Shionogi Study Title:	An Open-label, Multicenter, Single-arm, Phase 1 Study to Assess the Intrapulmonary Concentrations of Cefiderocol at Steady State in Hospitalized Subjects with Known or Suspected Bacterial Pneumonia on Treatment with Standard of Care Antibiotics and Requiring Mechanical Ventilation
Shionogi Study Number:	1713R2117
ClinicalTrials.gov Registration No.	NCT03862040
Study Document	Protocol Version 3 (Amendment 1) 02 Nov 2018

History of Protocol Amendments

Version 1 (Original)	30 Apr 2018
This version of the protocol was not used to enroll participants	
Version 2	02 Nov 2018

Clinical Study Protocol: 1713R2117

Study Title:	An Open-label, Multicenter, Single-arm, Phase 1 Study to Assess the Intrapulmonary Concentrations of Cefiderocol at Steady State in Hospitalized Subjects with Known or Suspected Bacterial Pneumonia on Treatment with Standard of Care Antibiotics and Requiring Mechanical Ventilation
Study Number:	1713R2117
IND Number:	116,787
Study Phase:	1b
Product Code Number:	Cefiderocol (S-649266)
Sponsor:	Shionogi Inc. 300 Campus Drive, Suite 300 Florham Park, NJ 07932 USA
Sponsor Contacts:	[redacted]
Medical Monitor (Shionogi):	[redacted]
Medical Monitor (CRO):	[redacted]

Issue Date:

Version 1 (Original):	30 Apr 2018
Version 2 (Amendment 1)	02 Nov 2018

Confidentiality Statement

SYNOPSIS

Study Title:

An Open-label, Multicenter, Single-arm, Phase 1 Study to Assess the Intrapulmonary Concentrations of Cefiderocol at Steady State in Hospitalized Subjects with Known or Suspected Bacterial Pneumonia on Treatment with Standard of Care Antibiotics and Requiring Mechanical Ventilation

Study Number:

1713R2117

Study Phase: 1b

Primary Objectives:

- To estimate the concentration of cefiderocol in epithelial lung fluid (ELF), at steady state in hospitalized subjects with known or suspected bacterial pneumonia being treated with standard of care (SOC) antibiotics and requiring mechanical ventilation
- To estimate the ratio of the concentration for cefiderocol in ELF relative to plasma ($R_{C,E/P}$) in hospitalized subjects with known or suspected bacterial pneumonia on treatment with SOC antibiotics and requiring mechanical ventilation

Study Design:

This is a multicenter, single-arm, open-label Phase 1b study to assess the intrapulmonary and plasma concentrations of cefiderocol at steady state after multiple-dose administration in hospitalized subjects with known or suspected bacterial pneumonia on treatment with SOC antibiotics and requiring mechanical ventilation. Subjects meeting eligibility criteria will receive 2-g doses of cefiderocol (or renally adjusted dose), administered intravenously over 3 hours, every 8 hours (q8h), or every 6 hours (q6h) if augmented renal function. Cefiderocol will be administered for an expected minimum of 3 doses and up to a total of 6 doses in subjects with normal or augmented renal function and subjects with mild, or moderate renal impairment, and for an expected minimum of 6 doses and up to a total of 9 doses in subjects with severe renal impairment. Bronchoalveolar lavage (BAL) procedure (Mini-BAL is not allowed in this study) will be conducted at 3rd dosing (or 6th for severe renal impairment subjects). If 3rd dosing is not convenient for the subject or the institution to perform the BAL procedure (or 6th dosing for severe renal impairment subjects), 4th, 5th, or 6th dosing could be considered as the timing for the BAL procedure (or 7th, 8th, or 9th dosing for severe renal impairment subjects).

Study Population:

Subjects with known or suspected bacterial pneumonia being treated with SOC antibiotics and requiring mechanical ventilation will be enrolled.

Criteria for Inclusion and Exclusion

Inclusion Criteria:

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

1. Subject is male or female,18-80 years (both inclusive) at the time written

informed consent is obtained

2. Subject has provided written informed consent or informed consent has been provided by subject's legally authorized representative (Note: Country-specific rules and/or local state laws and local Ethics Committee approval for legally authorized representative informed consent will determine whether or not and how a subject unable to comprehend or sign the informed consent is allowed to be enrolled in the study)
3. Subject has a clinical diagnosis of bacterial pneumonia, documented or suspected, (even if later known that the subject does not have bacterial pneumonia, discontinuation of the study is not necessary)
4. Subject is hospitalized and receiving SOC antibiotic treatment for pneumonia
5. Subject is mechanically ventilated and expected to remain mechanically ventilated for at least 48 hours (or 72 hours for subjects with severe renal impairment) after the first dose of cefiderocol
6. Subject has a life expectancy of at least 3 weeks from the Screening visit
7. Female meeting 1 of the following criteria:
    a. Surgically sterile (has had a hysterectomy and/or bilateral oophorectomy, or a bilateral salpingectomy or tubal ligation for the purpose of contraception for at least 6 weeks with appropriate documentation of such surgery)
    b. Postmenopausal (defined as older than 45 years of age with cessation of regular menstrual periods for at least 6 months and a history of a follicle-stimulating hormone level of > 40 mIU/mL, or amenorrhea for at least 12 months)
    c. Of childbearing potential and using combined (estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (including oral, intravaginal, injectable, implantable, and transdermal contraceptives), or an intrauterine device (IUD), or intrauterine hormone-releasing system for the entire duration of the study
    d. Of childbearing potential and practicing abstinence as a preferred and usual life style and/or agrees to continue practicing abstinence from Screening for the entire duration of the study
    e. Of childbearing potential and whose sole heterosexual partner has been successfully vasectomized and agrees to not have other heterosexual partners for the entire duration of the study

Exclusion Criteria:

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

1. Subject has a chemical/aspiration pneumonia that does not require antibiotic treatment (including aspiration of gastric acid, inhalation injury). The term chemical pneumonia refers to the aspiration of substances that are toxic to the lower airways causing chemical burn and injuries in the airway.
2. Subject has a history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam (Note: for β-lactams, a history of a mild rash followed by

uneventful re-exposure is not a contraindication to enrollment)

3. Subject has extensive cystic lesion(s) or severe structural abnormality (eg, cystic fibrosis, emphysema, cystic lesions of sarcoidosis or tuberculosis, post obstructive pneumonia due to lung cancer, etc) of the lung that hinders recovery of bronchoalveolar lavage fluid (BALF)
4. Subject is receiving peritoneal dialysis
5. Subject has severe renal impairment requiring hemodialysis (HD) or end-stage renal disease requiring HD with creatinine clearance (CrCl) < 15 mL/min
6. Subject is in refractory septic shock defined as persistent hypotension despite adequate fluid resuscitation or despite vasopressive therapy at Screening
7. Subject is a female who has a positive pregnancy test at Screening or who is lactating
8. Subject has received another investigational drug within 30 days prior to Screening
9. Subject has previously participated in this clinical study and has received at least 1 dose of cefiderocol
10. 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

Test Drug, Dose, and Mode of Administration:

Cefiderocol, 2 g, is to be administered intravenously q8h as a 3-hour infusion in subjects with normal, mild, moderate or severe renal function (or q6h if subject has augmented renal function) in addition to the subject's treatment with SOC. Dose adjustment for renal function is required, and the dosing recommendations are presented in the protocol, Section 3.1.

Control Drug, Dose, and Mode of Administration:

Not applicable

Duration of Treatment:

The treatment duration for cefiderocol is anticipated to be 3 to 4 days depending on the subject's renal function.

Prohibited Concomitant Therapy:

Not applicable

Efficacy Assessments:

Not applicable

Pharmacokinetic Assessments:

Pharmacokinetic (PK) assessments will be performed for ELF and plasma samples obtained from each subject. The ELF sample for determination of cefiderocol concentrations will be collected by BAL procedure 3, 5, or 7 hours, depending on the ELF cefiderocol concentration data obtained, after administration of at least 3 doses of cefiderocol in subjects with normal or augmented renal function and subjects with mild or moderate renal impairment and after administration of at least 6 doses of cefiderocol in subjects with severe renal impairment. A total of 4 blood samples for determination of

plasma cefiderocol concentrations will be collected at prespecified time points corresponding to the time point at which the ELF sample is collected. Pharmacokinetic assessment of concentration data from both ELF and plasma samples is planned to be performed for every 3 subjects to determine if modifications of the ELF sampling time point in subsequent subjects are needed.

Safety Assessments:

Subject safety will be assessed by the identification of adverse events (AEs) from the time of having signed informed consent to the end of the study, up to 7 days after the last dose of cefiderocol. Additional safety assessments include physical examinations, vital sign measurements, chest X-ray, and clinical laboratory tests.

Statistical Methods:

Pharmacokinetics

Individual plasma and ELF concentrations of cefiderocol will be listed and summarized by nominal sampling time with N, Mean, standard deviation (SD) 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 and maximum 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. Concentration ratios in ELF to plasma ($R_{C,E/P}$) in each subject will be calculated, listed, and summarized with number (N), Mean, SD, CV%, Geometric Mean and CV% Geometric Mean, and median, minimum and maximum values by nominal sampling time. The time courses of individual and mean plasma and ELF concentrations and individual and mean $R_{C,E/P}$ will be presented by appropriate graphics. Population PK analyses will be performed using a nonlinear mixed effects model approach.

Safety

The number and percentage of subjects who experienced at least 1 treatment-emergent adverse event (TEAE), deaths, serious adverse events (SAEs), and TEAEs leading to discontinuation will be summarized. The number of those TEAEs, which are counted by cases reported, will also be presented. Treatment-related TEAEs will be summarized in the same way as TEAEs for overall summary.

Study Duration:

Study duration for individual subjects: maximum of 13 days (Screening, approximately 2 days; Treatment Period, 3 to 4 days; Follow-up Period, 7 days)

Expected duration of the study: 8 months

Date of Original: 30 Apr 2018

Date of Latest Amendment: 02 Nov 2018

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ΔΔQTcF	placebo-corrected QTc intervals
%$fT_{>MIC}$	the percentage of the dosing interval for which the free-drug concentration in plasma exceeds the minimum inhibitory concentration
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BLA	β-lactamase
BLQ	below the limit of quantification
C_{BAL}	cefiderocol concentration in the supernatant BALF
CBC	Complete blood count
C_{ELF}	cefiderocol concentration in the ELF
CI	confidence interval
C_{max}	maximum plasma concentration
CrCl	creatinine clearance
CRO	clinical research organization
CSR	clinical study report
cUTI	complicated urinary tract infection
CT	computed tomography
CV%	coefficient of variation
DDI	drug-drug interaction
ECG	electrocardiogram/electrocardiography
EDC	electronic data capture
eCRF	electronic case report form
ELF	epithelial lining fluid
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
$fT_{>MIC}$	time during which plasma concentrations are above the mean inhibitory concentration
GCP	Good Clinical Practice
HABP	hospital-acquired bacterial pneumonia

HCABP	healthcare-associated bacterial pneumonia
HD	hemodialysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IgM	immunoglobulin M
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
LS	least squares
MATE	multidrug and toxin extrusion
MBL	metallo-β-lactamase
MDR	multidrug resistant
MedDRA	Medical Dictionary for Regulatory Activities
MIC	mean inhibitory concentration
NTC	nontreatment control
OAT	organic anion transporter
OATP1B3	organic anion transporting polypeptide 1B3
OCT	organic cation transporter
PD	pharmacodynamic(s)
PEEP	positive end-expiratory pressure
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PT-INR	prothrombin time-international normalized ratio
q6h	every 6 hours
q8h	every 8 hours
QT	QT interval (measure between Q wave and T wave in the heart's electrical cycle)
QTc	corrected QT
QTcF	Fridericia's corrected QT
$R_{C,E/P}$	ratio of the concentration for cefiderocol in epithelial lining fluid relative to plasma
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	standard of care

SOP	standard operating procedure
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TQT	thorough QT
ULN	upper limit of normal
$Urea_{,BAL}$	urea concentrations in the BALF
$Urea_{,SERUM}$	urea concentrations in the serum
VABP	ventilator-associated bacterial pneumonia
V_{BAL}	BALF volume
V_{ELF}	calculated volume of ELF
WBC	white blood cell
WHO	World Health Organization
XDR	extensively drug resistant

1. INTRODUCTION

1.1 Rationale of Study

The primary purpose of the current study is to estimate the degree of penetration of cefiderocol into infected lung tissue in hospitalized subjects with known or suspected bacterial pneumonia who are being mechanically ventilated. The lung penetration is considered as a surrogate pharmacodynamic (PD) marker for characterizing the effect of antibiotics on bacterial pneumonia. However, β-lactam antibiotics, including cephalosporins such as cefiderocol, have demonstrated a high degree of variability and varying degrees of penetration into the lung tissue (range: 30% to 100%), despite proven efficacy and wide-spread use of these agents to treat bacterial pneumonia [1]. Even with this limitation, evaluation of lung penetration is a generally recommended method for estimating investigational antibiotic efficacy. The concentration of cefiderocol in epithelial lining fluid (ELF) will be measured at steady state at up to 3 post infusion time points and compared with a corresponding concentration of cefiderocol in plasma to estimate the concentration in ELF to plasma ratio ($R_{C,E/P}$), representing the % penetration of cefiderocol into infected lung tissue. Each individual will contribute to one time point, and overall up to 18 subjects (a minimum of 3 subjects) are planned to be assessed in this study. The data from this study along with modeling and simulations will support the potential efficacy of cefiderocol in subjects with known or suspected bacterial nosocomial pneumonia due to Gram-negative bacteria.

