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
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Study Document	Statistical Analysis Plan Version 2 19 June 2019

History of Statistical Analysis Plan Amendments

Version 1 (Original)	06 April 2018
Version 2	19 June 2018
Revisions to Version 1 are document within Version 2	

[redacted]

Statistical Analysis Plan

Sponsor Name: Shionogi Inc

Protocol Number: 1713R2117

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

Protocol Version and Date: Final Version 2, 02 Nov, 2018

[redacted]

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1.1	19-Dec-2018	[redacted]	Revision Based on Sponsor's Comments on Version 1.0
1.2	26-Nov-2019	[redacted]	Revised Based on Sponsor's Comments on version 1.1

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

Approvals	
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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BAL	Bronchoalveolar Lavage
BALF	Bronchoalveolar Lavage Fluid
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CBC	Complete Blood Count
CRF	Case Report Form
CSR	Clinical Study Report
CrCl	Creatinine Clearance
CT	Computed Tomography
CV%	Coefficient of Variation
eCRF	Electronic Case Report Form
ELF	Epithelial Lining Fluid
EOI	End of Infusion
EOS	End of Study
EOT	End of Treatment
GGT	Gamma Glutamyltransferase
ICH	International Conference on Harmonization
IV	Intravenous
LLOQ	Lower Limit of Quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable

Abbreviation	Description
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
PT	Preferred Term
q6h	Every 6 Hours
q8h	Every 8 Hours
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	Standard of Care
SOI	Start of Infusion
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
TBL	Total Bilirubin
WHO	World Health Organization

2. Purpose

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

2.1. Responsibilities

Syneos Health will perform the statistical analyses.. Syneos Health will be responsible for the production and quality control of all tables, listings and figures (TLFs) with the guidance supplied by Shionogi Inc. The PK analysis will be carried out following this SAP with the guidance supplied by Shionogi Inc.

2.2. Brief Description

This is a phase 1b 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 standard of care (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 as described in Table 1) 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 every 8 hours q8h (or q6h if subject has augmented renal function) with the dosage specified in Table 1.

Table 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 protocol 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 serious adverse event (SAE), after administration of the last dose of cefiderocol. For both cases the EOS visit can be performed on-site or by telephone (see Figure 1). 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 adverse events (AEs) for 7 days after the last dose of study drug.

One epithelial lining fluid (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 protocol 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 volume of ELF (V_{ELF}) is adjusted for excess exogenous volume using the concentration of urea in blood and ELF (see protocol Section 7.6.4.1.3).

Safety assessments including physical examinations, vital sign measurements, chest X-ray 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 protocol Section 7.6), date and result will be entered in the source documents and the 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 is no SAE.

Figure 1 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, qh8 Initial dose must be within 48 to 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

qh8 = every 8 hours; q6h = every 6 hours; SOC = standard of care

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

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. Non-evaluable subjects will be replaced.

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. Study Objectives

3.1. Primary Objective

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 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

3.2. Subject Selection

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.

3.2.1. 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.

3.2.2. 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 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.

