV catheter used for administration of cefiderocol should be flushed with normal saline prior to administration of cefiderocol to confirm that the catheter is functioning and/or patency of the IV line and to remove traces of drugs previously administered through the line; flushing after each infusion is not necessary. Each subject will receive cefiderocol by IV infusion using an IV infusion pump to ensure delivery of the complete dose over 3 hours. Three (3) hours is the required duration to ensure adequate time over MIC for multidrug resistant Gram-negative infections. Shorter infusion times may be allowed in the multiple-dose phase if agreed on by the sponsor via the Request for Shortened Infusion Duration Form, and if in the best interest of the subject. Infusion time must be 3 hours in the single-dose phase.

The date, start and infusion duration of each cefiderocol IV infusion will be recorded in the eCRF. Any interruption in the infusion or adjustment in the rate of infusion should be recorded and should not exceed 5 to 10 minutes.

6. RESTRICTIONS

6.1 Prior Therapy

Prior antibiotic therapy is defined as any antibiotic administered for current infection. Prior therapy is defined as any therapy administered within 14 days prior to the first dose of study treatment.

Any prior therapy (prescription drugs, nonprescription drugs, procedures [eg, surgical or nonsurgical] with or without any medication) taken by the subject within 14 days prior to the first dose of study treatment in the study will be recorded in the eCRF and the information will include the name of drug used or procedures done, duration of treatment, and reason for use. If a drug is administered, dose, dosing frequency, and route of administration will also be included.

6.2 Concomitant Therapy

Concomitant therapy is defined as any therapy other than study treatment administered after the first dose of study treatment in the study. Concomitant medication information will be collected until the end of the study visit (EOS) in both phases of the study.

Concomitant therapy, including prescription or nonprescription medications and procedures, will be recorded in the eCRF and include the following information:

- Name of medication or procedure
- Start date
- Stop date
- Dose, dosing frequency, route of administration
- Reason for use

A concomitant antibiotic is defined as any antibiotic used to treat an infection other than the qualifying Gram-negative infection.

6.2.1 Prohibited Therapy

There are no prohibited medications in this study. Hemodialysis is an exclusion criterion (Section 4.3); therefore, if initiated during the study, should lead to subject withdrawal.

7. STUDY PROCEDURES AND METHODS OF ASSESSMENTS

The study procedures and the times procedures are to be performed are summarized in the Time and Events Schedule in Appendix 1.

7.1 Informed Consent

The investigator or subinvestigator will fully explain the nature of the study to the subject and subject's parent(s)/LAR by using the IRB/IEC-approved informed consent form (ICF) and assent form, if applicable. Prior to the initiation of any study procedures, informed consent will be obtained from the subject's parent(s)/LAR by the signing and dating of the ICF prior to the initiation of any study procedures. Subjects will be informed about the nature and duration of the study with written age-appropriate information, in language and terms they can understand. When appropriate, subjects must sign an assent form (age of assent to be determined by IRB/IEC or be consistent with local legal requirements). A copy of the signed and dated ICF and assent form will be given to the subject and subject's parent(s)/legal guardian. The signed and dated original consent and assent forms, if applicable, will be retained by the investigator.

The investigator or subinvestigator is responsible for ensuring that the subject understands the risks and benefits of participating in the study, including answering any questions the subject and subject's parent(s)/LAR may have throughout the study and sharing any new information in a timely manner that may be relevant to the subject's willingness to continue his/her participation in the study.

7.2 Medical History, Demographics, and Baseline Characteristic

A complete medical history, including prior or concomitant therapies (including prescription and nonprescription medications), will be taken at Screening. Medical history will include previous significant medical conditions (eg, cancer, inherited conditions), any concurrent medical conditions, surgical history, history of diagnosis, and history of treatment of current infection or other infections requiring antibiotic therapy. Demographics and baseline characteristics, including date of birth (month and year), if permitted according to local requirements, sex, ethnicity, race, body weight, and height will be recorded in the eCRF.

7.3 Enrollment in the Study and Dispensing Study Drug

After a subject is determined to be eligible according to the inclusion/exclusion criteria, the investigator or qualified designee will contact the IRT system for a subject identification number and provide the required information for study enrollment. If accepted, the subject will be enrolled in the study. After the subject is enrolled in the study, the investigator, subinvestigator, study pharmacist, or qualified designee will dispense the study treatment as specified in Section 5.

Pharmacokinetic assessments will be performed for all subjects. Enrollment will be stopped for the applicable cohort to allow for analysis of the PK data prior to moving from single-dose to multiple-dose in Cohorts 2, 3, and 4. Sites that are activated for enrollment

will be instructed via email or a phone call from the sponsor or CRO to pause enrollment in the relevant age cohort, until the available data have been processed and evaluated; additionally, IRT will be de-activated for that cohort to prevent further enrollment until data have been evaluated.

The phone call will be followed by written notification via "Dear Dr. Letter".

7.4 Pharmacokinetic Assessments

Pharmacokinetic studies in the paediatric population are generally conducted in patients with the disease to obtain data that better reflect clinical use of cefiderocol. The PK analyses in this study are mandatory and are being performed to determine PK parameters in different age groups to support cefiderocol dosing recommendations.

The total volume of blood withdrawn per subject in this study has been kept at a minimum by using micro tubes. The PK sampling schedule also allows for some flexibility in Cohorts 1 and 2, in terms of number of samples (3 to 5 samples, See Table 7-2 for PK sampling times).

Several approaches will be used to minimize the amount of blood drawn and/or the number of venipunctures:

- Due to the use of a sensitive assay for cefiderocol, the volume of blood required per sample is 180 µL, ie, 0.18 mL (0.36 mL in total for primary sample and back-up)
- To minimize discomfort of blood sampling, sites will be encouraged to use topical anesthesia to place IV catheters, to use indwelling catheters rather than repeated venipunctures for blood sampling, and to collect PK blood samples at the same time as routine, clinical blood samples are obtained, when possible
- The study uses PK and central laboratories experienced in handling small volumes of blood for PK analyses and for laboratory safety studies

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 volumes shown in Table 7-1:

Table 7-1 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

PK = pharmacokinetic

Cohorts 1 and 2: A total of 5 blood samples for determination of plasma cefiderocol concentrations will be collected from each subject as specified in Table 7-2. In the multiple-dose phase, sampling will be done during one 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 approved by the sponsor and is in the subject's best interests, it is acceptable 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 7-2 in the multiple-dose phase during one of the dosing intervals from the 6th to the12th dose of cefiderocol (multiple-dose phase).

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

Table 7-2 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
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. In the event that shorter infusion times are approved by the sponsor, the PK sampling time points will need to be adjusted as described in the laboratory manual. See the laboratory manual for more details on PK sampling and management.

If the line for PK sampling is the same line used for drug administration, the line needs to be flushed with normal saline to avoid mixing with the infused drug solution.

7.5 Safety Assessments

All safety assessments will be performed at prespecified time points per the Time and Events schedule in Appendix 1. All results will be entered in the eCRF.

7.5.1 Physical Examination

Prior to administration of cefiderocol on Day 1 (single- and multiple-dose phases), body weight only will be measured to determine the appropriate dose of cefiderocol to be administered (Section 5.3).

In the multiple-dose phase, in addition to prespecified time points, data from physical examinations performed at other time points as part of routine patient care will be collected during administration of cefiderocol until the last dose of study treatment. The physical examination should be performed according to the normal practice of the clinical study site by the investigator or subinvestigator.

7.5.2 Vital Sign Measurements

Vital sign measurements include blood pressure (systolic and diastolic), pulse rate, respiratory rate, and body temperature. In the multiple-dose phase, in addition to prespecified time points, data from vital sign measurements performed at other time points as part of routine patient care will be collected once daily during Screening and at least 3 times per day starting on Day 1 of the infusion and continuing during administration of study treatment until the last dose of study treatment.