1.2 Background and Rationale of Cefiderocol Development

The ability to treat bacterial infections due to multidrug resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria, 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 [2].

Since the description of imipenemase-1, a metallo-β-lactamase (MBL), in *P. aeruginosa*, oxacillinase-23, a serine carbapenemase, in *A. baumannii*, and *Klebsiella pneumoniae* carbapenemase-1 (KPC-1), a serine carbapenemase, in *K. pneumoniae,* carbapenemase-encoding genes have spread worldwide and are now distributed throughout different species of Gram-negative MDR bacteria. They are now responsible for a large and increasing number of nosocomial infections. These carbapenemases inhibit almost all β-lactam antibiotics, including carbapenems, and are reported mainly in Enterobacteriaceae, *A. baumannii*, and *P. aeruginosa* [2].

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). They are particularly prevalent among XDR *P. aeruginosa* [3, 4]. Not infrequently, more than 1 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, likely to be caused mainly by nosocomial carbapenemase-producing *K. pneumoniae* of all types [5].

The outcome of a carbapenem-resistant infection can often be fatal. Falagas et al (2014) 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 (relative risk 2.05, 95% confidence interval [CI] 1.56 to 2.69) [6].

Cefiderocol has an approved international nonproprietary name: cefiderocol. For purposes of this protocol, cefiderocol will be used to refer to the study drug.

Cefiderocol is being developed to address the unmet medical need to treat carbapenem-resistant infections caused by Gram-negative bacteria, including Enterobacteriaceae, *Pseudomonas, Stenotrophomonas*, and *Acinetobacter* species independent of the underlying mechanism of carbapenem resistance. Although cefiderocol was designed to have bacterial-killing ability for carbapenem-resistant species of Gram-negative bacteria, it also has improved bacterial-killing ability for common community-acquired Gram-negative infections, as demonstrated by reduced minimum inhibitory concentration (MIC) values (for additional information refer to the current Investigator's Brochure [IB]).

1.3 Biological Features of Cefiderocol for Injection

Cefiderocol is an injectable siderophore cephalosporin discovered and being developed by Shionogi & Co., Ltd., Osaka, Japan. The antibacterial activity of cefiderocol is based on the inhibition of Gram-negative bacterial cell wall synthesis.

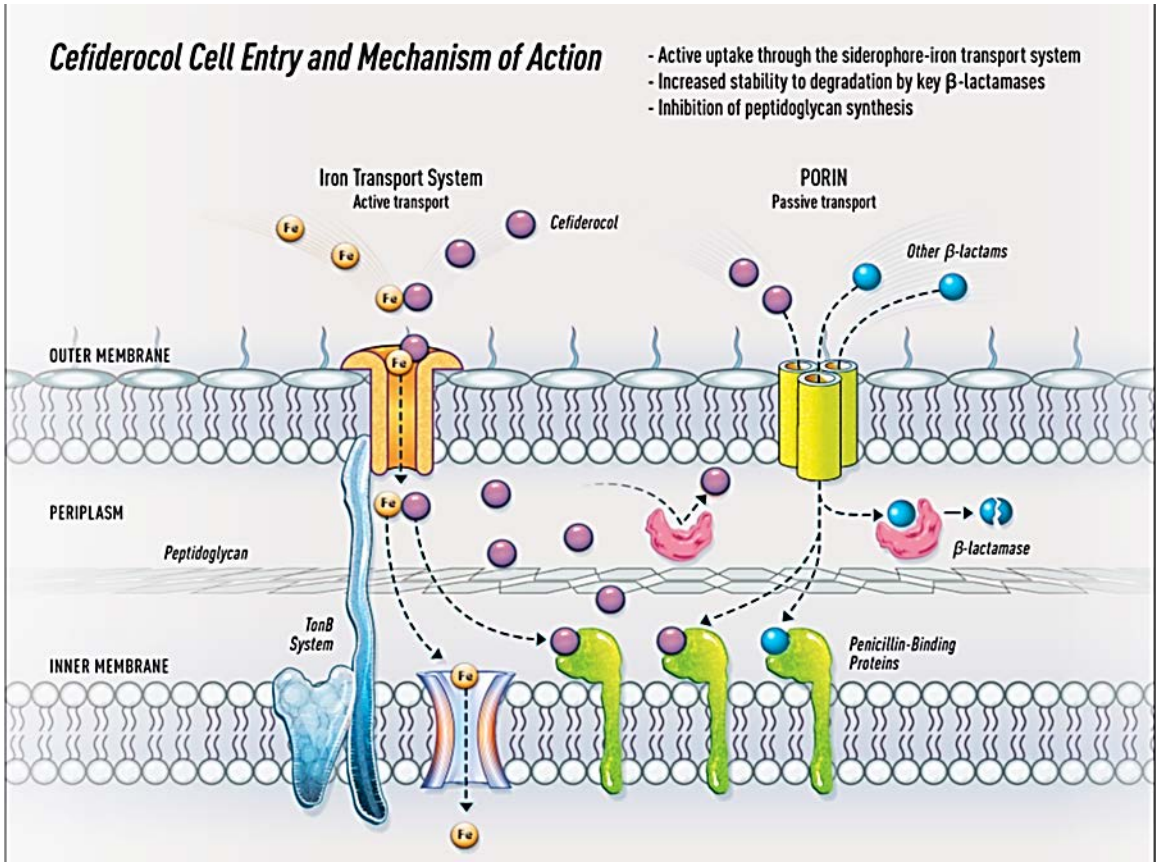
The chemical structure of cefiderocol is similar to cefepime, which is a fourth-generation cephalosporin with an extended spectrum of activity against Gram-positive and Gram-negative bacteria with greater activity against both types of organisms than third-generation agents. The major difference in the chemical structure of cefiderocol compared with cefepime is the presence of a catechol group on the side chain at position 3. Cefiderocol also has a pyrrolidinium group in the side chain at position 3 and a carboxypropanoxyimino group in the side chain at position 7 of the cephem nucleus. As

a consequence of its structure, cefiderocol has the following features in addition to the basic mechanism of action to inhibit cell wall synthesis:

1. A unique mode of action, which enhances entry into the periplasmic space of Gram-negative aerobic bacteria through the outer cell membrane. Cefiderocol forms complexes with trivalent iron and is transported via the active iron transport system common to Gram-negative bacteria. In this way, it also overcomes other mechanisms of resistance such as porin channel loss and efflux pumps.
2. Enhanced stability against β-lactamase (BLA) enzymes, including carbapenemases of the serine or MBL classes.
3. Enhanced activity against aerobic Gram-negative bacteria, especially Enterobacteriaceae, particularly *K. pneumoniae* and *E. coli*, and the nonfermenters *P. aeruginosa, S. maltophilia*, and *A. baumannii*.
4. No activity against Gram-positive bacteria and anaerobic bacteria.

The host's innate immune response to bacterial infection is to remove or severely limit the available free iron, an essential cation for bacterial growth [7]. In response, bacteria upregulate the production of extracellular molecules called siderophores that scavenge for available free iron [8]. Cefiderocol is a siderophore compound that binds free iron, and this antibiotic-iron complex is transported through the outer membrane of Gram-negative bacteria into the periplasmic space using the bacteria's active siderophore transport system [3, 7-12]. A graphic depiction of this process is presented in Figure 1-1. This process achieves bactericidal concentrations at relatively low blood concentrations of cefiderocol. Once inside the periplasmic space of the Gram-negative bacteria, cefiderocol is resistant to the usual mechanisms of degradation of β-lactam or carbapenem antibiotics by bacterial BLAs. The primary bactericidal activity is due to inhibition of bacterial cell wall synthesis.

Figure 1-1 Depiction of Cefiderocol Cell Entry and Mechanism of Action



Source: Shionogi Inc.

The greatest current unmet medical need is in the treatment of bacterial infections caused by MDR aerobic Gram-negative bacilli, broadly including the Enterobacteriaceae and the nonfermenters *P. aeruginosa, S. maltophilia,* and *A. baumannii*. Multidrug resistant bacteria, defined as > 3 class antibiotic resistance, include most Enterobacteriaceae producing AmpC, extended-spectrum BLAs, and serine BLAs. While they may be resistant to penicillins, cephalosporins, fluoroquinolones, and aminoglycosides, they have, for the most part, remained susceptible to carbapenems [3, 11, 12]. More recently, these same Enterobacteriaceae, particularly *K. pneumoniae* and *E. coli*, have acquired serine KPCs, oxacillinases, and MBLs (eg, Verona integron-encoded MBL, imipenemase, and New Delhi metallo-BLA-1) capable of hydrolyzing carbapenems [13-15]. Most of these bacteria remain susceptible only to polymyxins (polymyxin B or colistin), and thus should be considered XDR, not just MDR. The nonfermenters *P. aeruginosa, S. maltophilia,* and *A. baumannii* have also acquired carbapenemases and are also considered XDR bacteria [16]. Rarely, these XDR pathogens may also be resistant to polymyxins, and, therefore, can be considered pandrug resistant organisms, defined as resistant to all classes [16, 17].

The principal objective for cefiderocol clinical development is to demonstrate efficacy for the treatment of serious, life-threatening infections caused by Gram-negative bacteria, including Enterobacteriaceae and nonfermenters, such as *P. aeruginosa, S. maltophilia,* and *A. baumannii*. One of the most serious of these infections is pneumonia. Gram-negative pneumonia is almost always nosocomial, meaning it is associated with prior or current hospitalization or other contact with healthcare services [18]. Variably defined as hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), or healthcare-associated bacterial pneumonia (HCABP), when the infection is caused by Gram-negative bacteria, the outcomes are especially dire, with mortality rates approaching 60% [18-22]. Increasing antibiotic resistance among Gram-negative organisms, particularly that to aminoglycosides, fluoroquinolones, and cephalosporins, has limited therapeutic options to carbapenems and polymyxins [18-26]. Clinical trials in HABP/VABP/HCABP are particularly challenging due to the severity of illness, preexisting comorbidities, and controversies over study endpoints [27]. Recent clinical trials have failed to meet predefined endpoints for noninferiority (tigecycline, doripenem). Despite these setbacks, the need for new antibiotic treatments for Gram-negative infections has resulted in renewed interest in HABP/VABP as an important area for clinical investigation. Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have updated their clinical trial guidelines for these indications [28, 29].

1.4 Nonclinical Experience

In vitro, cefiderocol showed potent antibacterial activity against carbapenem-resistant Enterobacteriaceae, including MBL producing isolates, MDR *A. baumannii*, and MDR *P. aeruginosa*. Cefiderocol also showed more robust antibacterial activity than other β-lactam antibiotics in systemic, lung, urinary tract, and subcutaneous animal models of infection due to MDR *P. aeruginosa*, carbapenem-resistant *A. baumannii*, or enteric bacteria, such as extended-spectrum BLA-producing *E. coli* and *K. pneumoniae*.