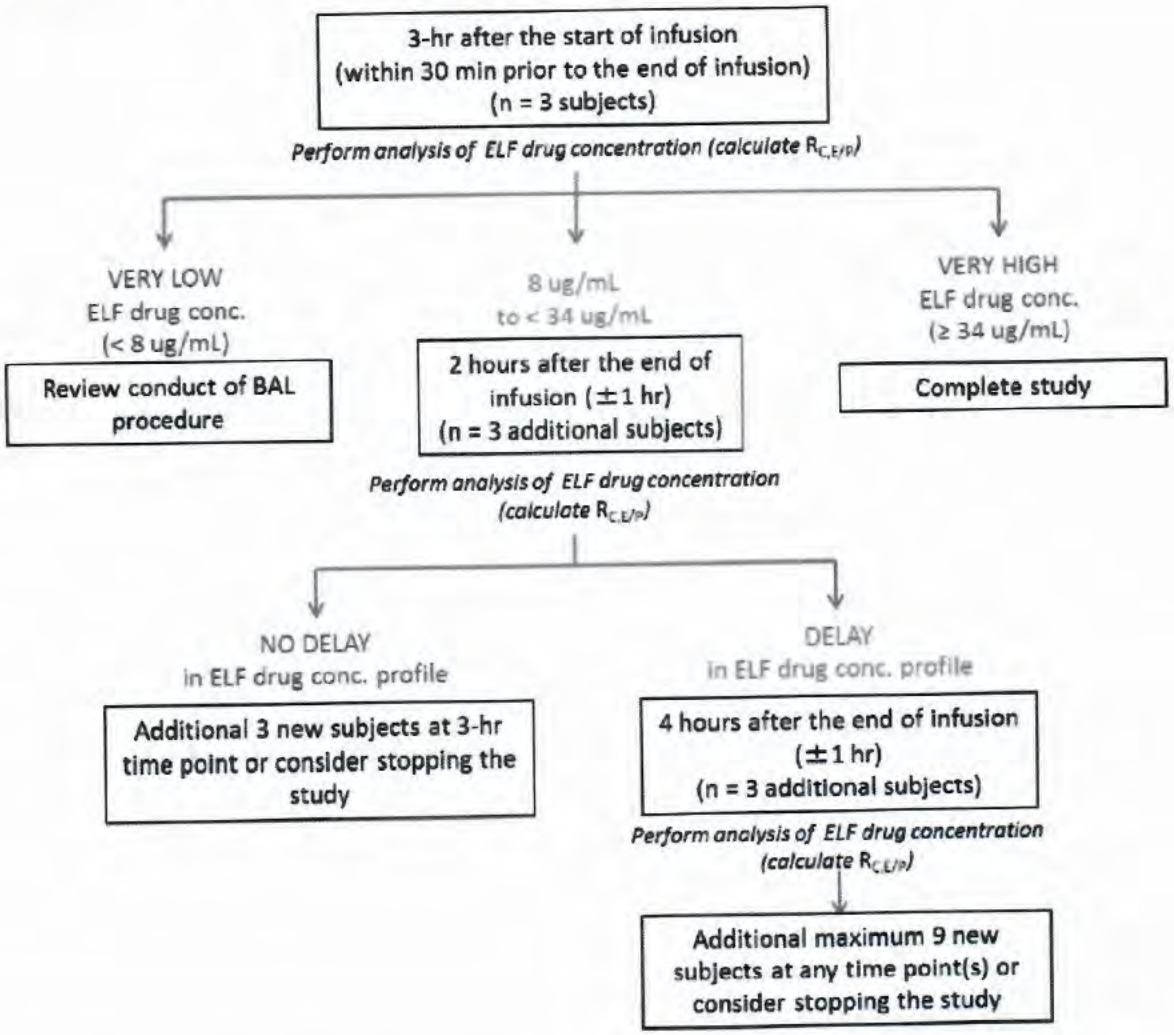
3.3. Determination of Sample Size

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.

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 2). Additional details for determining whether to proceed to each next step will be based on the data obtained for each category.

For the first 3 subjects enrolled, the ELF sample will be collected 3 hours after the start of infusion, within 30 minutes prior to the end of infusion (ie, 3-hour time point). Based on the cefiderocol concentrations in the ELF samples collected from the first 3 subjects at the 3-hour time point (refer to Figure 3: example sampling scheme, prespecified rule 1 and prespecified rule 2), 3 additional new subjects may be enrolled, from whom ELF samples will be collected 2 hours after the end of infusion if the data obtained from the first 3 subjects indicate delay in lung penetration. Furthermore, based on the available data from the first 3 subjects and the subsequent 3 subjects, if it is considered that there is a delay in lung penetration as calculated by $R_{C,E/P}$, 3 further additional subjects may be enrolled from whom ELF samples will be collected at 4 hours after the end of infusion. After PK assessments have been completed in the first 9 subjects, up to an additional 9 subjects may be enrolled from whom ELF samples will be collected at any time point(s). The choice of time points will be data driven. The total number of 18 evaluable subjects may be enrolled in this study.