7.5.3 Clinical Laboratory Tests

This is a safety and PK study; therefore, clinical laboratory tests are mandatory and will be performed for all subjects in both the single- and multiple-dose phase. The laboratory tests listed in Table 7-3 must be performed at Screening and within 24 hours of the cefiderocol infusion in the single-dose phase and at Screening, during cefiderocol treatment, and within 24 hours of the last dose of cefiderocol in the multiple-dose phase. Full details are listed in the Time and Events schedule in Appendix 1. In the multiple-dose phase, in addition to prespecified time points, data from clinical laboratory tests performed at other time points as part of routine patient care will be collected as clinically indicated during administration of study treatment until the last dose of study treatment. If clinically indicated, and if part of routine patient care, eGFR should be checked daily to determine whether dose adjustments should be made. See Section 7.5.3.1.2 for eGFR calculations and ranges.

7.5.3.1 Laboratory Parameters

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

The investigator or subinvestigator will assess whether any abnormal changes from Screening (within 4 days prior to the administration of the first dose of study treatment) or previous visit results, are clinically significant. The date of specimen collection (whether or not specimen was collected) will also be entered in the eCRF.

7.5.3.1.1 Clinical Laboratory Tests

Mandatory hematology, blood chemistry, and urinalysis parameters that will be assessed are presented in Table 7-3.

Table 7-3 Mandatory 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 Total bilirubin Total protein	Albumin Blood urea nitrogen Serum creatinine Blood glucose Sodium Potassium
Urinalysis (dipstick)[a]	Protein Glucose Bilirubin	Urobilinogen Occult blood Leukocyte esterase

a If the subject has a complicated urinary tract infection, urine microscopy and Gram stain should be performed if the local laboratory has capability (see Section 7.5.3.2). Dipstick is not required if microscopy is performed. Dipstick for leukocyte esterase is not required if urine microscopy shows white cells. If urine microscopy shows white cells and is cultured, no further characterization is needed.

The total volume to be drawn in the study may vary based on local/regional specific laboratory requirements and the clinical requirements for the individual subject. According to central laboratory, Eurofins, the average blood volume drawn for routine laboratory testing is 3.5 mL (minimum 1 mL, maximum 3.5 mL). As a general rule, total blood volume (including PK sampling) should not exceed 3% of the total blood volume over a period of 4 weeks, and should not exceed 1% at any single time. This recommendation leads to the allowable sample volumes, indicated in Table 7-4 below:

Table 7-4 Maximum Allowable Research-related Blood Sample Volumes

Body weight (kg)	Circulating total blood volume (mL)	Maximum allowable sample volume over 4 weeks (mL) – 3% of total blood volume	Maximum allowable sample volume at single time (mL) – 1% of total blood volume
2.5 to 5	250 to 500	7.5 to 15	2.5 to 5
5 to 12	480 to 960	14.4 to 28.8	4.9 to 9.6
12 to 20	960 to 1600	28.8 to 48	9.6 to 16
20 to 30	1600 to 2400	48 to 72	16 to 24
30 to 70	2400 to 5600	72 to 168	24 to 56

Source: Ethical considerations for clinical trials on medicinal products conducted with minors [9].

The estimated total amount of blood per cohort is listed in Table 7-5. The estimate is based on assumptions of 10 routine blood draws during the study. Fewer or more draws may be required based on clinical considerations.

Table 7-5 Total Average Blood Volume (Multiple-dose Phase)

Cohorts	1	2	3	4
Age	12 years to < 18 years	6 years to < 12 years	2 years to < 6 years	3 months to < 2 years
Total blood volume for PK samples	2.0 mL	2.0 mL	1.2 mL	1.2 mL
Assumed number of routine blood samples	10	10	10	10
Assumed amount per routine blood sample	3.5 mL	2.5 mL	1.5 mL	1.0 mL
Total blood volume for routine lab tests	35 mL	25 mL	15 mL	10 mL
Total blood volume	37 mL	27 mL	16.2 mL	11.2 mL

PK = pharmacokinetics

7.5.3.1.2 Estimated Glomerular Filtration Rate

Estimated GFR will be measured at Screening for subjects in the single-dose phase. In the multiple-dose phase, eGFR should be estimated at Screening and daily during treatment, if clinically indicated. Dose adjustments should be made reflecting the current CrCL (Section 5.2).

For ages ≥ 3 months to < 1 year, the eGFR will be based on the Schwartz equation [10]:

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

For ages ≥ 1 year to < 18 years, the eGFR will be based on the modified Bedside Schwartz equation [11]:

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

OR

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

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2
Scr (standardized serum creatinine) = mg/dL

Renal function ranges are provided in Table 7-6.

Table 7-6 Renal Function Ranges

Renal Impairment	Estimated Glomerular Filtration Rate (eGFR)
None (normal)	≥ 90 mL/min/1.73 m^2
Mild	60 to < 90 mL/min/1.73 m^2
Moderate	30 to < 60 mL/min/1.73 m^2
Severe	15 to < 30 mL/min/1.73 m^2

The single-dose phase will enroll subjects with an eGFR of ≥ 60 mL/min/1.73 m^2.

The multiple-dose phase will enroll subjects with an eGFR of ≥ 15 mL/min/1.73 m^2.

7.5.3.1.3 Pregnancy Test

A urine pregnancy test will be performed for females of childbearing potential only.

7.5.3.2 Microbiologic Cultures

Appropriate clinical specimens (eg, urine, blood, sputum, swabs) should be obtained if possible from all subjects prior to the start of any antibiotic treatments and also prior to starting study treatment. Clinical specimens for microbiologic cultures are to be sent to the local laboratory for identification of all pathogens causing the infection. Urine should be grown quantitatively with appropriate method-specific dilutions. Blood cultures should be collected if clinically indicated and sent to the local laboratory. After initiation of study treatment in the multiple-dose phase, clinical specimens should be obtained where possible, if clinically indicated. Culture results obtained prior to informed consent/assent, but directly related to the current infection, should be recorded and may form the basis for subject inclusion in the study.

Local culture results for subjects enrolled in the single-dose phase should be recorded in the subject medical records, and local culture results for subjects enrolled in the multiple-dose phase should be recorded in the eCRF. Identified isolates from subjects in the multiple-dose phase should be sent to the central laboratory.

If possible, all baseline microbiological specimens should also have a Gram stain performed. In addition, quantification results for cultures will be collected. The high-power microscopic view of the Gram stain can be used to characterize the general type of bacteria causing the infection (eg, a Gram-positive or a Gram-negative bacterial pathogen). A report of both inflammatory cells and bacteria is necessary. A Gram stain result showing the presence of Gram-negative bacteria is a primary indication of the infection that will be most appropriate for this study.

Inappropriate clinical specimens should not be used for confirmatory culture identification of causative pathogens.

All isolated pathogens will be frozen and stored for later shipping to the central laboratory. Detailed procedures for sample collection, handling, labeling, storage, and shipping will be provided in the separate study laboratory manual. Shipping labels, instructions for shipping, and courier service will be provided from the sponsor or CRO.

7.5.3.3 Sample Collection, Storage, and Shipping

Clinical specimens for clinical laboratory tests will be collected at specified time points by the investigator or qualified designee and sent to a local clinical laboratory for processing according to the clinical site SOPs.

7.5.4 Adverse Events Assessments

7.5.4.1 Definition and Assessment of Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product (including investigational drug) during the clinical investigation. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. If signs and/or symptoms are part of a diagnosis, the diagnosis should be reported as the AE rather than the individual signs and/or symptoms.

Adverse events will be found by the subject's or subject's parent(s)/LAR spontaneous complaint, subject comment cards, or as a result of nonleading questions, physical examination, vital signs, or laboratory tests. Adverse events include any occurrences that are new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Concurrent medical conditions present at baseline that worsen will be considered as AEs. The progression of the study qualifying infection (poor or no response, aggravation, or relapse of current infection) is not an AE (unless the outcome is serious) in the study. This statement applies until the Posttreatment visit. Any aggravation or relapse of the study qualifying infection after the Posttreatment visit should be considered an AE.

New onset infection involving another site such as BSI is considered an AE.

Hospitalizations for preplanned or elective procedures to treat a preexisting condition that did not worsen after study start will not be considered AEs or SAEs. The exception is when the subject experiences another event or has an outcome that is fatal, life-threatening, leads to prolonged hospitalization, or is considered to be clinically significant during/following the procedure.