As cefiderocol is not a substrate for human P-glycoprotein (P-gp), organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), organic cation transporter 2 (OCT2), multidrug and toxin extrusion 1 (MATE1), or multidrug and toxin extrusion protein 2 (MATE2-K), the risk for drug-drug interactions (DDIs) with cefiderocol mediated by these transporters is low. Since cefiderocol is not an inhibitor for human P-gp or bile salt export pump, the risk of a DDI with cefiderocol as a perturbator of these transporters is low. Cefiderocol, in a concentration-dependent manner, reduced the uptake and transcellular transport activity of each typical substrate via breast cancer resistance protein, organic anion transporting polypeptide 1B1, organic anion transporting polypeptide 1B3 (OATP1B3), organic cation transporter 1 (OCT1), MATE1, MATE2-K, OAT1, OAT3, and OCT2. The half maximal inhibitory concentration values for OAT1, OAT3, OCT1, OCT2, OATP1B3, and MATE2-K were calculated to be 141, 292, 1550, 2170, 2570, and 1230 µmol/L. The free concentration of maximum plasma concentration (C_{max}) value at the intended clinical dose (2 g, 3 times daily) was calculated to be 57.4 µmol/L (43.1 µg/mL) by multiplying the C_{max} (119 µmol/L [89.7 µg/mL]) and the in vitro free fraction ratio of cefiderocol in human at 100 µg/mL (48.2%). Cefiderocol

was suggested to have DDI potential on OAT1, OAT3, OCT1, OCT2, OATP1B3, and MATE2-K from the evaluation conducted in accordance with FDA draft guidance [30] and EMA guideline [31] of drug interaction, and therefore, a clinical DDI study was performed (Study 1521R2115). Topline data from that DDI study showed no significant effects on the pharmacokinetics (PK) of furosemide (an OAT1 and OAT3 substrate) or metformin (an OCT1, OCT2, and MATE2-K substrate). Coadministration of cefiderocol and rosuvastatin (an OATP1B3 substrate) increased the area under the concentration-time curve (AUC) for rosuvastatin by 21%, but because it is unlikely that oral medications such as rosuvastatin, other statins, or medications that are OATP1B3 substrates will occur during a treatment course requiring intravenous (IV) antibiotics, the potential for a clinically meaningful outcome in the clinically setting is considered to be low.

Refer to the current IB for additional details of completed studies.

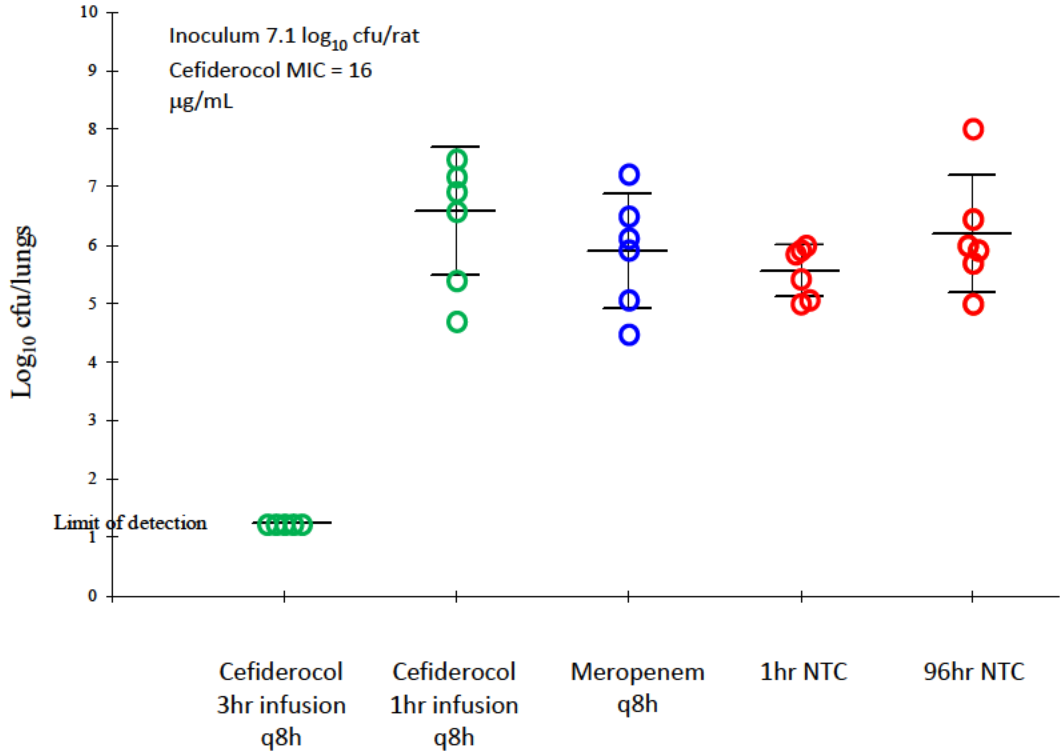
1.4.1 Pharmacokinetics/Pharmacodynamics

1.4.1.1 Animal Models of Efficacy

As with all β-lactams that target penicillin-binding proteins, the controlling PD parameter for cefiderocol is the percentage of the dosing interval for which the free-drug concentration in plasma exceeds the minimum inhibitory concentration (%$fT_{>MIC}$), and while the plasma PK measurements can determine the drug exposure over time, corrected for protein binding, the MIC remains the key variable in determining %$fT_{>MIC}$.

Shionogi has conducted a series of studies in animal models of infection, including urinary tract (murine), thigh (murine), and lung (murine and rat). In addition to the dose fractionation used in the murine models, the rat lung model was designed to reproduce human drug exposure, including infusion times of 1 and 3 hours (Figure 1-2).

Figure 1-2 **Efficacy of Cefiderocol (Human 3- and 1-hr Infusion of 2 g IV q8h) Compared with Meropenem (Human 1 g IV q8h) Against *K. pneumoniae* VA-384 in a Respiratory Tract Infection Model in Cannulated Rats**



cfu = colony-forming units; hr = hour; IV = intravenous; MIC = minimum inhibitory concentration; NTC = nontreatment control; q8h = every 8 hours

The results of the curative effect of the drug on carbapenem-resistant rat lung infections were better with a 3-hour infusion than a 1-hour infusion (for additional information refer to the current IB).

The pharmacokinetic/pharmacodynamic (PK/PD) parameter required for efficacy was determined in a murine thigh model of infection caused by 16 strains of Gram-negative bacteria with widely divergent MICs. The $\%fT_{>MIC}$ values of cefiderocol required for a static effect and 1-$\log_{10}$ reduction were approximately 60% to 70% and 70% to 80%, respectively. The $\%fT_{>MIC}$ values required for efficacy were similar among bacterial species (for additional information refer to the current IB).

In summary, the nonclinical data support the clinical development of cefiderocol as a potential human therapeutic agent against serious bacterial infections. The target PK/PD parameter is 70% to 80% of time during which plasma concentrations are above the mean inhibitory concentration ($fT_{>MIC}$).

1.5 Clinical Experience

1.5.1 Phase 1

The safety and tolerability of cefiderocol has been assessed in a total of 212 healthy adult subjects who participated in 6 clinical pharmacology studies (a single- and multiple-ascending dose study [Study 1203R2111], an intrapulmonary PK study [Study 1214R2112], a renal impairment study [Study 1222R2113], a mass balance study [Study 1516R2114], a thorough QT [TQT]/corrected QT [TQT_c] study [Study 1603R2116], and a 3-part drug interaction study [Study 1521R2115]). In these studies, healthy adult subjects or subjects with impaired renal function 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 over 1 or 3 hours. In general, cefiderocol was safe and well tolerated in the clinical pharmacology studies. There were no treatment-related or dose-dependent trends in vital sign measurements, electrocardiogram/electrocardiography (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, 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 primarily excreted unchanged (approximately 90%) in the urine (Study 1516R2114), has a plasma half-life of 2.75 hours, and is associated with linear PK in the therapeutic dose range with little accumulation after multiple-dose administration. After administration of single 100- to 2000-mg (2 g) doses, infused over 1 hour (single ascending dose study [Study 1203R2111]) and single 2- to 4-g doses, infused over 3 hours TQTc study (Study 1603R2116), the C_{max} and AUC of cefiderocol increased in proportion to the dose. After administration of multiple 2-g doses of cefiderocol every 8 hours (q8h) infused over 1 hour (once daily doses on Days 1 and 10 and q8h doses from Days 2 to 9), only a slight accumulation (1.05- to 1.16-fold) for the C_{max} and AUC of cefiderocol was observed, and plasma concentrations of cefiderocol reached steady state within 1 day of repeated administration (Study 1203R2111). After administration of a single 1000-mg (1-g) dose of [^{14}C]-cefiderocol, cefiderocol was the major component in plasma, accounting for 92.27% of the plasma AUC for total radioactivity. A degradation product, pyrrolidine chlorobenzamide, accounted for 4.70% of the plasma AUC for plasma total radioactivity, with all other metabolites each accounting for < 2% of the plasma AUC for plasma total radioactivity (Study 1516R2114). The majority (98.6%) of total radioactivity was excreted unchanged in urine, with negligible amounts (2.8%) excreted in feces (Study 1516R2114).

A Phase 1 study to assess the repolarization effects of cefiderocol on the human heart was conducted as a TQTc study (Study 1603R2116) in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 Guidance and subsequent Questions & Answers. The first part of the study consisted of a sequential-group safety and tolerability study in which the safety of the supratherapeutic dose of cefiderocol was confirmed. The second part of the study consisted of a TQTc study in which single 2-g (therapeutic) and 4-g (supratherapeutic)

doses of cefiderocol administered as 3-hour infusions were assessed along with placebo (to cefiderocol) and moxifloxacin (active control) in a double-blind, crossover design in a total of 48 subjects.

The point estimates of the least squares (LS) means of baseline and placebo-corrected QTc intervals (ΔΔQTcF) calculated using Fridericia's correction for the 2- and the 4-g doses of cefiderocol were < 5 msec and the upper bounds of the 1-sided 95% CI were < 10 msec at all postinitiation of the infusion time points. For the moxifloxacin treatment, a prolongation of Fridericia's corrected QT (QTcF) interval was observed for all time points from 1 to 10 hours postdose, confirming that a positive effect on the QTcF interval could be detected in the study (the lower bound of 1-sided 95% CI of LS means in the ΔΔQTcF > 5 msec). The results indicate that single 2- and 4-g doses of cefiderocol did not prolong the ΔΔQTcF interval to a level of regulatory concern and met the criteria stipulated in the ICH E14 guideline associated with a negative TQT study (Study 1603R2116).

1.5.2 Phase 2 and Phase 3

1.5.2.1 Phase 2 Complicated Urinary Tract Infections

A Phase 2 study of the safety and efficacy of cefiderocol administered at a 2-g dose over a 1- hour infusion to 300 subjects with complicated urinary tract infections (cUTIs) has been completed (Study 1409R2121). The results support the safety profile of cefiderocol in a subject population using the same dose (2 g, q8h) proposed for this study.

1.5.2.2 Phase 3

A pathogen-based, Phase 3 study in subjects with evidence of carbapenem resistance, Gram-negative infections at various infection sites (CREDIBLE-CR, Study 1424R2131) and a Phase 3 study in subjects with pneumonia (APEKS-NP, Study 1615R2132) are currently on-going.

Refer to the current IB for additional details of completed studies.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

- To estimate the concentration of cefiderocol in ELF, at steady state in hospitalized subjects with known or suspected bacterial pneumonia being treated with standard of care (SOC) antibiotics and requiring mechanical ventilation
- To estimate the ratio of the concentration for cefiderocol in ELF relative to plasma ($R_{C,E/P}$) in hospitalized subjects with known or suspected bacterial pneumonia on treatment with SOC antibiotics and requiring mechanical ventilation

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multicenter, single-arm, open-label study to assess the intrapulmonary and plasma concentrations of cefiderocol at steady state after multiple-dose administration in hospitalized subjects with known or suspected bacterial pneumonia on treatment with SOC antibiotics and requiring mechanical ventilation.

Screening of subjects will occur within 48 hours prior to administration of the first dose of cefiderocol on Day 1 of the study. A minimum of 3 (and up to approximately 18) qualified subjects will receive an initial 2-g dose (or renally adjusted dose) of cefiderocol on Day 1 (within 72 hours of the start of potentially effective treatment with SOC antibiotics for bacterial pneumonia) and subsequently receive cefiderocol q8h (or q6h if subject has augmented renal function) with the dosage specified in Table 3-1.

Table 3-1 Cefiderocol Dosing and Bronchoalveolar Lavage Procedure for Various Degrees of Renal Function

Creatinine Clearance	Dosage	Number of Doses Prior to Performing BAL
Augmented renal function (CrCl ≥ 120 mL/min)[a]	2 g, q6h, 3-hour infusion	3-6 doses
Normal renal function (CrCl < 120 mL/min) [a]	2 g, q8h, 3-hour infusion	3-6 doses
Mild renal impairment (CrCl 60 to < 90 mL/min) [a]	2 g, q8h, 3-hour infusion	3-6 doses
Moderate renal impairment (CrCl 30 to < 60 mL/min) [a]	1.5 g, q8h, 3-hour infusion	3-6 doses
Severe renal impairment (CrCl 15 to < 30 mL/min) [a]	1 g, q8h, 3-hour infusion	6-9 doses

BAL = bronchoalveolar lavage; CrCl = creatinine clearance; q8h = every 8 hours; q6h = every 6 hours

a Creatinine clearance will be calculated by Cockcroft-Gault equation at Screening.