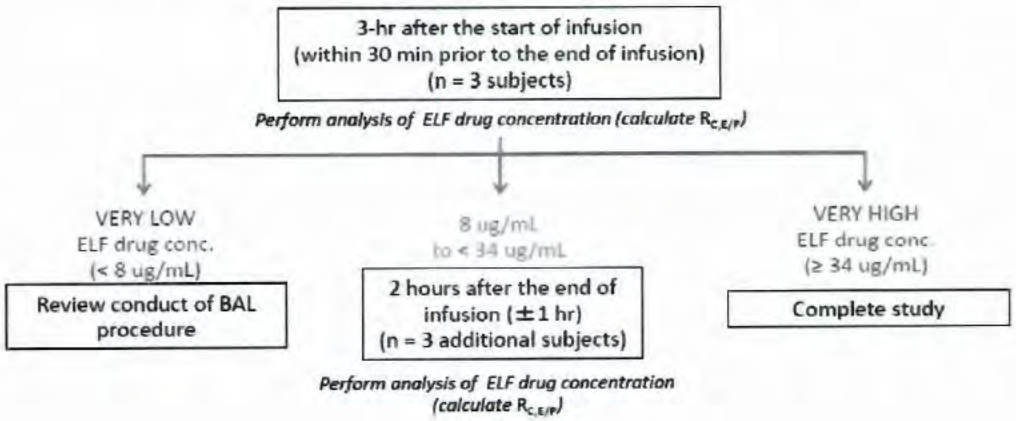
Figure 2 Epithelial Lining Fluid Sampling Procedure Schematic



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

An example sampling procedure scheme for the algorithm described above is described in Figure 3 below. Note that the final sampling scheme will be provided in the clinical study report (CSR). The sampling procedure will be determined by the sponsor in discussion with the investigator, and will be documented.

Figure 3 Adaptive Design: Pre-specified Rule 1 (3 hours time point*)



Case	Very Low	Medium	Very High	Decision
1-a	3 subjects	0 subject	0 subject	Review BAL procedure or consider stopping the study
1-b	2 subjects	1 subject	0 subject	Move on to next time point(2 hours after end of infusion)
1-c	2 subjects	0 subject	1 subject	Move on to next time point(2 hours after end of infusion)
1-d	1 subject	2 subjects	0 subject	Move on to next time point(2 hours after end of infusion)
1-e	1 subject	0 subject	2 subject	Move on to next time point(2 hours after end of infusion)
1-f	1 subject	1 subject	1 subject	Move on to next time point(2 hours after end of infusion)
1-g	0 subject	3 subjects	0 subject	Move on to next time point(2 hours after end of infusion)
1-h	0 subject	2 subjects	1 subject	Move on to next time point(2 hours after end of infusion)

1-i	0 subject	1 subject	2 subjects	Move on to next time point(2 hours after end of infusion)
1-j	0 subject	0 subject	3 subjects	Complete the study

Adaptive Design: Pre-specified Rule 2 (2 hours after end of infusion time point)

Case	No delay	Delay	Decision
2-a	3 subjects	0	Additional 3 subjects at 3 hour time point or consider stopping the study
2-b	2 subjects	1 subject	Move on to next time point(4 hours after end of infusion)
2-c	1 subject	2 subjects	Move on to next time point(4 hours after end of infusion)
2-d	0 subject	3 subjects	Move on to next time point(4 hours after end of infusion)

*3 hours after the start of infusion, within 30 minutes prior to the end of infusion

3.4. Treatment Assignment & Blinding

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).

This is an open-label study. No unblinding is needed.

3.5. Administration of Study Medication

The dose of cefiderocol administered to each subject will be determined based on renal function as described in this section. 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 a renally adjusted dose) of cefiderocol infused intravenously over 3 hours, q8h (or q6h for 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 2). Any dosing modifications based on the dosing recommendations will be agreed to by the investigator and documented.

Table 2 Dosing Recommendations of Cefiderocol Based on Renal Function

Creatinine Clearance	**Dosage**	**Number of Dosing to Perform 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.

3.6. Study Procedures and Flowchart

The study procedures and the times to be performed are summarized in the Time and Events Schedule in Table 3.