The investigator or subinvestigator is responsible for assessing AEs. Adverse events should be fully investigated and recorded in detail including onset date, end date, date of outcome assessment (if outcome is other than not recovered, recovering, or unknown), severity, seriousness with a category of seriousness, causal relationship with the study treatment, action taken to manage the AE, and outcome of the AE in the eCRF.

7.5.4.2 Assessment Period

Adverse events will be collected and monitored from the time signed informed consent/assent is obtained through the end of study (EOS) visit or 28 (+ 7) days after administration of cefiderocol in the single-dose phase or 28 (+ 7) days after administration of the last dose of study treatment (cefiderocol and SOC combination,

cefiderocol alone [if Gram-negative infection confirmed in the multiple-dose phase]) in the multiple-dose phase. If a subject withdraws early from the study or is prematurely discontinued from study treatment by the investigator, the investigator will make an effort to collect AEs for 28 (+ 7) days after administration of the last dose of study treatment. Subjects with ongoing AEs will be monitored until either resolution or stabilization is achieved, the subject is referred for continued care to another healthcare professional or until a determination of the cause being unrelated to the study treatment or study procedure is made, or the subject is lost to follow-up. Investigator causality must be included with all SAEs reported to the sponsor. Serious AEs with missing investigator causality will be followed up by the CRO urgently until a response is provided to the sponsor.

Serious adverse events occurring after the subject's completion of the study (EOS) are addressed in Section 7.5.4.7.2.

7.5.4.3 Severity

The severity of an event will be graded by the investigator or subinvestigator according to the following definitions:

- **Mild:** A finding or symptom is minor and does not interfere with usual daily activities.
- **Moderate:** The event causes discomfort and interferes with usual daily activity or affects clinical status.
- **Severe:** The event causes interruption of the subject's usual daily activities or has a clinically significant effect.

All severity grades identified during the period in which the AE occurred will be recorded in the eCRF.

7.5.4.4 Relationship to the Study Treatment

The causal relationship of an event to cefiderocol will be determined by the investigator or subinvestigator according to the following criteria:

- **Related:** An AE which can be reasonably explained as having been caused by cefiderocol. For example, the occurrence of the AE can be explained by any of the following: a pharmacological effect of cefiderocol (eg, a similar event had been reported previously); an increase/decrease of the dose affects the occurrence or seriousness of the AE; or all other causative factors (eg, medical history, concomitant medication etc.) can be ruled out after careful analysis of sufficient information.
- **Not related:** An AE which cannot be reasonably explained as having been caused by cefiderocol.

Related events are defined as those events that are treatment related and treatment emergent.

7.5.4.5 Expectedness

Expected AEs for cefiderocol are listed under Expected Adverse Reactions in Section "Undesirable Effects" of the "Summary of Data and Guidance for Investigators" in the current IB for cefiderocol.

7.5.4.6 Adverse Event Assessment of Clinical Laboratory and Other Safety Parameters

For any abnormal laboratory test results (hematology, blood chemistry, or urinalysis) or other safety assessments (eg, physical examination, vital signs) that occur or worsen following exposure to cefiderocol from baseline, the investigator or subinvestigator will consider whether those results are clinically significant. Abnormal laboratory test results are defined as values outside the RR. For test results which are abnormal at baseline and significantly worsen following the initiation of the study, the investigator or subinvestigator must also consider whether those results are clinically significant. Any test results which are considered to be clinically significant by the investigator or subinvestigator are to be recorded as AEs. If abnormal laboratory finding is associated with disease or organ toxicity, the investigator should report only the disease or organ toxicity as an AE. These AEs should also be assessed as to whether or not they meet the definition of serious and should be reported accordingly.

The investigator or subinvestigator will consider test results to be clinically significant in the following circumstances (at their own discretion in the other circumstances):

- Clinical laboratory test results that lead to any of the outcomes included in the definition of an SAE (Section 7.5.4.7.1).
- Clinical laboratory test results that lead to a change in dosing of study treatment or discontinuation from the study.
- Clinical laboratory test results that lead to a concomitant drug treatment or other therapy.
- Clinical laboratory test results that require additional diagnostic testing (except for a confirmatory test) or other medical intervention.
- Clinical laboratory test results that meet the management and discontinuation criteria for abnormal liver function tests or transaminase elevations identified in Appendix 2.

In addition, when any test result meets the management and discontinuation criteria for liver function abnormalities or transaminase elevations (Appendix 2), the results of further assessments and required follow-up should be recorded in the Liver Event Form in the eCRF.

7.5.4.7 Serious Adverse Events

7.5.4.7.1 Definition

An SAE is defined by regulation as any AE occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening condition
- Hospitalization or prolongation of existing hospitalization for treatment
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important condition

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Abnormal liver function tests and the process to deal with then are described in Appendix 2. The investigator or subinvestigator will determine the seriousness of an AE.

An elective procedure, identified at baseline, not associated with a worsening of a known underlying medical condition is not considered an AE, and therefore will not be considered an SAE despite requiring hospitalization. However, complications of a procedure will be considered an AE and may be considered an SAE if hospitalization is prolonged (or any other SAE criteria is met). A hospitalization or prolongation of a hospitalization for reasons other than an AE would not be considered an SAE.

7.5.4.7.2 Reporting Serious Adverse Events

All SAEs must be reported to the clinical research organization (CRO)/sponsor in detail in the eCRF SAE Form in the electronic data capture (EDC) within 24 hours from the time the investigator first becomes aware of the SAE.

All SAEs must be reported regardless of causal relationship to cefiderocol and the reporter must provide a causality assessment. When reporting SAEs, the investigator should record the diagnosis whenever possible. If no diagnosis is available at the time of reporting, individual signs and symptoms can be reported.

In rare and exceptional circumstances, such as unavailability of EDC system, for reports occurring in subjects who consented but were screening failures, or for reporting instances of partner pregnancy of a male subject; sites may submit paper reports to the CRO via email or fax, within 24 hours of awareness to [redacted] Global Safety and Pharmacovigilance group:

Fax: [redacted]

Email: [redacted]

A template of the paper SAE Form and further instructions can be found in the Site Regulatory Binder.

Once EDC is functional again, sites must enter reports previously sent via fax or email into EDC.

If the sponsor requires a follow-up assessment, the investigator should provide new information to the CRO as it becomes available via EDC by adding the follow-up information to the SAE EDC Form. Discharge summaries, consultant reports (from other departments or other hospitals), autopsy reports, or other relevant documents must be evaluated by the investigator and all relevant information must be reported. Copies of these reports may also be requested by the sponsor.

Appropriate remedial measures should be taken by the investigator using his/her best medical judgment to treat the SAE. These measures and the subject's response to these measures should be recorded. Clinical, laboratory, and diagnostic measures should be employed by the investigator as needed to adequately determine the etiology of the event.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation (EOS visit). However, if the investigator learns of SAEs occurring after the AE assessment period specified in Section 7.5.4.2, considered related to cefiderocol by the investigator, the SAEs must be reported to the CRO/sponsor via email or fax at the same fax and email for reporting SAE information above in this section. Investigator assessment of causality must be included with all SAEs reported to the sponsor. Serious adverse events with missing investigator causality will be followed up by the CRO urgently until response is provided to the sponsor.

The sponsor will be responsible for reporting SAEs to the regulatory authorities as required by the applicable regulatory requirements.

7.5.4.8 Special Situations - Abuse, Misuse, Overdose, and Medication Error

All Special Situations must be reported to the CRO/sponsor's medical monitor in detail in the eCRF Special Situations Report Form in EDC as soon as possible from the time the investigator first becomes aware of the Special situation. In the event that EDC is not available, sites may submit paper reports to the CRO via email or fax at the same fax and email for reporting SAE information in Section 7.5.4.7.2.

Abuse, misuse, overdose, or medication error of cefiderocol (as defined below) must be reported to the CRO or sponsor by the investigator using a Special Situations Report Form as soon as possible. If there is an associated AE, the investigator will enter the information in the eCRF and no SAE submission is required. If there are associated SAEs, the investigator will complete and submit an SAE Form in EDC as well.