The dose of cefiderocol administered to each subject will be determined by the investigator based on dosing recommendations (see Section 5.2). End of Treatment (EOT) assessments will occur within 24 hours after administration of the last dose of cefiderocol, or at early termination. The End of Study (EOS) visit will occur 7 days (± 3 days) if there is no SAE, after administration of the last dose of cefiderocol. For both cases EOS visit can be performed on-site or by telephone (see Table 3-2). If an SAE is observed it must be reported to Safety and all SAEs, regardless of causality, will be followed until resolution, stabilization, the condition becomes chronic, or the subject is lost to follow-up. The investigator will make an effort to collect AEs for 7 days after the last dose of study drug.

One ELF sample for determination of cefiderocol concentrations will be collected by bronchoalveolar lavage (BAL) procedure at 3, 5, or 7 hours, depending on the ELF cefiderocol concentration data obtained, after administration of at least 3 doses of

cefiderocol in subjects with normal or augmented renal function and subjects with mild or moderate renal impairment and after administration of at least 6 doses of cefiderocol in subjects with severe renal impairment. In addition, data from any BAL procedures performed during the study as part of routine patient care will also be collected as part of study data. A total of 4 blood samples for determination of plasma cefiderocol concentrations will be collected at prespecified time points corresponding to the dose after which the ELF sample is collected. Ongoing PK assessment of concentration data from both ELF and plasma samples will be performed for every 3 subjects to determine if modifications of the ELF sampling time point in subsequent subjects are needed. All revised sampling time point modifications will be provided by the sponsor, discussed with the investigator, and documented (see Section 7.5).

Blood and ELF samples will be collected also for determination of urea concentration. Urea is used as an endogenous marker of ELF because urea is small and relatively nonpolar and can travel across membranes freely to reach the outer surfaces of alveoli. The concentration of urea in ELF is considered to be same as the serum urea concentration, implying complete distribution. Therefore, the calculated volume of ELF (V_{ELF}) is adjusted for excess exogenous volume using the concentration of urea in blood and ELF (see Section 7.6.4.1.3).

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 cefiderocol. In addition, data will be captured at various time points during the study from safety assessments (physical examinations, vital sign measurements, chest X-rays, and clinical laboratory tests) performed as part of routine patient care (see Section 7.5.2.1), date and result will be entered in the source documents and the electronic case report form (eCRF). Adverse events will be monitored throughout the study from the time informed consent is obtained until 7 days after administration of the last dose of cefiderocol if there are no SAEs.

Table 3-2 Study Schematic

Screening	Cefiderocol Administration	End of Treatment	End of Study Visit[a]
Within 48 hours prior to the administration of the first dose of cefiderocol	Minimum of 3 doses (up to a total of 6 doses) in subjects with normal renal function and subjects with mild or moderate renal impairment, q8h; and with augmented renal function, q6h Minimum of 6 doses (up to a total of 9 doses) in subjects with severe renal impairment, q8h Initial dose must be within 72 hours of the start of treatment with SOC antibiotics for bacterial pneumonia	Within 24 hours after administration of the last dose of cefiderocol or early termination	7 days (± 3 days) after administration of the last dose of cefiderocol

q8h = every 8 hours; q6h = every 6 hours: SOC = standard of care

a End of Study Visit can be performed on-site or by telephone

3.2 Rationale for Study Design and Control Group

This study is an open-label, multicenter, single-arm study and is being conducted to estimate the degree of penetration of cefiderocol into infected lung tissue, as measured by plasma and ELF cefiderocol concentrations.

The study will be conducted in an open-label (unblinded) manner considering that the primary purpose of the study is focused on PK parameter assessments, which are objective rather than subjective endpoints and therefore do not require blinding for unbiased interpretation. Accordingly, no control group is necessary to achieve the study objectives.

The 2-g dose (or renally-adjusted dose) of cefiderocol infused intravenously over 3 hours, selected for the proposed study is the anticipated therapeutic dose of cefiderocol. Furthermore, 3 doses of cefiderocol in subjects with normal or augmented renal function and subjects with mild or moderate renal impairment, and 6 doses of cefiderocol in subjects with severe renal impairment will be administered in order to achieve steady state at the time the primary study assessments are performed. The recommended blood sampling scheme for determination of plasma cefiderocol concentrations provides a collection interval that will allow the PK profiles for cefiderocol to be adequately characterized. The ELF sample, along with a blood sample, will initially be obtained at the time point where cefiderocol is expected to achieve C_{max}.

The study population consists of subjects with known or suspected bacterial pneumonia. Currently, the available concentration data for cefiderocol in ELF, a surrogate for lung tissue penetration, is in healthy subjects where approximately 24% plasma unbound concentrations were measured in ELF. However, the ELF data determined in healthy subjects may not be representative of the degree of penetration in patients with infected

lungs due to a variety of considerations including alterations in blood flow and degree of penetrability resulting from thickened secretions.

A minimum of 3 subjects will be enrolled to provide a summary of cefiderocol concentrations in ELF in hospitalized subjects with known or suspected bacterial pneumonia being treated with SOC antibiotics and requiring mechanical ventilation. However, if necessary, up to approximately 18 subjects may be enrolled to ensure adequate information is obtained to meet the objectives of this study. Nonevaluable subjects will be replaced. See Section 7.5.2 for more details.

3.3 Study Duration

3.3.1 Study Duration in Individual Subjects

The maximum duration of study participation for an individual subject, from the time of Screening (within 48 hours prior to the administration of the first dose of cefiderocol) to the EOS visit (up to 7 days after administration of the last dose of cefiderocol), is 13 days. Cefiderocol dosing will be terminated once the BAL procedure has been performed and ELF samples, plasma PK samples, and urea samples have been collected for analyses at which time no further cefiderocol dosing will be permitted.

3.3.2 Planned Study Duration

The expected time for study completion, from first subject in to last subject last visit is approximately 8 months.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1 Study Population

Subjects with known or suspected bacterial pneumonia being treated with SOC antibiotics and requiring mechanical ventilation who fulfill the following eligibility criteria will be enrolled.

4.2 Inclusion Criteria

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

1. Subject is male or female, 18-80 years (both inclusive) at the time written informed consent is obtained
2. Subject has provided written informed consent or informed consent has been provided by subject's legally authorized representative (Note: Country-specific rules and/or local state laws and local Ethics Committee approval for legally authorized representative informed consent will determine whether or not and how a subject unable to comprehend or sign the informed consent is allowed to be enrolled in the study)
3. Subject has a clinical diagnosis of bacterial pneumonia, documented or suspected, (even if later known that the subject does not have bacterial pneumonia, discontinuation of the study is not necessary)
4. Subject is hospitalized and receiving SOC antibiotic treatment for pneumonia
5. Subject is mechanically ventilated and is expected to remain mechanically ventilated for at least 48 hours (or 72 hours for subjects with severe renal impairment) after the first dose of cefiderocol
6. Subject has a life expectancy of at least 3 weeks from the Screening visit
7. Female meeting 1 of the following criteria:
    a. Surgically sterile (has had a hysterectomy and/or bilateral oophorectomy, or a bilateral salpingectomy or tubal ligation for the purpose of contraception for at least 6 weeks with appropriate documentation of such surgery)
    b. Postmenopausal (defined as older than 45 years of age with cessation of regular menstrual periods for at least 6 months and a history of a follicle-stimulating hormone level of > 40 mIU/mL, or amenorrhea for at least 12 months)
    c. Of childbearing potential and using combined (estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (including oral, intravaginal, injectable, implantable, and transdermal contraceptives), or an intrauterine device (IUD) or intrauterine hormone-releasing system for the entire duration of the study
    d. Of childbearing potential and practicing abstinence as a preferred and usual life style and/or agrees to continue practicing abstinence from Screening for the entire duration of the study

e. Of childbearing potential and whose sole heterosexual partner has been successfully vasectomized and agrees to not have other heterosexual partners for the entire duration of the study

4.3 Exclusion Criteria

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

1. Subject has a chemical/aspiration pneumonia that does not require antibiotic treatment (including aspiration of gastric acid, inhalation injury). The term chemical pneumonia refers to the aspiration of substances that are toxic to the lower airways causing chemical burn and injuries in the airway.
2. Subject has a history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam (Note: for β-lactams, a history of a mild rash followed by uneventful re-exposure is not a contraindication to enrollment)
3. Subject has extensive cystic lesion(s) or severe structural abnormality (eg, cystic fibrosis, emphysema, cystic lesions of sarcoidosis or tuberculosis, post obstructive pneumonia due to lung cancer, etc) of the lung that hinders recovery of bronchoalveolar lavage fluid (BALF)
4. Subject is receiving peritoneal dialysis.
5. Subject has severe renal impairment requiring hemodialysis (HD) or end-stage renal disease requiring HD with creatinine clearance (CrCl) < 15 mL/min
6. Subject is in refractory septic shock defined as persistent hypotension despite adequate fluid resuscitation or despite vasopressive therapy at Screening
7. Subject is a female who has a positive pregnancy test at Screening or who is lactating
8. Subject has received another investigational drug within 30 days prior to Screening
9. Subject has previously participated in this clinical study and has received at least 1 dose of cefiderocol
10. 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.

4.4 Screen Failures

Screen failures are defined as subjects who provide consent to participate in the study but are not subsequently dosed in the study. Minimal information will include informed consent date, baseline subject characteristics, all eligibility criteria not met, reasons for screen failure including reporting of AEs that lead to screen failure if applicable, and any SAEs and will be entered in the source documents and the eCRF.

Subjects who do not meet the criteria for participation in the study (screen failure) may be rescreened only once in this study. Rescreened subjects should be assigned a new subject number to distinguish it from the initial Screening.

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

The investigator will make every reasonable attempt to complete the study for each study subject.

A subject may withdraw consent to participate in the study at any time, for any reason.

The investigator or subinvestigator may discontinue a subject from study drug 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 drug
- The subject recovers from the infection prior to the BAL procedure and inflammation no longer exists in the lung
- The subject is unable to undergo the BAL procedure or unable to provide an appropriate ELF sample
- The subject is proved to be ineligible for the study after the initiation of study
- The investigator or subinvestigator determines that the subject should be discontinued from the study drug based on the management and discontinuation criteria for abnormal liver function tests (Appendix 2)
- The investigator or subinvestigator determines that the subject should be discontinued from study drug for any other reasons (eg, extubation)
- The study is prematurely terminated

In the event a subject withdraws consent or a subject is prematurely discontinued from study drug by the investigator or subinvestigator, the investigator or subinvestigator will promptly notify the sponsor. If a subject is prematurely discontinued from study drug by the investigator or subinvestigator, EOT (or early termination) procedures including physical examination, vital sign measurements, and clinical laboratory tests will be performed. The reporting of AEs will be obtained until the EOS visit, which occurs 7 days after the last dose of cefiderocol if there is no SAE. If an SAE is observed it must be reported to Safety and all SAEs, regardless of causality, will be followed until resolution, stabilization, the condition becomes chronic, or the subject is lost to follow-up. The investigator will make an effort to collect AEs for 7 days after the last dose of study drug.

If a subject withdraws or is discontinued from study or study drug, a replacement subject may be enrolled if deemed appropriate by the sponsor.

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

5. STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Test Drug

Cefiderocol will be supplied in vials containing 1 g of cefiderocol as a white to light yellow cake or powder, manufactured by Shionogi & Co., Ltd. Each cefiderocol vial will be reconstituted in 0.9% saline (normal saline) to produce a clear solution and then extracted for further dilution in normal saline to prepare an infusion solution with a final concentration of at least 20 mg/mL for IV administration.

Each dose of cefiderocol will be prepared by the study pharmacist 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.

5.2 Treatments to be Administered

The dose of cefiderocol administered to each subject will be determined based on renal function as described in this section (see Table 5-1). Dosing recommendations for subjects with moderate or severe renal impairment and subjects with augmented renal clearance are provided. For all subjects serum creatinine levels should be checked once daily to determine whether dose adjustments of cefiderocol should be made.