Table 3 Time and Events Schedule

	Screening[a]	Treatment Period											EOS Visit[b]
		Day 1				Day 2			Day 3			EOT[k]	
Hour	Day -2 to -1	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 Events; eCRF = Electronic Case Report Form; ELF = Epithelial Lining Fluid; EOS = End of Study; EOT = End of Treatment; SAE = Serious Adverse Event

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 pre-dose (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 established to confirm the 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.

4. Endpoints

4.1. Safety Endpoints

The following safety and tolerability endpoints will be evaluated:

- Adverse Events
- Vital signs (blood pressure, pulse rate, respiratory rate, body temperature)
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Physical examination findings
- Chest x-rays

4.2. Pharmacokinetic Endpoints

4.2.1. Plasma PK Endpoints

- Plasma cefiderocol concentrations listing
- Plasma cefiderocol concentrations summary

4.2.2. PK Endpoints in ELF

- ELF cefiderocol concentrations listing
- ELF cefiderocol concentrations summary
- Concentration ratios in ELF to plasma($R_{C,E/P}$) listing
- Concentration ratio in ELF to plasma($R_{C,E/P}$) summary

5. Analysis Populations

5.1. Safety population

The Safety population includes all enrolled subjects who receive at least 1 dose of the study drug. The population will be analyzed as treated.

5.2. Pharmacokinetic Concentration Population

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.

5.3. Protocol Deviations

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

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

6. General Aspects for Statistical Analysis

6.1. General Methods

6.1.1. Summary Statistics

All analyses and summaries will be produced using Statistical Analysis System (SAS®) version 9.4 or higher. Summaries will be presented by overall unless otherwise specified.

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

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

All subject study data, including data not appearing in tables, will be presented in by subject data listings. Individual subject data, PK data, and any derived data will be presented by subject. All pre- and post-dose assessments including repeat and unscheduled assessments will be included in the data listings. Due to the small study size, only the following 4 analysis data sets [Subject Level Analysis Dataset (ADSL), Analysis Dataset containing PK Concentrations (ADPC) and Trial Element Drug Name, Dosage, Unit (ADXB)] will be generated for the study. As such, all study data will be presented in the form of data listings only, with the exception of PK endpoints that will also include summaries for selected tables and figures.

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

Summary statistics calculated for PK data are described in SAP Section 8 – analysis of pharmacokinetics.

6.1.2. Reporting Precision

Summary statistics will be presented to the following degree of precision (see Table 4):

Table 4 Reporting Precision

Statistics	**Degree of Precision**
Individual ELF concentration	Three significant digits
Individual $R_{C,E/P}$	Three significant digits
Mean (arithmetic and geometric), Median, SD, SE, Quartiles, Confidence limit boundaries	PK[a]: The same number of significant digit as the original data Others: One more significant digit than the original data
Minimum, Maximum	PK[a]: The same number of significant digit as the original data Others: The same number of decimal places as the original data
Percent, Coefficient of variation, Geometric coefficient of variation	One decimal place

[a] Plasma and ELF cefiderocol concentrations and $R_{C,E/P}$

All fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 - 0.30, not .12 - .30).

6.2. Key Definitions

Baseline Value: Unless otherwise specified, baseline value is the last non-missing value prior to the first dose of study drug.

Day 1: Day 1 is defined as the day of the first dose of study drug.

Study Day: For events that occur before the first dose of study drug, study day = date of the event – first dose date; for events that occur on or after the first dose of study drug, study day = date of the event – first dose date + 1.

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

6.3. Missing Data

In general, missing data will not be imputed. All analyses will be based on observed cases.

The handling of missing PK data is detailed in SAP Section 8 – analysis of pharmacokinetics.

6.3.1. Handling of Missing Dates/Months/Years for Adverse Events

Adverse events with incomplete onset dates will be handled as follows for the sole purpose of determining treatment emergence (TEAE is defined in Section [redacted] 9.3):

- If the start/end date of an AE is partially missing, the date will be compared as far as possible with the date of the start of administration of study drug. The AE will be assumed to be treatment emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach).
- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date is before study drug administration.