- **Abuse** - persistent or sporadic, intentional excessive use of an investigational product(s), which is accompanied by harmful physical or psychological effects.
- **Misuse** - intentional and inappropriate use of an investigational product(s) other than as directed or indicated at any dose.
- **Overdose** - intentional or unintentional intake of investigational product(s) in excess of the assigned dose in the protocol.
- **Medication Error** - any unintended error in the prescribing, dispensing or administration of an investigational product(s). Cases of subjects missing doses of investigational product(s) are not considered reportable as medication error.

7.5.4.9 Pregnancy

If a female subject becomes pregnant during the study, the investigator (or subinvestigator) will immediately discontinue the study treatment. Instances of pregnancy of a female subject must be reported to the CRO in detail in the eCRF Pregnancy Test (Urine) Form in EDC within 24 hours from the time the investigator first becomes aware of the pregnancy of the female subject. Additionally, the investigator (or subinvestigator) will need to also report the completed Pregnancy paper Form via email or fax, within 24 hours of awareness, to [redacted] Global Safety and Pharmacovigilance group using the same fax and email procedures for SAE reporting in Section 7.5.4.7.2.

Pregnancy complications and elective terminations for medical reasons must also be reported as an AE or sponsor SAE as appropriate. Spontaneous abortions must be reported as an SAE. The outcome of the pregnancy (ie, birth, miscarriage, abortion) should be followed by the investigator and must also be reported using the Pregnancy Form, which must be submitted to the CRO, if there is an issue preventing submission to the CRO.

Furthermore, the investigator must attempt to collect pregnancy information on any female partners of male subjects, who become pregnant during the study. A specific pregnant partner consent form for the pregnant partner of a male subject is available according to local regulations and must be completed prior to reporting to the sponsor information on the pregnant partner and child. Instances of pregnancy of a female partner of a male subject must be reported to the CRO via email or fax, within 24 hours of awareness, to the CRO.

Instances of pregnancy of a female partner of a male subject must be reported to the CRO at the fax number or email for SAE reporting in Section 7.5.4.7.2 using the Pregnancy Form found in the Site Regulatory Binder. Pregnant Partner and Child reports must not be reported in EDC, as they pertain to individuals who are not study subjects.

Cefiderocol is not genotoxic; therefore, no requirements for male subjects to use barrier contraceptives exist.

7.5.4.10 Treatment-emergent Adverse Events

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

7.6 Efficacy Assessments (Multiple-dose Phase Only)

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

7.6.1 Physician Clinical Response

For the primary analysis, the clinical response will be a dichotomy (cure or failure) based on the clinical outcome as assessed by the investigator, taking into consideration objective data (eg, body temperature, white blood cell count, urinalysis).

7.6.1.1 Clinical Outcomes

The following clinical outcomes in the multiple-dose phase will be characterized at EOT, at the Posttreatment visit, and at EOS (conducted on site or as a phone call).

7.6.1.1.1 HAP/VAP/cIAI

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms of pneumonia/cIAI.
- **Clinical Failure:** No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of pneumonia/cIAI; reappearance of signs and/or symptoms of pneumonia/cIAI; development of new signs and/or symptoms of pneumonia/cIAI requiring antibiotic therapy other than, or in addition to, study treatment therapy; progression of chest radiographic abnormalities; or death due to pneumonia/cIAI.
- **Indeterminate:** Lost to follow-up such that a determination of clinical cure/failure cannot be made.

7.6.1.1.2 Complicated Urinary Tract Infection

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms of cUTI, or return to preinfection 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 treatment therapy; or death due to cUTI.
- **Indeterminate:** Lost to follow-up such that a determination of clinical cure/failure cannot be made.

7.6.1.1.3 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 treatment therapy; or death due to BSI/sepsis.
- **Indeterminate:** Lost to follow-up such that a determination of clinical cure/failure cannot be made.

7.6.2 Microbiological Response

An overall per-subject microbiological response will be determined at the Posttreatment Visit (7 [± 4] days) following EOT and EOS (if available) based on available information provided by the site's SOC for this population.

7.6.2.1 Microbiological Outcomes

An overall per-subject microbiological outcome for the specimens collected and obtained at any time after initiation of study treatment will be determined based on the individual microbiological outcomes for each baseline Gram-negative pathogen. The microbiological outcomes determined by investigator will also be entered in the eCRF. Emergent (ie, nonbaseline) pathogens are considered separately, and do not affect the per-subject microbiological outcome.

7.6.2.1.1 HAP/VAP/cIAI and BSI/Sepsis

- **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.
- **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.

7.6.2.1.2 cUTI

- **Eradication:** A urine culture shows the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ colony forming units (CFU)/mL are reduced to $< 10^3$ CFU/mL.
- **Persistence:** A urine culture shows that the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFU/mL grows $\geq 10^3$ CFU/mL.

- **Indeterminate:** No urine culture obtained or additional antibiotic therapy for the treatment of the current infection including missed sampling.

7.7 Appropriateness of Measurements

The proposed safety assessment (physical examinations, vital sign measurements, and clinical laboratory tests) and timing of assessments are considered appropriate to adequately monitor and assess the safety of cefiderocol in paediatric subjects 3 months to < 18 years of age. The assessments of safety are typical for research studies in adults and therefore are also considered to be appropriate to provide a comprehensive assessment of safety in the paediatric population. Because cefiderocol is not associated with a risk for QTcF prolongation based on a negative thorough QT/QTc study (Study 1603R2116), ECGs will not be performed in the current study.

The proposed blood sampling scheme for determination of plasma cefiderocol concentrations is considered sufficiently accurate to estimate PK parameters in the paediatric population using a population PK model.

Efficacy parameters are exploratory study objectives, considering that the primary objectives of the current study are safety and PK (to confirm dosing recommendations) in paediatric subjects 3 months to < 18 years of age. Additionally, because the study is open label and because cefiderocol will be administered concurrently with SOC antibiotics, efficacy assessments will intentionally be not rigorous, but rather obtained to provide supplemental information regarding the use of cefiderocol in the paediatric population clinically.

7.8 Acceptable Time Windows

Measurements for safety, PK, and efficacy endpoints will be performed according to the schedule of assessments in Appendix 1. The time windows displayed in Table 7-7 are the acceptable time windows for information collection; time windows for analyses will be stated in the statistical analysis plan (SAP). The actual sampling date and time will be recorded in the eCRF.

Table 7-7 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 the 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

8. STUDY ACTIVITIES

Study activities are presented in Section 7 and in the Time and Events Schedule in Appendix 1. The activities related to collection of study information and samples should not impair the normal SOC of the individuals consenting to be in the study.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

The statistical analysis and PK analysis will be performed by the sponsor or designee. The detailed statistical analysis methods will be specified in an SAP and PK analysis plan according to this section of the protocol. For the analyses changed from those outlined in the protocol, the reason for changes from the protocol will be described in the SAP. The first draft of the SAP will be available before the first subject is dosed, and any subsequent minor changes to the SAP will be finalized before database lock. As this is an open-label study, any changes made to the SAP after the first draft may be based on unblinded data.

Unless otherwise noted, continuous variables will be summarized by using the number of nonmissing observations (N), arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum values as summary statistics; categorical variables will be summarized by using the frequency count and the percentage of subjects in each category as summary statistics.

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

No inferential statistical testing will be performed in this study.

In general, all tables will be presented by cohort and treatment regimen (ie, single-dose or multiple-dose). Individual subject data, PK data, and any derived data will be presented and listed by subject. All analyses and tabulations will be performed by using both the SAS Version 9.4 or higher and/or WinNonlin Version 6.2.1 or higher.

9.2 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 EMA's scientific paediatric 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.

The design of the paediatric study and the number of subjects included in each cohort and overall was discussed, agreed and approved by PDCO and is in line with the 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.