Beginning on Day 1, subjects will be administered 2-g doses (or renally adjusted dose) of cefiderocol infused intravenously over 3 hours, q8h (or q6h for subjects with augmented renal function), for an expected minimum of 3 doses and up to a total of 6 doses in subjects with normal or augmented renal function and subjects with mild or moderate renal impairment, and for an expected minimum of 6 doses and up to a total of 9 doses in subjects with severe renal impairment. Cefiderocol dosing will be terminated once the BAL procedure has been performed and ELF samples, plasma PK samples, and urea samples have been collected for analyses at which time no further cefiderocol dosing will be permitted. After initiation of cefiderocol administration, doses of cefiderocol administered to each subject may be adjusted based on changes in renal function as assessed daily by CrCl (using the Cockcroft-Gault equation) and according to the dosing recommendations for subjects (see Table 5-1). Any dosing modifications based on the dosing recommendations will be agreed to by the investigator and documented. Please see the Renal Function and Dose Adjustment Log in the pharmacy manual.

Table 5-1 Dosing Recommendations of Cefiderocol Based on Renal Function

Creatinine Clearance	Dosage
Augmented renal function (CrCl ≥ 120 mL/min)[a]	2 g, q6h, 3-hour infusion
Normal renal function (CrCl < 120 mL/min)[a]	2 g, q8h, 3-hour infusion
Mild renal impairment (CrCl 60 to < 90 mL/min)[a]	2 g, q8h, 3-hour infusion
Moderate renal impairment (CrCl 30 to < 60 mL/min)[a]	1.5 g, q8h, 3-hour infusion
Severe renal impairment (CrCl 15 to < 30 mL/min)[a]	1 g, q8h, 3-hour infusion

CrCl = creatinine clearance; q6h = every 6 hours; q8h = every 8 hours

a Creatinine clearance will be calculated by Cockcroft-Gault equation at Screening.

5.3 Selection and Timing of Dose for Each Subject

Dosing recommendations were developed based on PK parameters estimated for subjects with bacterial pneumonia from a population PK model using PK data from healthy adult subjects to target equivalent systemic exposure (AUC) in the study population. Specifically, a population PK model was developed based on the data obtained from healthy adult subjects and subjects with cUTIs, where doses adjusted to be equivalent to a 2-g dose of cefiderocol, q8h, and infused over 1 or 3 hours, were administered. Cefiderocol is renally excreted and requires dosage adjustment based on renal function estimated from serum creatinine concentration. Dosage adjustment based on reduced renal function will be made by the investigator or a qualified designee. Dosage adjustments for cefiderocol for subjects with various degrees of renal function are found in Table 5-1.

5.4 Method of Assigning Subjects to Treatment Groups

This is a single-arm study and each qualified subject with normal or augmented renal function or mild or moderate renal impairment will receive administration of an expected minimum of 3 doses and up to a total of 6 doses while subjects with severe renal impairment will receive administration of an expected minimum of 6 doses and up to a total of 9 doses.

If rescreening of a subject takes place, the rescreening subject number will be 100 more than the original (eg, Subject Number 001 will be replaced by Subject Number 101).

5.5 Blinding

This is an open-label study.

5.6 Packaging and Labeling

Cefiderocol will be provided in vials containing 1 g of cefiderocol. Each vial will be labeled with the name of the active ingredient, protocol number, dosage form, strength, storage conditions, sponsor's name and address, and cautionary statements according to Federal Regulations.

5.7 Storage and Accountability

Cefiderocol vials will be stored in a tight, light-resistant container at 2ºC to 8ºC (36ºF to 46ºF), and must be protected from light.

The investigator will ensure that all study drug is stored and dispensed in accordance with the protocol and pharmacy manual concerning the storage and administration of investigational drugs. All drug supplies must be kept in a secure locked area with access limited to those authorized by the investigator.

The qualified designee will maintain accurate records on the following information: receipt and condition of all study drugs, date of the receipt, when and how much study drug 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 all used and unused clinical supplies will be performed. The study drug must not be used for any purpose other than the present study.

5.8 Investigational Product Retention at Study Site

At the end of the study, all used and unused clinical supplies (cefiderocol) will be held at the study site although those supplies will not be required to be stored under the storage conditions defined above. All the used and unused clinical supplies must be returned to the sponsor (or designee) as per the sponsor's written instructions or destroyed as per the clinical research organization's (CRO's) or local standard operating procedures (SOPs) upon agreement and written approval of the sponsor.

5.9 Treatment Compliance

Start times and end times of the administration of IV treatments and the approximate extent of completion of all infusions will be recorded in the source documents and the eCRF. Any interruption or adjustment of the rate of an infusion will be noted in the source documents and the eCRF. The reason for interruption or adjustment also will be noted in the source documents and the eCRF.

6. RESTRICTIONS

6.1 Prior Therapy

Prior therapy is defined as any therapy administered within 14 days prior to administration of the first dose of cefiderocol on Day 1 of the study.

Any prior therapy (prescription drugs, over-the-counter drugs, procedures [eg, surgical or nonsurgical related to infection treatment or treatment-related complications such as dialysis] with or without any medication) taken by the subject within 14 days prior to the day of signing informed consent for the study, will be recorded in the source documents and the eCRF and the information will include name of drug used or procedures done, duration of treatment, and reason. If a drug is administered, route of administration will also be included.

6.2 Concomitant Therapy During the Study

Concomitant therapy is defined as any therapy administered after administration of the first dose of cefiderocol until the EOS visit.

Cefiderocol will be administered in combination with a SOC treatment regimen.

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

- Name of medication or procedure
- Start date
- Stop date
- Route of administration
- Reason for use

6.2.1 Prohibited Therapy

Not applicable.

7. STUDY PROCEDURES AND METHODS OF ASSESSMENTS

The study procedures are summarized in the Time and Events Schedule in Appendix 1.

7.1 Informed Consent

Informed consent will be obtained for all subjects prior to performing any study related procedures. A subject cannot be entered in the study until he/she or his/her legally authorized representative has signed and dated the informed consent form (ICF).

The investigator or qualified designee will fully explain the nature of the study to the subject, or, if the subject is unable to give consent him/herself, to the subject's legally authorized representative using the Institutional Review Board (IRB)-approved ICF. When the subject or his/her legally authorized representative agrees that he/she can participate in the study, the subject or his/her legally authorized representative must voluntarily sign an ICF prior to the initiation of any study procedures. A copy of the signed and dated ICF will be given to the subject or legally authorized representative. The signed and dated original ICF will be retained by the investigator. The date ICF was signed will be recorded in the source documents and the eCRF.

The investigator, or qualified designee is responsible for ensuring that the subject (or legally authorized representative) understands the risks and benefits of participating in the study, including answering any questions the subject (or legally authorized representative) 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 Baseline, Subject Characteristics, and Medical History

A complete medical history including prior or concomitant antibiotics will be taken at Screening. Demographics and baseline characteristics, including date of birth, initials, sex, ethnicity, race, body weight, and height will be recorded in the source documents and the eCRF.

7.3 Enrollment in the Study and Dispensing Study Drug

After a subject has signed informed consent, the investigator, or designee will enter the new subject into EDC by which a subject identification number will be assigned in EDC. If the subject is eligible according to the inclusion/exclusion criteria, the subject will enter the treatment period of the study. The investigator or subinvestigator will assign the appropriate dosage to the subject depending on the subject's renal function. The site pharmacist will prepare and dispense the study drug as specified in Section 5.2.

7.4 Efficacy Assessments

There are no efficacy assessments in this study.

7.5 Pharmacokinetics Assessments

Pharmacokinetic assessments will be performed for plasma and ELF samples obtained from each subject. The ELF and plasma sample collections must be done in connection with the same cefiderocol infusion. Detailed procedures for sample collection, handling, labeling, storage, and shipment to the bioanalytical laboratory will be provided by the sponsor in study-specific laboratory manual(s). Please see Appendix 2 of the protocol for more details on PK and urea sampling.

7.5.1 Plasma Samples

A total of 4 blood samples for determination of plasma cefiderocol concentrations will be collected at prespecified time points after administration of at least 3 doses of cefiderocol in subjects with normal or augmented renal function and subjects with mild or moderate renal impairment, and after administration of at least 6 doses of cefiderocol in subjects with severe renal impairment: (1) 1 hour after the start of infusion, (2) 3 hours after the start of infusion (within 30 minutes prior to the end of infusion), (3) 2 hours after the end of infusion (within ± 1 hour), and (4) 4 hours after the end of infusion (within ± 1 hour). The plasma PK samples will be collected at time points around the same cefiderocol infusion that the BAL procedure is performed. A blood sample for urea assessment will be collected as part of plasma sample collection within 30 minutes prior to the BAL procedure.

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

7.5.2 Epithelial Lining Fluid Sample

A single BAL procedure must be performed by a medical doctor such as the principal investigator or subinvestigator. Mini-BAL is not allowed in this study.

One ELF sample will be collected per subject for the determination of cefiderocol concentration by BAL procedure on the inflamed section of the lung (ie, a lobe where pneumonia is expected to be present, based on the last chest radiologic imaging) after administration of at least 3 doses of cefiderocol in subjects with normal renal function or augmented renal function and subjects with mild or moderate renal impairment and after administration of at least 6 doses of cefiderocol in subjects with severe renal impairment. If it is not convenient for the subject or the institution to perform the BAL procedure after the 3rd dosing (or 6th dosing for severe renal impairment subjects), the 4th, 5th, or 6th dosing could be considered as the timing for the BAL procedure (or the 7th, 8th, or 9th dosing for severe renal impairment subjects).

The ELF sample for the determination of cefiderocol concentrations will be collected by BAL procedure 3, 5, or 7 hours after administration of cefiderocol depending on the data obtained during the conduct of the study (see Appendix 2). The ELF sample will be analyzed for white blood cell count and differential as well as urea.

Pharmacokinetic assessments in ELF will be performed for all subjects. After the enrollment and collection of PK samples from the first 3 subjects, the sites that are activated for enrollment will be instructed, via a phone call from the sponsor or CRO, to pause enrollment until the available data has been processed and evaluated. The phone call will be followed by written notification via “Dear Dr Letter” with copy to the CRO.

The data obtained from the first 3 subjects will be evaluated by the sponsor, and the BAL collection time point for the ELF sample may subsequently be modified in accordance with the outlined procedure (see Figure 7-3 and Appendix 2).The sampling time point may be adjusted 3 times during the study, each time after evaluation of 3 subjects’ PK data. Upon evaluation of data, sponsor or CRO will notify sites via phone call and “Dear Dr Letter” with copy to the CRO about any changes in BAL sampling time point. Sites are required to provide written acknowledgement of receipt of changed BAL sampling time point.

A sampling procedure scheme will be provided in the study Statistical Analysis Plan (SAP) prior to the first subject dosing in the study. The final sampling scheme will be presented in the clinical study report (CSR). The sampling procedure will be determined by the sponsor based on available data, and will be documented.

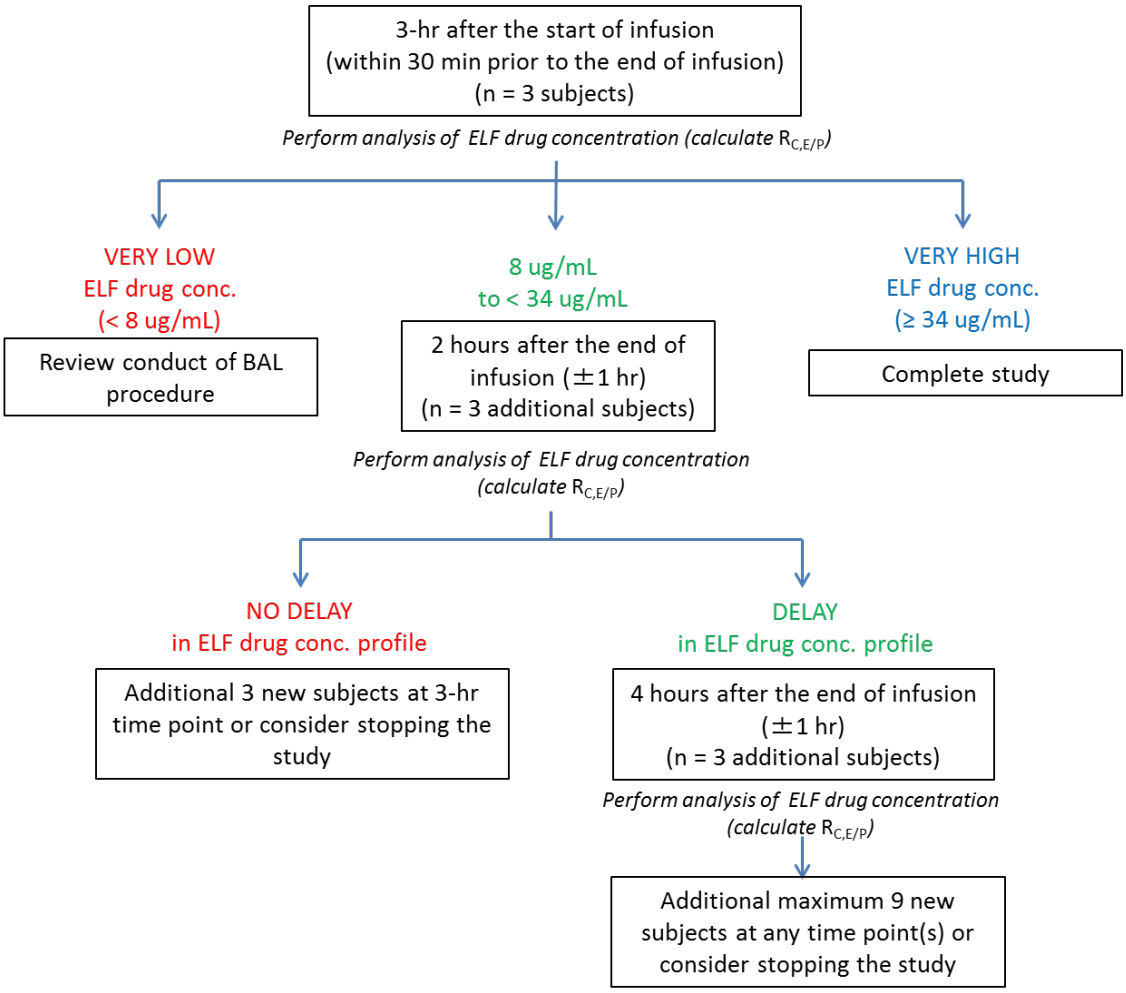
After PK assessments have been completed and evaluated in a total of 9 subjects split evenly in the 3 sampling steps depicted in Figure 7-3, up to 9 additional subjects may be enrolled from whom ELF samples will be collected at time point(s) specified by the sponsor. The total number of 18 evaluable subjects may be enrolled in this study. Nonevaluable subjects will be replaced with new subjects.