The original partial or missing date will be shown in listings of AEs.

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

Prior or concomitant therapies with incomplete start dates will be handled as follows for the sole purpose of determining whether a non-study therapy is a concomitant therapy:

- If the start/stop date of a therapy is partially missing, the date will be compared as far as possible with the date of the start of administration of study drug. The therapy will be assumed to be concomitant if it cannot be definitively shown that the stop date is before the start of administration of study drug, or the start date is after the last visit of the study.
- If the start and stop dates are both completely missing, a therapy will be considered concomitant.

The original partial or missing date will be shown in listings of all non-study medications.

6.4. Visit Windows

Visits specified in the electronic case report form (eCRF) will be used for this study.

Measurements will be performed according to the Time and Events Schedule in protocol Appendix 1.The acceptable time deviations relative to the time points specified in Appendix 1 are shown in Table 5. Every effort should be made to adhere as closely as possible to procedure time points specified.

Table 5 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)

Unscheduled visits after first dose of study drug will not be included in by-visit summary tables, unless otherwise specified. Data from unscheduled visits will be included in listings. If multiple records exist at the same visit/time-point, the latest record will be used for the purpose of summary tables.

6.5. Pooling of Centers

No center pooling will be employed.

7. Demographic, Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

A listing of subject enrollment, and a separate listing of subjects disposition including subjects that have discontinued or are early withdrawals will also be provided.

7.2. Inclusion/Exclusion Criteria

All inclusion/exclusion criteria definitions will be listed. Inclusion/exclusion criteria deviations will be listed by subject. A listing of subjects excluded from each analysis population will also be produced.

7.3. Demographic and Baseline Characteristics

Demographic variables including date of birth, initials, age (as recorded in the source documents and the eCRF), sex, race, ethnicity, height (cm), and weight (kg) are collected. Demographics and informed consent data will be listed by subject for all the subjects in the Safety Population.

Baseline characteristics including the clinical diagnosis data of pneumonia, diagnosis methods, and symptoms, will be listed by subject using the Safety Population. The hospitalization and ventilation data, including start and end date/time, will be listed by subject using the Safety Population.

7.4. Medical History

Medical history will be coded to MedDRA terms, using Version 21.1 or higher. Medical history findings will be listed by subject using the Safety Population.

7.5. Prior and Concomitant Therapies

The original verbatim terms of the prior and concomitant therapies collected in the eCRF will be coded using the World Health Organization (WHO) Drug Dictionary Version B3 Global September 2018. The version used will be documented in a footnote to the listing.

Prior and concomitant therapies data will be listed chronologically by subject and will include the data collected in the eCRF, along with the coded variables. The listing will be based on the Safety Population.

All therapies administered during clinic visits are expected to have complete dates and times. In the event of a missing start date or time associated with a concomitant therapies, treatment emergence/assignment will be imputed using the algorithm described in Section 6.3.2. Dates and times will not be imputed.

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

7.5.2. Concomitant Therapy

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

Cefiderocol will be administered in combination with an 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

8. Analysis of Pharmacokinetics

Syneos Health will be responsible for the statistical analysis, production and quality control of TLFs of the PK data. The PK data will be analyzed using SAS® version 9.4 or higher. The PK analyses will be performed on PK population.

8.1. PK Sampling Schedule

Plasma samples:

Time Point	Window
1 hr after the SOI	
3 hr after the SOI (close to EOI)	Within 0.5 hr prior to the EOI
2 hr after the EOI	Within ± 1 hr
4 hr after the EOI	Within ± 1 hr

EOI = end of infusion; hr = hour; SOI = start of infusion.

Samples are taken after administration of at least 3 doses of cefiderocol in subjects with normal 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.

ELF samples:

Time Point	Window
3 hr after the SOI (close to EOI) for first three subjects	Within 0.5 hr prior to the EOI
2 hr after the EOI*	Within ± 1 hr
3 hr after the EOI*	Within ± 1 hr
4 hr after the EOI*	Within ± 1 hr

**Refers to Protocol Figure 7-3 decision tree for these additional subjects.*

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).