9.3 Analysis Populations

The following analysis populations will be analyzed for this study based on enrolled subjects with good clinical practice (GCP) compliance. The Intent-to-treat (ITT) and Microbiological ITT (MITT) populations will be defined only for subjects in the multiple-dose phase.

- **Safety population** includes all enrolled subjects who receive at least 1 dose of cefiderocol.
- **Pharmacokinetic Concentration population** includes all enrolled subjects who have received at least 1 dose of cefiderocol and have at least 1 PK blood sample. This population will be used for the concentration listing.
- **Pharmacokinetic Concentration Summary population** includes all enrolled subjects who have received 1 dose of cefiderocol in the single-dose phase and ≥ 4 doses of cefiderocol in the multiple-dose phase of the study and those 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 the concentration-time data and the concentration data summary.
- **ITT population** includes all enrolled subjects who receive at least 1 dose of cefiderocol
- **MITT population** includes all ITT subjects who have a baseline Gram-negative pathogen in the multiple-dose phase

9.4 Handling of Missing Data

Handling of missing data will be specified in the SAP.

9.5 Subject Disposition

Among the enrolled subjects, the number and percentage of subjects who complete the study and the number and percentage of subjects who prematurely discontinue the study will be summarized. In addition, reasons leading to study discontinuation will be summarized for each cohort and treatment regimen. The number of subjects included in each analysis population and the percentage of subjects enrolled to cohort will also be presented.

9.6 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with summary statistics by cohort and treatment regimen for the Safety, ITT, and MITT populations using summary statistics.

9.7 Extent of Exposure and Treatment Compliance

Exposure to the cefiderocol will be listed and summarized.

9.8 Prior Therapies

Prior therapies for drugs will be coded using the World Health Organization (WHO) Drug Dictionary. All prior therapy(ies) will be listed and summarized for the safety population.

9.9 Concomitant Therapies

Concomitant therapies for drugs will be coded using the WHO Drug Dictionary. Subjects who received concomitant therapy(ies) will be listed and summarized for the Safety population.

9.10 Pharmacokinetic Analysis

Individual plasma concentrations of cefiderocol will be listed and summarized by cohort, phase (single- and multiple-dose phases), infusion time (1, 2, and 3 hours), and nominal sampling time using descriptive statistics and coefficient of variation (CV%, calculated by SD/mean × 100), geometric mean (Geometric Mean) and coefficient of variation for geometric mean (CV% Geometric Mean), and median, minimum (Min) and maximum (Max) values. The CV% Geometric Mean will be calculated according to a formula CV% Geometric Mean = $[\exp(sd^2)-1]^{1/2} \times 100$, where sd is the standard deviation for natural log (ln)-transformed data. The time course of individual and mean plasma concentrations will be presented by appropriate graphics.

Population PK analyses 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.

9.11 Safety Analysis

9.11.1 Adverse Events

Adverse events will be classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be used for the safety analyses (Section 7.5.4.10) and are referred to as an AE in this section. The number of subjects who experience at least 1 TEAE, treatment-emergent SAE, significant TEAE, and TEAE leading to withdrawal will be counted. The number of TEAEs, which are counted by cases reported, will also be presented. Treatment-related AEs will be summarized by the same as TEAE category of overall summary.

A summary of TEAE by MedDRA system organ class and preferred term will be presented. The summary for severity and outcome will be presented by system organ class and preferred term.

All AEs will be listed.

9.11.2 Vital Signs

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 treatment administration within each respective study part.

9.11.3 Clinical Laboratory Analysis

Summary statistics for select laboratory parameters will be presented for each scheduled time point measured and for the change from baseline to each time point. Baseline will be the last value obtained prior to study treatment administration within each respective phase of the study.

9.11.4 Physical Examination

All physical examination data will be listed by subject.

9.12 Efficacy Analyses

Efficacy analyses will be performed only for subjects in the multiple-dose phase of the study for the MITT and ITT analysis populations.

9.12.1 Efficacy Endpoints

The efficacy endpoints include the following variables:

- Clinical outcome
- Microbiological outcome per pathogen/subject

9.12.2 Analyses of Efficacy Endpoints

- Clinical outcome: the number and proportion of subjects in each category will be calculated for each time point.
- Microbiological outcome: the number and proportion of subjects in each category will be calculated for each time point.

In addition, efficacy endpoints will be analyzed by cefiderocol alone and cefiderocol in combination with SOC.

9.13 Data Review

The decision to move to the next cohort will be based on the review of results of the PK analysis. Details will be specified in the PK analysis plan.

Data analysis for data safety monitoring board (DSMB) will also be performed as specified in the DSMB charter.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Study Administrative Structure

Sponsor:	Shionogi B.V. Kingsfordweg 151 Amsterdam, 1043GR The Netherlands Tel: [redacted]
Sponsor's contact:	[redacted] Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA Tel: [redacted]
Sponsor's chief medical officer:	[redacted] Shionogi & Co., Ltd.
Medical monitor:	[redacted] Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA Tel: [redacted]
Study monitoring:	[redacted]
Central laboratory for North America and South America:	Eurofins Central Laboratory 2430 New Holland Pike Lancaster PA 17601 USA Tel: [redacted] Fax: [redacted]
Clinical Laboratory for Europe:	Eurofins Central Laboratory Bergschot 71 4817 PA Breda The Netherlands Tel: [redacted] Fax: [redacted]
Clinical Laboratory for Asia-Pacific:	Eurofins Central Laboratory 1 International Business Park # 01-16 The Synergy 609917 Singapore Tel: [redacted] Fax: [redacted]

Bioanalytical laboratory:	Keystone Bioanalytical, Inc. 501 Dickerson Road North Wales, PA 19454 USA Tel: [redacted] or [redacted] Fax: [redacted]
Microbiological laboratory:	International Health Management Associates, Inc. 2122 Palmer Drive Schaumburg, IL 60173 USA Tel: [redacted] Fax: [redacted]

10.2 Institutional Review Board or Independent Ethics Committee Approval

The IRB/IEC will safeguard the rights, safety, and well-being of the subjects by reviewing the following study documents: the protocol, ICF, written information on subject recruitment procedures (if applicable), other written information given to the subjects, IB, safety updates, annual progress reports (if applicable), and any significant revisions to these documents. The investigator or the sponsor will provide these study documents to the IRB/IEC. The IRB/IEC will be appropriately constituted in accordance with ICH GCP, and local requirements, as applicable. The study will be undertaken only after the IRB/IEC has given full approval and the investigator has received documentation of the approval.

Amendments to the protocol will be subject to the same requirements as the initial review. The investigator will submit all periodic reports and updates as required by the IRB/IEC. The investigator will inform the IRB/IEC of any reportable AEs.

10.3 Ethical Conduct of the Study

The study will be conducted in accordance with all appropriate regulatory requirements and under the protocol approved by the IRB/IEC. The study will be conducted in accordance with current ICH GCP, all appropriate subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki.

10.4 Informed Consent and Assent Process

The investigator will generate informed consent/assent form(s) for the study that comply with the ICH GCP and regulatory requirements. The sponsor will review the proposed informed consent/assent form(s). The consent/assent form(s) will include all the elements required by the ICH GCP and any additional elements required by local regulations and will be reviewed and approved by the appropriate IRB/IEC before use. The sponsor must agree to any changes to the proposed ICF suggested by the investigator prior to submission to the IRB/IEC, and the IRB/IEC approved version must be provided to the site monitor after IRB/IEC approval.

The investigator or subinvestigator will explain the nature, purpose and methods, reasonable anticipated benefits and potential hazards of the study to the subject and subject's parent(s)/LAR in simple terms by using the informed consent/assent form(s) approved by the IRB/IEC before the subject is entered the study. The method of obtaining and documenting informed consent/assent will comply with ICH GCP and all applicable regulatory requirement(s).