The BAL procedure will be detailed in a study-specific laboratory manual provided by the sponsor. The subject should be monitored per SOC and as clinically indicated.

If the local laboratory performs a microbiology test using the BAL sample, the result must be recorded in the source documents and the eCRF.

Refer to lab manual for BAL procedure and ELF sampling details.

Figure 7-3 Epithelial Lining Fluid Sampling Procedure Schematic



BAL = bronchoalveolar lavage; conc. = concentration; ELF = epithelial lining fluid; hr = hour; min = minutes; $R_{C,E/P}$ = ratio of the concentration for cefiderocol in ELF relative to plasma

7.5.2.1 Ventilator Parameters

Within 30 minutes prior to the start of the BAL procedure, the following ventilator parameters will be captured from all subjects: respiratory rate (breaths/minute) and positive end-expiratory pressure (PEEP). The results will be entered in the source documents and the eCRF.

7.6 Safety Assessments

7.6.1 Physical Examination

A complete physical examination will be performed at Screening. Symptom-driven physical examination relevant to the subject's current condition will be performed as clinically indicated (see Appendix 1) and at the investigator's discretion from predose until end of treatment. Body weight in kilograms and height in centimeters will be obtained at Screening. The physical examination should be performed according to the normal practice of the clinical study site by the investigator or subinvestigator. Clinically

significant findings on physical examination will be recorded as an AE in the source documents and the eCRF. Weight and height will be entered in the source documents and the eCRF.

7.6.2 Vital Signs

Blood pressure (systolic/diastolic), body temperature, pulse rate, and respiratory rate will be measured at Screening and at specified time points.

The vital signs will be recorded once a day during Screening and at least 3 times a day at approximately evenly-spaced intervals across the 24-hour day, starting on Day 1 of the infusions and continuing while the subject is receiving cefiderocol.

Vital signs obtained through continuous monitoring methods, including intra-arterial catheters, may be used to record blood pressure, body temperature, and heart rate.

The investigator or subinvestigator will consider whether changes from baseline are clinically significant (see also Section 7.6.5). Results of blood pressure, body temperature, pulse rate, and respiratory rate will be entered in the source documents and the eCRF.

7.6.3 Chest X-Ray

A chest X-ray will be performed at Screening or within 48 hours of Screening per Appendix 1 and will be considered as baseline. Data from chest X-rays performed as part of routine patient care will be collected throughout the study. A computed tomography (CT) scan can be a substitute of chest X-ray if taken according to local SOC. The results will be entered in the source documents and the eCRF.

Results of chest X-rays will be entered in the source documents and the eCRF.

7.6.4 Clinical Laboratory Tests

Clinical laboratory tests will be performed at prespecified time points per the Time and Events Schedule in Appendix 1. 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 from the first dose of cefiderocol, during administration of cefiderocol until the last dose of cefiderocol. Clinical laboratory tests during the treatment period will be symptom-driven and at the investigator's discretion.

Routine samples such as hematology and blood chemistry parameters will be measured at a local laboratory, and the results will be entered in the eCRF. PK samples and other specialized samples for testing will be analyzed at a central laboratory and 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.

Date of specimen collection and whether or not specimen was collected will also be entered in the source documents and the eCRF.

7.6.4.1 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 reference ranges are implemented during the study conduct.

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

7.6.4.1.1 Routine Laboratory Tests

Routine hematology and blood chemistry parameters that will be assessed at local laboratory are presented in Table 7-1. Mandatory laboratory tests are, complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), total bilirubin (TBL), blood urea nitrogen, serum creatinine, blood glucose, serum or urine pregnancy test (female only) at Screening. The results will be entered in the source documents and the eCRF.

If a microbiology test has been performed (before or during Screening) to confirm the clinical diagnosis, the result from the test done closest to the day of screening or on the day of screening should be recorded in the source documents and the eCRF.

Table 7-1 Routine Laboratory Tests

Category	Evaluation Parameters	
Hematology tests	Hematocrit* Hemoglobin* Platelet count*	RBC* WBC count with differential* and morphology incidences
Blood chemistry tests	Aspartate aminotransferase* Alanine aminotransferase* Gamma glutamyltransferase* Alkaline phosphatase* Total bilirubin* LDH C-reactive protein Total protein Albumin	Blood urea nitrogen* Serum creatinine* Blood glucose* Uric acid Electrolytes (sodium, potassium, chloride, calcium, magnesium, and bicarbonate)
Other	Serum or urine pregnancy test at Screening (females only)*	

LDH = lactate dehydrogenase; RBC = red blood cell; WBC = white blood cell

*mandatory laboratory tests

7.6.4.1.2 Creatinine Clearance

Creatinine clearance will be calculated from serum creatinine by Cockcroft-Gault formula as described below to assess renal function and will be recorded in the source documents and the eCRF.

- **Cockcroft-Gault formula**
  CrCl (mL/min) = (Weight [kg]) × (140 - age in years)/(72 × serum creatinine [mg/dL]) x (0.85 if female)

7.6.4.1.3 Serum and ELF Sample Collection for Urea Analysis

A blood sample will be collected for urea analysis from each subject prior to and within 30 minutes to the start of the BAL procedure.

The ELF sample collected from the BAL procedure will be used for urea analysis.

7.6.4.1.4 Pregnancy Tests

A serum or urine pregnancy test will be performed at Screening for female subjects of childbearing potential only.

7.6.4.2 Sample Collection, Storage, and Shipping

Routine laboratory samples 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.

BAL and blood samples for PK and urea assessment will be collected, processed, frozen and stored locally until shipped to the central laboratory for analyses.

Details can be found in the study lab manual.

7.6.5 Adverse Event Assessments

7.6.5.1 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 course of a 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 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 investigator or subinvestigator is responsible for assessing AEs. Adverse events should be fully investigated and recorded in detail in the source documents and the eCRF, including onset date, end date, of, severity, seriousness (with seriousness criteria), relationship with the study drug, action taken to manage the AE, and the outcome of the AE, including the date.

7.6.5.2 Assessment Period

Adverse events will be collected from the time signed informed consent is obtained through the EOS visit (up to 7 days) after administration of the last dose of the study drug. If a subject is prematurely discontinued from study drug by the investigator or subinvestigator, the investigator will make an effort to collect AEs for 7 days after the last dose of study drug. All SAEs, regardless of causality, will be followed until resolution, stabilization, the condition becomes chronic, or the subject is lost to follow-up.

7.6.5.3 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

The highest severity grades identified during the period in which the AE occurred will be recorded in the source documents and the eCRF and the SAE or other expedited form as required.

7.6.5.4 Relationship to the Study Drug

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

- **Related:** An AE that can be reasonably explained as having been caused by the study drug. For example, the occurrence of the AE can be explained by any of the following: a pharmacological effect of the study drug (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 that cannot be reasonably explained as having been caused by the study drug.

7.6.5.5 Expectedness

An AE is considered expected if it is listed in Expected Adverse Reactions in Section “Undesirable Effects” of “SUMMARY OF DATA AND GUIDANCE FOR INVESTIGATORS” in the current IB for cefiderocol.

7.6.5.6 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 the study drug from baseline, the investigator or subinvestigator will consider whether those results are clinically significant. Abnormal laboratory test results are defined as values outside the reference range. For test results that 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 that are considered to be clinically significant by the investigator or subinvestigator are to be recorded as AEs in the source documents and the eCRF. 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 (see Section 7.6.5.7.1)
- Clinical laboratory test results that lead to a change in dosing of study drug or discontinuation from the study
- Clinical laboratory test results that lead to a concomitant medication 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 3.

In addition, when any test result meets the management and discontinuation criteria for abnormal liver function tests (Appendix 3), the results of further assessments and required follow-up should be recorded in the Liver Event Form.

7.6.5.7 Serious Adverse Events

7.6.5.7.1 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 an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical intervention to prevent 1 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. The investigator or subinvestigator will determine the seriousness of an AE. Clinical laboratory liver test results that meet the following criteria are considered to be an SAE (See Appendix 3):

Test result in which aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x the upper limit of normal (ULN) and TBL > 2 x ULN.

Hospitalization for preplanned procedures or for an elective procedure 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 hospitalization or prolongation of a hospitalization for reasons other than an AE would not be considered an SAE.

7.6.5.7.2 Reporting Serious Adverse Events

All SAEs must be reported to the CRO or sponsor in detail on the SAE Form or via electronic data capture (EDC) within 24 hours from the time point when the investigator first becomes aware of the SAE. If EDC becomes unavailable, all SAEs must be reported to the CRO or sponsor in detail utilizing the SAE form. All SAEs must be reported regardless of causal relationship to the study drug. A sample of the paper SAE Form and further instructions can be found in the Site Regulatory Binder. Follow-up information on the SAE may be requested by the sponsor.

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 the event of any SAE reported or observed during the study, whether or not attributable to the study drug, site personnel must report the SAE via the EDC or if the EDC is unavailable, prepare an SAE Form and fax or e-mail the completed form within 24 hours to:

OR

If the sponsor requires a follow-up assessment, the investigator should enter new information into the EDC or by using the SAE Form if the EDC is unavailable. 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; however do not send hospital medical records to the sponsor unless specifically requested.

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 in the source documents and the eCRF. Clinical, laboratory, and diagnostic measures should be employed by the investigator as needed to adequately determine the etiology of the event.

Any SAE occurring after AE assessment period specified in Section 7.6.5.2 that is considered to be related to the study drug by the investigator, must be reported to the CRO or the sponsor.

The investigator will be responsible for reporting all SAEs to the IRB with the local regulatory requirement, as well as the sponsor. The sponsor will be responsible for reporting SAEs to the regulatory authorities as required by the applicable regulatory requirements.

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

Abuse, misuse, overdose, or medication error of the study drug (as defined below) must be reported to the CRO by the investigator using a Special Situations Report Form within 24 hours of becoming aware (refer to Section 7.6.5.7.2 for reporting destination to the CRO; INC SAE Hotline). If SAE is suspected, the investigator will enter the SAE in the EDC.

- **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 or labeling.

- **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.

7.6.5.9 Pregnancy

If a female subject becomes pregnant during the study, the investigator (or subinvestigator) will immediately discontinue the study drug. All pregnancy exposures that occur after the first dose of the study drug until the EOS visit must be reported within 24 hours from the time point when the investigator first becomes aware of the pregnancy and the Pregnancy Form will be submitted to the CRO or sponsor by the investigator (refer to Section 7.6.5.7.2 for reporting destination to the CRO; INC SAE Hotline). Pregnancy complications and elective terminations for medical reasons must also be reported as an AE or 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 or sponsor.

7.6.5.10 Treatment-emergent Adverse Events

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

7.7 Appropriateness of Measurements

The safety and PK evaluations selected for the study are typical for this subject population and type of investigation, and utilize widely accepted methods. The BAL procedure used in this study to obtain the ELF samples is known to be a safe and well-established clinical procedure [32].

7.8 Allowable Time Window

Measurements will be performed according to the Time and Events Schedule in Appendix 1, and the acceptable time deviations relative to the time points are specified in Table 7-2 below. Every effort should be made to adhere as closely as possible to procedure time points specified.

Table 7-2 Allowable Time Window

Study Activity	Specified Time or Day	Acceptable Time Window
Blood sample collection at 1 hour after the start of infusion for PK		± 15 minutes
ELF and blood sample collection at 3 hours after the start of infusion for PK		Within 30 minutes prior to the end of infusion
ELF and blood sample collection at 2 hours or 4 hours after the end of infusion for PK		± 1 hour
Blood sample collection corresponding with ELF sample collection for PK		± 5 minutes after ELF sample collection
Safety assessments		± 1 hour
EOT assessments	24 hours after the last dose of cefiderocol	+ 1 day
EOS visit	7 days after the last dose of cefiderocol	± 3 days

ELF = epithelial lining fluid; EOS = End of Study; EOT = End of Treatment; PK = pharmacokinetic(s)

8. STUDY ACTIVITIES

Study Activities are presented in the Time and Events Schedule (Appendix 1).

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 a SAP 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 noted in the CSR.

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

No inferential statistical testing will be performed in this study. No efficacy measurements will be recorded or tabulated.

All subject study data, including data not appearing in tables, will be presented in by subject data listings. Individual subject data, PK data, and any derived data will be presented by subject. All analyses and tabulations will be performed using both the SAS® Version 9.1 or higher and WinNonlin® Version 6.2.1 or higher.

9.2 Determination of Sample Size

A minimum of 3 subjects will be enrolled to provide a summary of cefiderocol concentrations in ELF in hospitalized subjects with known or suspected bacterial pneumonia being treated with SOC antibiotics and requiring mechanical ventilation. However, if necessary, up to approximately 18 subjects may be enrolled to ensure adequate information is obtained to meet the objectives of this study. No formal calculations were performed to determine sample size for this study. Section 7.5.2 outlines the algorithm regarding number of subjects to be enrolled in this study.

9.3 Analysis Populations

The following analysis populations will be examined in this study:

- **The Safety population** includes all enrolled subjects who receive at least 1 dose of the study drug. The population will be analyzed as treated.
- **The PK concentration population** includes all subjects who receive at least 1 dose of cefiderocol and have at least 1 evaluable concentration of cefiderocol in BALF. This population will be used for the concentration listing. This population will also be used for plotting of the concentration-time data and the concentration summary.

9.4 Handling of Missing Data

Missing data will not be imputed. All analyses will be based on observed cases.

9.5 Subject Disposition

Among the subjects enrolled into the study, 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. The number of subjects included in each analysis population will also be presented.

9.6 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics for the safety population.

9.7 Extent of Exposure and Treatment Compliance

The study drug exposure and compliance will be listed.

9.8 Prior Therapies

Prior therapies for drugs will be coded using the World Health Organization (WHO) Drug Dictionary. Subjects who have received prior therapy(ies) will be listed 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 for the safety population.

9.10 Efficacy Analysis

There will be no efficacy analysis for this study.

9.11 Safety Analyses

The safety population will be used for all safety analyses.

9.11.1 Adverse Events

Adverse events will be classified by System Organ Class and Preferred Term using Medical Dictionary for Regulatory Activities (MedDRA). Of reported AEs in the eCRF, TEAEs will be used for safety analyses. The definition of TEAE is described in Section 7.6.5.10. Treatment-emergent AE will be referred to as an AE in this section.

The number and percentage of subjects who experienced at least 1 TEAE, deaths, SAEs, and TEAEs leading to discontinuation will be summarized. The number of those AEs, which are counted by cases reported, will also be presented. Treatment-related AEs will

be summarized in the same way as AEs for overall summary. The definition of treatment-related AE is described in Section 7.6.5.4.

For the summary of AE by MedDRA System Organ Class and Preferred Term the number of subjects who have experienced AEs will be presented with the percentage of subjects. 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

All vital sign data will be listed.

9.11.3 Clinical Laboratory Analysis

All clinical laboratory data will be listed.

9.12 Pharmacokinetic Analysis

For each subject, the concentration of cefiderocol in ELF will be calculated and determined according to the following procedures.

Calculation of cefiderocol concentration in ELF:

$$V_{ELF} = V_{BAL} \times (Urea,_{BAL}/Urea,_{SERUM})$$
$$C_{ELF} = C_{BAL} \times (V_{BAL}/V_{ELF})$$

V_{ELF} represents the calculated volume of ELF, V_{BAL} is the BALF volume. $Urea,_{BAL}$ and $Urea,_{SERUM}$ are the urea concentrations in the BALF and serum, respectively. C_{ELF} and C_{BAL} is the cefiderocol concentration in the ELF and the supernatant BALF, respectively.

Individual plasma and ELF concentrations of cefiderocol will be listed and summarized by nominal sampling time with N, Mean, SD, and coefficient of variation (CV%, calculated by SD/Mean × 100), Geometric Mean and coefficient of variation for geometric mean (CV% Geometric Mean), and median, minimum, and maximum values. The CV% Geometric Mean will be calculated according to a formula:

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

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

Concentration ratios in ELF to plasma ($R_{C,E/P}$) in each subject will be calculated, listed, and summarized with N, Mean, SD, CV%, Geometric Mean and CV% Geometric Mean, and median, minimum and maximum values by nominal sampling time.

The time courses of individual and mean plasma and ELF concentrations and individual and mean $R_{C,E/P}$ will be presented by appropriate graphics.

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

For calculation of ELF concentration, the BALF concentration below the limit of quantification (BLQ) will be treated as zero (0). For summary of ELF concentration, the ELF concentration of zero will be included for calculations of Mean, SD, CV%, minimum, median and maximum and treated as missing for calculations of Geometric Mean value and CV% Geometric Mean.

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

If the plasma concentration is not quantifiable, the $R_{C,E/P}$ will not be calculated. If the plasma concentration is quantifiable and the ELF concentration is zero, $R_{C,E/P}$ will be calculated as zero (0). The $R_{C,E/P}$ of zero will be included for calculations of Mean, SD, CV%, minimum, median and maximum and treated as missing for calculation of Geometric Mean value and CV% Geometric Mean.

Population PK analyses will be performed using a nonlinear mixed effects model approach. NONMEM® Version 7.3 or higher will be used for the analyses. Population PK analyses will be performed and reported separately by the Clinical Pharmacology & Pharmacokinetics of Shionogi & Co., Ltd.

9.13 Other Analysis

No other analysis is planned.

9.14 Interim Analysis

Pharmacokinetic assessments for ELF will be performed for every 3 subjects. Based on the preceding data obtained thus far, the BAL collection time point for the ELF sample may subsequently be modified in accordance with the outlined procedure (see Figure 7-3). Additional details for determining whether to proceed to each next step will be based on the data obtained for each category.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Study Administrative Structure

Sponsor:	Shionogi Inc. 300 Campus Drive Florham Park, NJ 07932 USA
Sponsor's Contacts:	[redacted]
[redacted]	[redacted]
Medical Monitor (Shionogi):	[redacted]
Medical Monitor (CRO):	[redacted]
Investigator and Study Site:	Multicenter
Study Monitoring:	[redacted]
Bioanalytical Laboratory:	[redacted]

10.2 Institutional Review Board or Independent Ethics Committee Approval

The IRB 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. The IRB will be appropriately constituted in accordance with ICH GCP, and local requirements, as applicable. The study will be undertaken only after the IRB has given full approval and the investigator has received a document being approved.

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. The investigator will inform the IRB 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. 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 Process

The sponsor will provide the investigators with a proposed ICF that complies with the ICH GCP guidelines and regulatory requirements. The investigator will review the ICF for the study and make any necessary changes according to local regulations. The sponsor must review and agree to any changes to the proposed ICF suggested by the investigator prior to submission to the IRB, and the IRB approved version must be provided to the site monitor after IRB approval.

The consent form 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 before use.

The investigator, or qualified designee will explain the nature, purpose, methods, reasonable anticipated benefits, and potential hazards of the study to the subject or, if incapacitated, to his/her legally authorized representative in simple terms by using the ICF before the subject is entered into the study. The method of obtaining and documenting informed consent will comply with ICH GCP and all applicable regulatory requirements.

10.5 Subject Confidentiality

Procedures for protecting subject privacy must adhere to applicable data privacy laws and regulations. In order to maintain subject privacy, all eCRFs, study drug 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 Insurance 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 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 the protocol. The study monitoring will be performed by a representative of the sponsor (site monitor) through on-site monitoring visits as frequently as necessary and frequent communications (e-mail, letter, telephone, and fax). The site monitor will review data recorded in the eCRFs, verify the eCRFs entries with direct access to source documents, collect any safety information on subjects, verify that amounts of unused study drug are accurate, and check retention of source documents and essential documents.

10.7 Case Report Forms and Source Documents

10.7.1 Case Report Forms

An eCRF will be created for each subject who signed informed consent. The investigator or qualified designee will transcribe historical information and relevant data, as specified by the protocol, into the eCRF for each subject. All subject data from study visits must be legibly collected on source documents and eCRF entry completed in accordance with the eCRF Completion Guidelines. Electronic case report forms data entry is performed by the investigator, subinvestigator, and study coordinator who are authorized in to do data entry by the delegation log or other 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. The following data can be recorded directly on an eCRF as source data:

- Reason for use of prior therapy or concomitant therapy
- Severity, seriousness, and relationship of an AE, and its causal relationship to the study drug
- Clinical comments

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, 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 a document within the study site.

10.7.3 External Data

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

- Concentration data of cefiderocol and urea
- PK analyses results derived from concentration data

10.8 Committees

10.8.1 Case Review Committee

No case review committee will be established for this study.

10.8.2 Independent Data Monitoring Committee

No independent data monitoring committee will be established for this study.

10.8.3 Other Committees

No other committees will be established for this study.

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 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 drug 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 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 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 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 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 by the investigator and any deviations or modifications require expedited review and approval by the IRB. After the investigator obtained approval/favorable opinion from the IRB, 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. All protocol deviations will be collected and reported.

10.11 Data Management

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

10.12 Retention of Data

The study documents must be maintained as specified in the ICH GCP and as required by the applicable regulatory requirements. 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 requirements, whichever is latest

However, the duration of retention may be prolonged in accordance with an agreement with the sponsor. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility.

10.13 Quality Control and Assurance

The sponsor or designee will implement and maintain quality control and quality assurance 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.

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.

The key design elements of this protocol may be posted in a publicly accessible database(s), eg, ClinicalTrials.gov, European registries, and the Japan Pharmaceutical Information Center Clinical Trial Information (JAPIC CTI).