10.5 Subject Confidentiality

Procedures for protecting subject privacy must adhere to applicable data privacy laws and regulations. To maintain subject privacy, all eCRFs, cefiderocol accountability records, study reports, and communications will identify the subject by the subject identification code. The investigator will grant site monitor(s) and auditor(s) of the sponsor or designee and regulatory authority(ies) access to all source documents for verification of data collected in the eCRFs and for verification of the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations. The investigator and the sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, Health Information Portability and Accountability Act [HIPAA]). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject data is collected in the eCRFs during the study will be documented in an anonymous fashion and the subject will only be identified by the subject identification code. In the emergent or rare event that it is necessary to identify a subject for safety or regulatory reasons, the sponsor and the investigator are bound to keep this information confidential.

10.6 Study Monitoring

The sponsor or designee will monitor the study to ensure that the study is conducted in accordance with ICH GCP requirements and protocol. The study monitoring will be performed by a representative of the sponsor through central, remote, and/or on-site monitoring as frequently as necessary and frequent communications (email, letter, telephone, and/or fax). The site monitor or representative of the sponsor will review data recorded in the eCRFs, verify the eCRFs entries with direct access to source documents, collect any safety/efficacy information on subjects, verify that amounts of unused cefiderocol are accurate, and check retention of source documents and essential documents. Remote source data verification may be implemented if applicable and according to local laws and regulations.

10.7 Case Report Forms and Source Documents

10.7.1 Case Report Forms

Electronic case report forms (eCRFs) will be created using an EDC system and made available for each subject with signed informed consent/assent into which the investigator will transcribe historical information and relevant data, as specified by the protocol. All

subject data from study visits must be legibly collected on source documents and promptly entered in the eCRF in accordance with the specific instructions in the eCRF Completion Guidelines. Data entry is performed by the investigator, subinvestigator, and study coordinator who are authorized in site personnel documentation. The investigator must ensure that data reported in the eCRF is accurate, complete, and timely, prior to signing the eCRFs to verify the integrity of the data recorded. When the sponsor or designee generates a query to a participating study site, an authorized user will update the eCRF data or provide a query response as appropriate.

Reference ranges, for both local and central laboratories, for all protocol-specified laboratory tests will be collected prior to study site initiation. Reference ranges for all laboratory tests will be updated if the lab is recalibrated during the study.

10.7.2 Source Data and Source Documents

Source documentation supporting the eCRF data should indicate the subject's participation in the study and should legibly document the dates and details of study procedures, AEs, and subject status. However, the following data can be recorded directly on an eCRF as source data:

- Reason for use of prior therapy or concomitant therapy
- Severity and seriousness of an AE, and its causal relationship to the study treatment
- Clinical comments to entries made in the eCRF

The investigator must maintain source documents such as laboratory reports, and complete medical history and physical examination reports. All the source documents must be accessible for verification by the site monitor, auditor, the IRB/IEC, and inspections of regulatory authority. Direct access to these documents must be guaranteed by the investigator, subinvestigator, or study coordinator, who must provide support at all times for these activities. For all sources of original data required to complete the eCRF, the nature and location of the source documents will be identified by the sponsor and the site staff. If electronic records are maintained at the study site, the method of verification must be specified in document within the study site. All source documents should meet Attributable, Legible, Contemporaneous, Original and Accurate (ALCOA) requirements.

10.7.3 External Data

The following data will be reported in separate documents from eCRFs.

- Concentration data of cefiderocol
- Pharmacokinetic analyses results derived from concentration data
- Central laboratory data

10.8 Committees

10.8.1 Data Safety Monitoring Board

An evaluation of safety and efficacy data will be performed by the DSMB according to the DSMB charter. The DSMB will communicate their recommendations to the sponsor based on their data review. The recommendations may include, but are not limited to, continuing, stopping, or modifying the study; they will also provide the reason for each recommendation.

10.9 Termination or Suspension of the Study

10.9.1 Termination or Suspension of the Entire Study

The sponsor may prematurely terminate or suspend the study at any time for the following reasons:

- Ensuring safety of the study is difficult due to safety concerns (eg, occurrence of many treatment-related SAEs)
- Achieving the purpose of the study is considered impossible (eg, interim data suggesting lack of efficacy/safety, inadequate recruitment of subjects)

If the study is prematurely terminated or suspended, the sponsor should promptly inform the investigators. The investigator or subinvestigator should promptly inform the participating subjects and change the study treatment to other appropriate therapy(ies).

For withdrawal criteria for individual subjects, see Section 4.5.

10.9.2 Termination or Suspension of the Study by Study Site

The investigator may prematurely terminate or suspend the study in the study site with agreement of the sponsor at any time when the investigator considers that ensuring safety of the study is difficult due to safety concerns (eg, occurrence of many SAEs).

The sponsor may request the investigator to prematurely terminate or suspend the study in the study site at any time when major violations/deviations of protocol, other procedures, and ICH GCP compliance were not improved.

If the study site is prematurely terminated or suspended from the study, the investigator or subinvestigator should promptly inform the corresponding IRB/IEC and participating subjects and change the study treatment to other appropriate therapy(ies).

10.10 Protocol Modifications and Deviations

The investigator will conduct the study in compliance with the protocol provided by the sponsor and approval/favorable opinion given by the IRB/IEC and the regulatory authority(ies). Modifications to the protocol should not be performed without agreement of both the investigator and the sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the

modification is needed to eliminate an immediate hazard(s) to subjects or for other inevitable medical reasons.

The investigator or subinvestigator should document any deviation from the protocol and the reason. If the investigator deviates from the protocol or makes a change to the protocol to eliminate an immediate hazard(s) to subjects, the record should be immediately submitted to the sponsor, the study site, and the IRB/IEC by the investigator and any deviations or modifications require expedited review and approval by the IRB/IEC. After the investigator obtained approval/favorable opinion from the IRB/IEC, the investigator should obtain a written agreement of the sponsor.

When deviation from the protocol is required to eliminate immediate hazard(s) to subjects or for other inevitable medical reasons, the investigator will contact the sponsor, if circumstances permit, to discuss the planned course of action. Any deviations from the protocol must be fully documented on source documentation.

10.11 Data Management

The sponsor or designee will be responsible for data management. Procedures will be specified in study documents including but not limited to the Data Management Plan.

10.12 Retention of Data

The study records and documents, including ICFs, must be retained by the investigator as specified in the ICH GCP unless applicable local regulatory requirements require a longer retention period. The investigator and study site should take measures to prevent these documents from being accidentally or prematurely damaged. If the sponsor is granted manufacturing and marketing approval for the drug, the sponsor will promptly notify the head of the study site in writing.

Records will be retained for the longest of the following periods:

- At least 2 years after the last marketing application approval
- Two years after formal discontinuation of the clinical development of the investigational product
- Other period according to applicable local laws, regulations, and other regulatory retention requirements, whichever is latest

However, the duration of retention may be prolonged in accordance with an agreement with the sponsor. In the event that the institution or investigator is unable or unwilling to retain study records as outlined in the clinical study agreement, the institution or investigator shall notify the sponsor, and the sponsor shall be entitled, at its expense, to take custody of the study records. In no event shall any study records be transferred to another location or be destroyed or disposed of without the prior written consent of the sponsor.

10.13 Quality Control and Assurance

The sponsor or designee will implement and maintain quality control (QC) and quality assurance (QA) procedures with written SOPs to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof; in accordance with the ICH GCP and as required by the applicable regulatory requirements. Training necessary for the study will be provided to investigators and study site personnel prior to the initiation of the study.

Training necessary for the study will be provided to investigators and study site personnel prior to the initiation of the study.

10.14 Publication and Disclosure Policy

All information regarding cefiderocol supplied by the sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and must not use it for other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical trial will be used toward the development of cefiderocol and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

The sponsor will retain ownership of all data. All proposed publications based on the study will be subject to the sponsor's approval requirements.

Information about this protocol will be posted in a publicly accessible database (clinicaltrials.gov) in accordance with all applicable regulatory requirements.

10.15 Financial Disclosure

The information on financial disclosure for investigators will be addressed in a separate agreement between the sponsor and the investigator.

11. REFERENCE LIST

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Appendix 1 Time and Events Schedule

Single-dose Phase (Cohorts 1, 2, 3, and 4)	**Screening[a]**	**Treatment**						**EOT[b]**	**EOS[c]**
Day	**-4 to Start of Treatment**	**1**						**2**	**28 (+ 7) Days After Dosing**
Hour		0	1	3	3.5	5	8	24	
Administrative Procedures									
Informed consent/assent	X								
Inclusion/exclusion criteria	X								
Medical history	X								
Signs and symptoms	X							X	
Demographics & baseline characteristics	X								
Review of prior/concomitant medications	X ←	→	→	→	→	→	→	→	X
Clinical Procedures									
Physical examination	X							X	
Vital sign measurements	X		X				X	X	
Mandatory clinical laboratory tests (see Table 7-3)	X							X	
eGFR[e]	X								
Pregnancy test[f] (urine)	X								
Adverse event monitoring	X ←	→	→	→	→	→	→	→	X
Liver Event Form (if criteria in Appendix 2 are met)	X ←	→	→	→	→	→	→	→	X
Study Treatments									
Administration of cefiderocol study drug[g]		X →	→	X					
Pharmacokinetic Assessments									
Cohorts 1 and 2: Blood sample collection[h]			X	X	X	X	X		
Cohorts 3 and 4: Blood sample collection[i]				X		X	X		

eGFR = estimated glomerular filtration rate; EOS = End of Study; EOT = End of Treatment; IV = intravenous

a Screening will occur within 4 days prior to Treatment Day 1 or on Treatment Day 1.

b EOT assessment will occur within 24 hours after administration of study treatment or at early termination.

c EOS visit will occur 28 (+ 7) days after administration of study treatment, on-site or via telephone call.

d Body weight measurement only at Screening.

e eGFR (based on Schwartz equation [10] if ≥ 3 months to < 1 year of age and modified Bedside Schwartz equation [11] if ≥ 1 to < 18 years of age) will be estimated at Screening and predose (if more than 24 hours after Screening). See Section 7.5.3.1.2 for eGFR calculations and ranges.

f Female subjects of childbearing potential only.

g Cefiderocol administered as an IV infusion over 3 hours. Infusion time must be 3 hours in the single-dose phase, but may be shortened in the multiple-dose phase.

h Cohorts 1 and 2: Blood samples will be collected: 1, 3 (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, 5, and 8 hours after the start of infusion.

i Cohorts 3 and 4: Blood samples will be collected 3 (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), 5, and 8 hours after the start of infusion.

Multiple-dose Phase (Cohorts 2, 3, and 4)	**Screening[a]**	**Treatment Days**			**EOT[b]**	**Post-treatment**	**EOS[c]**
Study Day	**-4 to Start of Treatment**	**1**	**2 to 4**	**5 to 14**		**7 (± 4) days after EOT**	**28 (+ 7) days after last dose**
Administrative Procedures							
Informed consent/assent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Signs and symptoms	X				X	X	
Demographics & baseline characteristics	X						
Review of prior/concomitant medications	X ←	→	→	→	→	→	X
Clinical Procedures							
Physical examination	X	X[d]	X[d]	X[d]	X		
Vital sign measurements[f]	X	X	X	X	X		
Mandatory clinical laboratory tests (see Table 7-3)	X	X	X	X[e]	X[e]	X	
eGFR[g]	X	X	X	X	X		
Microbiologic cultures[h]	X	X	X	X[e]	X[e]	X	
Pregnancy test[i] (urine)	X						
Adverse event monitoring	X ←	→	→	→	→	→	X
Liver Event Form (if criteria in Appendix 2 are met)	X ←	→	→	→	→	→	X
Study Treatments							
Administration of cefiderocol study drug[j]		X	X	X			
Pharmacokinetic Assessments							
Cohort 2: blood sample collection[k]			X	X			
Cohorts 3 and 4: blood sample collection[l]			X	X			
Efficacy Assessments							
Clinical outcome[m]					X	X	X
Microbiological outcome (if available)[n]					X	X[n]	X

eGFR = estimated glomerular filtration rate; EOS = End of Study; EOT = End of Treatment; IV = intravenous; q8h = every 8 hours; SOC = standard of care

a Screening will occur within 4 days prior to Treatment Day 1 or on Treatment Day 1.

b EOT assessments will occur within 24 hours after administration of the last dose of study treatment or at early termination.

c EOS visit will occur 28 (+ 7) days after administration of study treatment; on-site or via phone call.

d Body weight measurement only, if clinically indicated and otherwise physical examinations should be symptom focused.

e Clinical laboratory tests are mandatory at Screening, Day 1, one of the Days 2 to 4, one of the Days 5 to 14, and Posttreatment. If performed, as part of routine patient care, data from all additionally performed physical examinations and clinical laboratory will be collected during administration of study treatment until the last dose of study treatment.

f Vital sign measurements will be taken 1 hour postdose, and prior to initiation of the next dose of study treatment. Data from vital sign measurements performed at other time points as part of routine patient care will be collected once daily during Screening and at least 3 times per day starting on Day 1 and continuing during administration of study treatment until the last dose of study treatment.

g eGFR (based on Schwartz equation [10] if ≥ 3 months to < 1 year of age and modified Bedside Schwartz equation [11] if ≥ 1 to < 18 years of age) will be estimated at Screening and daily during treatment if clinically indicated. See Section 7.5.3.1.2 for eGFR calculations and ranges.

h Microbiologic samples should be obtained for all subjects before the first dose of study treatment; it's allowed to use samples obtained prior to informed consent, but directly related to the current infection. After initiation of study treatment, urine, blood or other samples, should be obtained where possible if clinically indicated. Identified isolates from subjects in the multiple-dose phase should be sent to the central laboratory.

i Female subjects of childbearing potential only.

j Multiple doses of cefiderocol administered as an IV infusion over 3 hours, q8h, beginning on Day 1 and continuing for an expected 5 to 14 days. Note: Shorter infusion times may be allowed in the multiple-dose phase if agreed on by the sponsor and in the best interest of the subject via the Request for Shortened Infusion Duration Form. In special circumstances, treatment beyond 14 days may be allowed following review and approval of individual cases by the Shionogi medical monitor via the Treatment Extension Form.

k Cohort 2: Blood samples will be collected once at each time point: at 1, 3 (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, 5, and 8 hours after the start of infusion for the single dose and Cohort 2 for the multiple dose phase during one of the dosing intervals from the 6th to the 12th dose of cefiderocol. Pharmacokinetic sampling schedule is shown in Table 7-2.

l Cohorts 3 and 4: Blood samples will be collected once at each time point at 3 (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), 5, and 8 hours after the start of infusion for the single dose and during one of the dosing intervals from the 6th to the 12th dose of cefiderocol during the multiple dose phase. Pharmacokinetic sampling schedule is shown in Table 7-2.

m Clinical outcome assessments will be performed at EOT, Posttreatment, and EOS if available; additional clinical outcome assessments may be performed as part of routine patient care.

n Microbiological specimens may be collected as part of routine patient care and time points are not otherwise prespecified per protocol (EOT, Posttreatment Visit, and EOS, if applicable). In subjects where it is not possible to obtain a posttreatment culture and/or EOS culture, determination of presumed microbiological eradication maybe made based resolution of all presenting clinical sign and symptoms of the infection (clinical cure).

Appendix 2 Management and Discontinuation Criteria for Abnormal Liver Function Tests

Management and Discontinuation Criteria for Abnormal Liver Function tests have been designed to ensure subject safety and evaluate liver event etiology. (See Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, FDA: Jul 2009) [8].

Abnormal Liver Chemistry Criteria

The investigator or subinvestigator must review study subject laboratories to identify if any levels meet the following criteria:

a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN)
b. AST or ALT > 3 × ULN and total bilirubin (TBL) > 2 × ULN or PT-INR > 1.5, if PT-INR is measured
c. AST or ALT > 3 × ULN with signs or symptoms compatible with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, eosinophilia [> 5%])

Action to be taken by Investigator

If any one of abnormal liver chemistry criterion is met, the investigator or subinvestigator must do the following:

- Subjects must be instructed to discontinue study immediately. The investigator or subinvestigator should not re-challenge the subject with the investigational product without consulting the sponsor.
- Following the initial observed elevation, every effort should be made to have the subject reassessed within 48 to 72 hours to repeat liver function chemistries and for further hepatic evaluation.
- Every effort should be made to have the subjects monitored 2 to 3 times per week until liver function chemistries (ALT, AST, alkaline phosphatase [ALP], TBL) resolve, stabilize, or return to within the normal range or to baseline levels.
- This event must be reported to the sponsor as soon as possible but no later than 72 hours of learning after its occurrence on the Liver Event Form in the eCRF.
- Consultation with a specialist such as a hepatologist is considered.
- Liver imaging (ie, ultrasound, magnetic resonance imaging (MRI), computerized tomography) is considered.