10.15 Financial Disclosure

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

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Appendix 1 Time and Events Schedule

	Screening[a] Day -2 to -1	Treatment Period											EOS Visit[b]
		Day 1				Day 2			Day 3			EOT[k]	
Hour		**Predose[c]**	**0**	**8**	**16**	**24**	**32**	**40**	**48**	**56**	**64**		
Administrative Procedures													
Informed consent	X												
Inclusion/exclusion criteria	X												
Medical history	X												
Demographics and baseline characteristics	X												
Review of prior and concomitant medications	X----------												----------X
Clinical Procedures													
Physical examination	X[d]	X[e]		X[e]			X[e]			X[e]		X	
Vital sign measurements[f]	X	X		X			X			X		X	
Chest X-ray[g]	X			X			X			X		X	
Clinical laboratory tests[h]	X			X			X			X		X	
Creatinine clearance (to adjust cefiderocol dose)[i]	X	X		X			X			X			
Pregnancy test[j]	X												
Adverse event monitoring[l]	X----------												----------X
Study Treatments													
Administration of study drug[m]			X	X	X	X	X	X	X	X	X		

AE = adverse event; eCRF = electronic case report form; EOS = End of Study; EOT = End of Treatment; SAE = serious adverse event

PK and urea sampling details and time points are described in Appendix 2.

a Screening will occur within 48 hours prior to the administration of the first dose of cefiderocol.

b The EOS visit will occur 7 days (± 3 days) after administration of the last dose of cefiderocol. The EOS visit can be performed on-site or by telephone.

c Predose assessments will occur within 24 hours prior to the administration of the first dose of cefiderocol; if Screening occurs < 24 hours prior to administration of the first dose of cefiderocol then predose assessments do not need to be performed.

d A complete physical examination, including measurement of body weight and height, will be performed at Screening only.

e A symptom-driven physical examination relevant to the subject's current condition will be performed as part of routine patient care and at the investigator's discretion from predose (if applicable), through the first dose of cefiderocol, during administration of cefiderocol, and until the last dose of cefiderocol.

f Blood pressure (systolic/diastolic), body temperature, pulse rate, and respiratory rate will be measured at Screening and at least 3 times a day at approximately evenly spaced intervals across the 24-hour day, starting on Day 1 of the infusions and continuing while the subject is receiving cefiderocol.

g Data from chest X-rays performed as part of routine patient care will be collected at Screening and throughout the study in accordance with routine patient care; any chest X-ray taken within 48 hours of randomization can be considered as Screening (or baseline) chest X-ray. A computed tomography scan can be a substitute of chest X-ray if taken according to local standard of care.

h Data from clinical laboratory tests performed as part of routine patient care will be collected at Screening and from the first dose of cefiderocol, during administration of cefiderocol, and until the last dose of cefiderocol. Clinical laboratory tests during the treatment period will be symptom-driven and at the investigator's discretion. If a microbiology test has been performed to confirm the clinical diagnosis (before or during Screening), the results should be recorded in the source documents and the eCRF.

i Creatinine clearance must be calculated at Screening and daily during treatment period to determine cefiderocol dose.

j Female subjects of childbearing potential only.

k EOT assessments will occur within 24 hours after administration of the last dose of cefiderocol or at early termination.

l If an SAE is observed it must be reported to Safety and all SAEs, regardless of causality, will be followed until resolution, stabilization, the condition becomes chronic, or the subject is lost to follow-up. The investigator will make an effort to collect AEs for 7 days after the last dose of study drug.

m Multiple doses of cefiderocol administered as an intravenous infusion over 3 hours, every 8 hours (q8h), or every 6 hours (q6h) if augmented renal function, beginning on Day 1 and continuing for an expected minimum of 3 doses and up to a total of 6 doses in subjects with normal or augmented renal function and subjects with mild or moderate renal impairment and for an expected minimum of 6 doses and up to a total of 9 doses in subjects with severe renal impairment. Dose adjustments will be made based on renal function according to dosing recommendations per protocol. Dosing scheme of q6h is not illustrated in the Schedule of Events Table as it is expected to a rare situation.

Appendix 2 PK and Urea Samples

Bronchoalveolar lavage procedure will be conducted after the 3rd dose (or 6th dose for severe renal impairment subjects). If it is not convenient for the subject or the institution to perform the BAL procedure after the 3rd dose (or 6th dose for severe renal impairment subjects), the 4th, 5th, or 6th dose may be considered as the timing for the BAL procedure (or the 7th, 8th, or 9th dose for severe renal impairment subjects). A total of 4 blood samples for determination of plasma cefiderocol concentrations will be collected at prespecified time points after the dose at which the ELF sample is collected. Part of the ELF sample will be analyzed for urea.

PK data (both blood and ELF) will be evaluated by Sponsor for every 3 subjects to determine if modifications of the ELF sampling time point in subsequent subjects are needed (see Figure 7-3). The CRO will inform study sites upon evaluation of ELF sampling time point, which scenario and BAL time point to follow. Study sites must confirm receipt of the email.

A blood sample collection for urea analysis will be performed within 30 minutes prior to the start of the BAL procedure. Within 30 minutes prior to the start of the BAL procedure, the following ventilator parameters will be captured: respiratory rate (breaths/minute) and PEEP. Blood sample collections for pharmacokinetic analysis will be performed after the same dose as the ELF sample collection at: (1) 1 hour after the start of infusion, (2) 3 hours after the start of infusion (within 30 minutes prior to the end of infusion), (3) 2 hours after the end of infusion (within ± 1 hour), and (4) 4 hours after the end of infusion (within ± 1 hour).

Blood and ELF samples will be obtained from each subject following the time points in one of the 3 scenarios listed in the tables below:

	3rd dose of cefiderocol (or subsequent dose)[a]			
	1 hr after start of infusion	3 hrs after start of infusion	2 hrs after end of infusion	4 hrs after end of infusion
Plasma PK	X	X	X	X
Serum Urea[b]		X		
BAL PK and Urea		X		

BAL = bronchoalveolar lavage; hrs = hour(s); PK= pharmacokinetic

	3rd dose of cefiderocol (or subsequent dose)[a]			
	1 hr after start of infusion	3 hrs after start of infusion	2 hrs after end of infusion	4 hrs after end of infusion
Plasma PK	X	X	X	X
Serum Urea[b]			X	
BAL PK and Urea			X	

BAL = bronchoalveolar lavage; hrs = hour(s); PK= pharmacokinetic

Scenario 3: The next set of subjects enrolled (3 additional) will undergo BAL procedure 4 hours after the end of infusion as well as plasma PK and urea assessments in ELF and serum

	3rd dose of cefiderocol (or subsequent dose)[a]			
	1 hr after start of infusion	3 hrs after start of infusion	2 hrs after end of infusion	4 hrs after end of infusion
Plasma PK	X	X	X	X
Serum Urea[b]				X
BAL PK and Urea				X

BAL = bronchoalveolar lavage; hrs = hour(s); PK= pharmacokinetic

After the third scenario, sponsor may decide to enroll up to nine additional subjects and the timing of the BAL procedure will be determined based on the information collected from the initial 9 subjects (Scenario 1-3).

*a) 6th dose for subjects with severe renal impairment

*b) A blood sample collection for urea together with PK analysis will be performed within 30 minutes prior to the start of the BAL procedure

PK results (blood and ELF) will be reviewed by Sponsor promptly after the first 3 subjects to determine if modifications of the ELF sampling time need to be adjusted for subsequent subjects enrolled. The CRO (Syneos Health) will inform the investigator and research staff of any sampling time adjustments promptly after the sponsor review and determination. The investigator will be required to confirm receipt of the adjustment information via email or other written document as appropriate.

Appendix 3 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: July 2009) [33].

1. Abnormal Liver Chemistry Criteria:

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

a. AST or ALT > 5 × ULN (if baseline ALT is ≤ ULN);
b. AST or ALT > 8 × ULN;
c. AST or ALT > 3 × ULN and total bilirubin (TBL) > 2 × ULN or PT-INR > 1.5, if PT-INR measured*;
d. AST or ALT > 3 × ULN (if baseline ALT is ≤ ULN) with signs or symptoms compatible with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash or eosinophilia [> 5%])

OR

e. AST or ALT > 3 × increase from baseline ALT or AST with signs or symptoms compatible with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash or eosinophilia [> 5%])

* Unless an alternative explanation for PT-INR > 1.5, such as the concomitant use of warfarin, is present.

2. Action to Be Taken by Investigator:

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

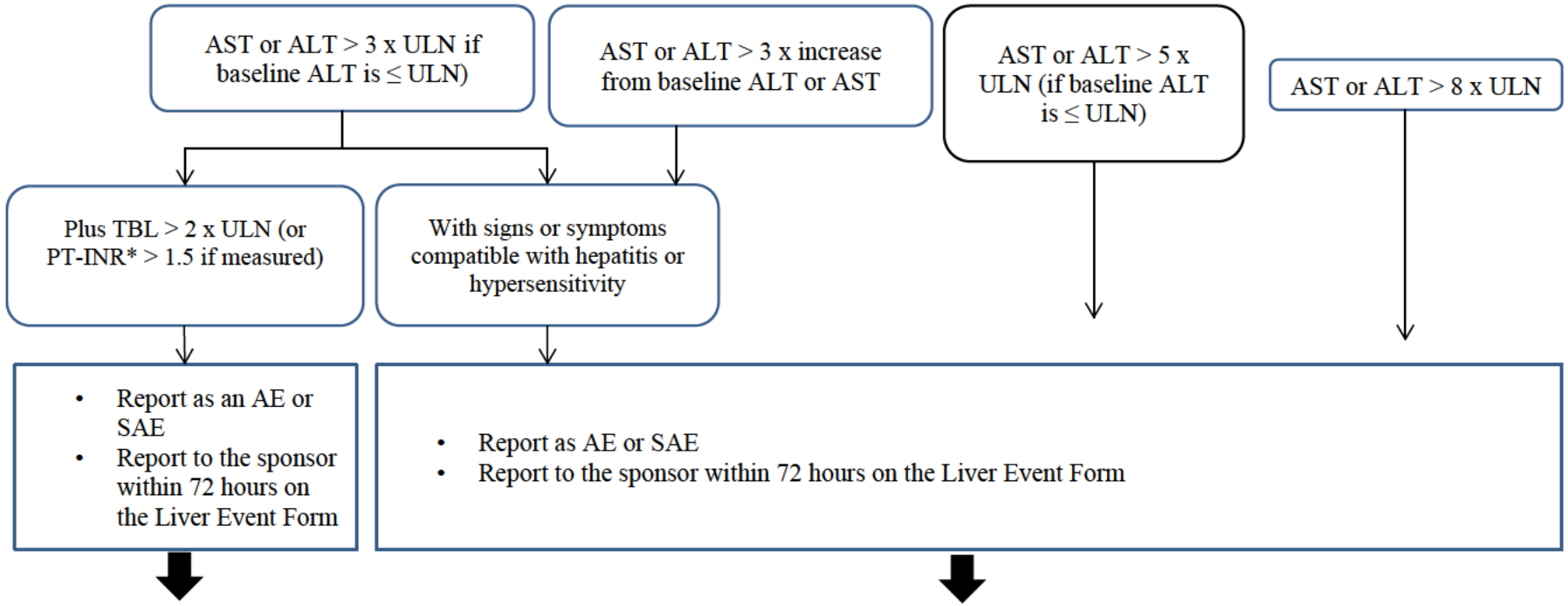
- This event must be reported to the sponsor as soon as possible but no later than 72 hours of learning after its occurrence on the Liver Event Form.
- For criteria c, the case must also be reported as an SAE, unless an alternate explanation exists.
- Following the initial observed elevation, every effort should be made to have the subject return to the clinic within 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, ALP, TBL) resolve, stabilize or return to within the normal range or to baseline levels.
- Consultation with a specialist such as a hepatologist is considered.
- Liver imaging (ie, ultrasound, magnetic resonance imaging [MRI], CT scan) is considered.

3. 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:

- Clinical sign and symptoms course
- Alcohol use
- Risk factors for nonalcoholic steatohepatitis (NASH) 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 (HBc antibody)
    - Hepatitis C RNA
    - Hepatitis E IgM antibody
    - Cytomegalovirus IgM antibody
    - Epstein-Barr viral capsid antigen IgM antibody
  - For subjects with TBL of > 1.5 ULN, conjugated bilirubin should be measured
  - CBC with differential to assess for eosinophilia

Management and Discontinuation Criteria for Abnormal Liver Function Tests: Algorithm



- Following the initial observed elevation, every effort should be made to have the subject return to the clinic within 72 hours to repeat liver function chemistries and for further hepatic evaluation.
- Subjects must be monitored 2 to 3 times per week until liver function chemistries (ALT, AST, ALP, TBL) resolve, stabilize or return to within the normal range or to baseline levels.
- Consultation with a specialist such as a hepatologist is considered.
- Liver imaging (ie, ultrasound, magnetic resonance imaging, computerized tomography) is considered.
- When restarting drug, refer to the document content.

* Unless an alternative explanation for PT-INR > 1.5, such as the concomitant use of warfarin, is present.

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PT-INR = prothrombin time-international normalized ratio; SAE = serious adverse event; TBL = total bilirubin; ULN = upper limit of normal

Appendix 4 Sponsor's Signature

Approval of the Protocol

Product Name: Cefiderocol

Study Protocol Title: An Open-label, Multicenter, Single-arm, Phase 1 Study to Assess the Intrapulmonary Concentrations of Cefiderocol at Steady State in Hospitalized Subjects with Known or Suspected Bacterial Pneumonia on Treatment with Standard of Care Antibiotics and Requiring Mechanical Ventilation

Study Protocol Number: 1713R2117

Version Number: 2.0

Issue Date: 02 Nov 2018

Sponsor Signatory:

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

[redacted]

Date: day-month-year

Appendix 5 Investigator's Signature

Study Title:	An Open-label, Multicenter, Single-arm, Phase 1 Study to Assess the Intrapulmonary Concentrations of Cefiderocol at Steady State in Hospitalized Subjects with Known or Suspected Bacterial Pneumonia on Treatment with Standard of Care Antibiotics and Requiring Mechanical Ventilation
Study Number:	1713R2117
Date of Original:	30 Apr 2018
Date of Latest Amendment:	02 Nov 2018

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: _____

Printed Title:_____

Printed Affiliation:_____