For criterion b, the case must be reported as an SAE.

If laboratory values are normalizing, follow-up reports with these values are required once the values have normalized.

If the laboratory values are significantly worsening, follow-up reports are required each time the subject is monitored for these values, ie, 2 to 3 times per week.

Follow-up Examination

If any of the abnormal liver chemistry criteria are met, the following assessments should be performed at the Follow-up visit(s) and documented in the Liver Event Form in the eCRF:

- Clinical signs and symptoms course
- Alcohol use
- Risk factors for nonalcoholic steatohepatitis such as diabetes, obesity and hypertriglyceridemia
- Autoimmune hepatitis/cholangitis
- Wilson's disease
- Laboratory Assessments
  - Viral hepatitis serology
  - Hepatitis A immunoglobulin M (IgM) antibody
  - Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (IgM)
  - Hepatitis C RNA
  - Hepatitis E IgM antibody
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody
  - For subjects with TBL > 1.5 ULN, conjugated bilirubin should be measured.
  - Complete blood count with differential to assess for eosinophilia

Appendix 3 Sponsor's Signature

Form 511-01

Protocol Approval

Product Name: Cefiderocol (S-649266)

Study 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

Study Protocol Number: 1802R2135

Version Number: Version 7

Issue Date: 18 Nov 2021

Sponsor signatory:

This clinical study protocol was subject to critical review and has been approved by the sponsor:

Refer to electronic signature page

[redacted]
Shionogi & Co., Ltd.
ID: [redacted]

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Appendix 4 Investigator's Signature

Study 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
Study Number:	1802R2135
Date of Protocol:	10 Jul 2019
Date of Latest Amendment:	18 Nov 2021

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Printed Name: _____

Title: _____

Affiliation: _____

Electronic Signature Page for VV-CLIN-084521 v1.0

Final Approval	[redacted] 19-Nov-2021 00:34:00 GMT+0000

Electronic Signature Page for VV-CLIN-084521 v1.0

PROTOCOL VERSION 7, AMENDMENT 6
SUMMARY OF CHANGES

Study 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

Date of Amendment: 18 Nov 2021

Version: 7

Date of Previous Version: 04 Mar 2021

Amendment Summary: Revisions to the protocol and the rationales for these revisions are provided by section below. The protocol was amended to allow treatment beyond 14 days in special circumstances, following review and approval of individual cases by the Shionogi medical monitor. Strikethrough text was deleted, and underlined text was added. Minor editorial changes such as word changes, spelling, sentence structure, and document formatting revisions are not summarized.

Section	Revision	Rationale
Synopsis Study Design	Subjects 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.	To allow treatment beyond 14 days in special circumstances
Synopsis Criteria for Inclusion and Exclusion and 4.3 General Exclusion Criteria	Details on the underlying features and signs and symptoms of a cUTI were provided.	Clarification

Section	Revision	Rationale
Synopsis Duration of Treatment	Multiple-dose phase: expected ~~minimum of~~ 5 ~~days~~ to ~~a maximum of~~ 14 days (a minimum of 6 doses will be permissible if, in the opinion of the investigator, it is in the subject's best interest). In special circumstances, treatment beyond 14 days may be allowed following review and approval of individual cases by the Shionogi medical monitor.	To allow treatment beyond 14 days in special circumstances
Synopsis Study Duration	Study duration for individual subjects is approximately 28 days in the single-dose phase and 42 days (or longer if treatment beyond 14 days is allowed by the Shionogi medical monitor) in the multiple-dose phase from the time of the first drug infusion.	To allow treatment beyond 14 days in special circumstances
3.1 Overall Study Design and Plan	Cohorts 2, 3, and 4 will each consist of both a single-dose phase and a multiple-dose phase (an expected 5 ~~days~~ to ~~a maximum of~~ 14 days).	To allow treatment beyond 14 days in special circumstances
	Subjects 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.	To allow treatment beyond 14 days in special circumstances
	In special circumstances, treatment beyond 14 days may be allowed following review and approval of individual cases by the Shionogi medical monitor via the Treatment Extension Form.	To allow treatment beyond 14 days in special circumstances

Section	Revision	Rationale
3.3.1 Study Duration for Individual Subjects	In the multiple-dose phase (administration for 5 to 14 days), the maximum duration of study participation for a subject from Randomization (Day 1) to the EOS visit (28 [+ 7] days after administration of the last dose of study treatment) is 42 days (assuming 14 days of treatment).	To allow treatment beyond 14 days in special circumstances
5.2 Treatments to be Administered	For all subjects enrolled in the multiple-dose phase of the study, cefiderocol doses may be adjusted based on changes in renal function as assessed ~~by if clinically indicated, and if part of routine patient care,~~ eGFR ~~should be checked daily~~ (using the Schwartz equation [10] if ≥ 3 months to < 1 year of age and modified Bedside Schwartz Equation [11] if ≥ 1 to < 18 years of age) and according to the dosing recommendations for subjects with moderate or severe renal impairment (Table 5-3) ~~to determine whether dose adjustments should be made~~.	Clarification
	In the multiple-dose phase, subjects will be administered doses of cefiderocol infused IV over 3 hours, q8h, beginning on Day 1 and continuing for an expected ~~minimum of 5 days to a maximum of 14 days total~~ 5 to14 days (in addition to SOC), within 72 hours of the start of potentially effective treatment with SOC antibiotics for cUTI, HAP, or VAP.	To allow treatment beyond 14 days in special circumstances

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Section	Revision	Rationale
	In special circumstances, treatment beyond 14 days may be allowed following review and approval of individual cases by the Shionogi medical monitor. To apply for this, a Treatment Extension Form should be completed and submitted to the Shionogi medical monitor on Day 12 or earlier (if over the weekend) to ensure continuity of treatment.	To allow treatment beyond 14 days in special circumstances
7.5.2 Vital Sign Measurements	In the multiple-dose phase, in addition to prespecified time points, data from vital sign measurements performed at other time points as part of routine patient care will be collected once daily during Screening and at least 3 times per day ~~at approximately evenly spaced intervals across the 24-hour day~~ starting on Day 1 of the infusion and continuing during administration of study treatment until the last dose of study treatment.	Clarification
7.5.3.1.1 Clinical Laboratory Tests	Table 7-3 a If the subject has a complicated urinary tract infection, urine microscopy and Gram stain should be performed if the local laboratory has capability (see Section 7.5.3.2). Dipstick is not required if microscopy is performed. Dipstick for leukocyte esterase is not required if urine microscopy shows white cells. If urine microscopy shows white cells and is cultured, no further characterization is needed.	Clarification
7.8 Acceptable Time Windows	Table 7-7 Row added for Dosing interval ± 15 minutes	To allow for a 15-minute window between 8-hour dosing intervals

Section	Revision	Rationale
Appendix 1 Time and Events Schedule	d Body weight measurement only at Screening. ~~Vital signs as clinically indicated.~~	Clarification
	j Multiple doses of cefiderocol administered as an IV infusion over 3 hours, q8h, beginning on Day 1 and continuing for an expected ~~minimum of~~ 5 ~~days~~ to ~~a maximum of~~ 14 days. Shorter infusion times may be allowed in the multiple-dose phase if agreed to by the sponsor and in the best interest of the subject via the Request for Shortened Infusion Duration Form. <u>In special circumstances, treatment beyond 14 days may be allowed following review and approval of individual cases by the Shionogi medical monitor via the Treatment Extension Form.</u>	To allow treatment beyond 14 days in special circumstances