Blood and ELF samples will be collected also for determination of urea concentration. Urea is used as an endogenous marker of Epithelial Lining Fluid (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 volume of ELF (VELF) is adjusted for excess exogenous volume using the concentration of urea in blood and BAL.

8.2. Plasma PK Endpoint

- Plasma cefiderocol concentrations listing
- Plasma cefiderocol concentrations summary

8.3. PK Endpoints in ELF

- ELF cefiderocol concentrations listing
- ELF cefiderocol concentrations summary
- $R_{C,E/P}$: concentration ratios of ELF divided by time matched plasma sample

8.4. Presentation of Concentration Data

8.4.1. Handling of dropouts, missing data, or data below the lower limit of quantification (BLQ)

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

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

For calculation of ELF concentration, the BALF concentration 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.

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

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

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

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.

The lower limit of quantification (LLOQ) of cefiderocol is 0.1 µg/mL for plasma samples, and 0.005 µg/mL for ELF samples. The concentration below the LLOQ (BLQ) will be reported as "< x.xx" in listings.

8.4.2. Listing and Presentation of individual PK data

The Safety Population will be used for all individual plasma and ELF sampling collection time and concentration listings, while all summaries and graphics will be conducted using the PK Concentration Population.

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.

The calculation of C_{ELF} is possible to be simplified without V_{BAL} as follows:

$$C_{ELF} = C_{BAL} \text{ X } Urea_{,SERUM}/Urea_{,BAL} \quad (1)$$

The advantage of using equation (1) and not the previously provided equations would be that one do not need to calculate total volume of BAL samples. The total volume of BAL samples in this study is the sum of the three sample volumes for BAL collected on each subject. The first BAL volume was used for washout. In the eCRF, the total volume of BAL was determined as the total volume of recovered BAL samples, which is a sum of BAL volumes 2 and 3 with exclusion of volume 1 considered for washout, because drug concentrations and urea concentrations in BALF are derived from the recovered BAL samples. . However, the total volume of BAL is re-calculated in the analysis dataset for the study to include BAL volume 1.

Concentration ratios in ELF to time matched 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 following individual plots will be produced for:

- Individual subject linear and semi-logarithmic concentration vs time plots using actual sample times (a line to connect all time points of plasma concentration; a datapoint for

[redacted]

ELF concentration in the same plot in different symbol, color, and marker) – One subject per plot.

- Spaghetti plot linear and semi-logarithmic plasma concentration vs time plots using actual sample times (a line to connect all time points of plasma concentration; a datapoint for ELF concentration in the same plot in different symbol, color, and marker) - all Individual subjects combined (one line per each subject).
- Scatter plot linear and semi-logarithmic ELF concentration vs time plots using actual sample times - all Individual subjects combined (one datapoint per each subject).
- Individual subject $R_{C,E/P}$ vs time plots using actual sample times for BALF (a datapoint in the same plot in different symbol, color, and marker).

8.4.3. Summary of PK concentrations

Descriptive statistics, including N, Mean, SD, CV%, Geometric Mean and CV% Geometric Mean, and median, minimum and maximum values by nominal sampling time will be presented for plasma concentration, ELF concentration, and $R_{C,E/P}$. BLQ values will be handled according to the rules described in section 8.4.1.

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

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

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

The following mean plots will be produced:

- The arithmetic mean plasma concentration with SD vs time profiles will be plotted by dose regimen within the same figure on linear scale and semi-logarithmic scales using nominal sampling times.
- The arithmetic mean plasma and ELF concentration with SD vs time profiles will be plotted in all patients (regardless of dose regimens) on linear scale and semi-logarithmic scales.
- The arithmetic mean $R_{C,E/P}$ with SD vs time profiles will be plotted using nominal sampling times (regardless of dose regimens).

9. Safety

The population used for safety analyses will be the Safety Population. Safety will be assessed on the basis of AE reports, clinical laboratory data, physical examinations, vital signs, and chest X-ray or any other imaging. By-subject listings of the safety assessments will be provided for all the subjects.

9.1. Extent and Duration of Exposure

Investigational product administration records will be listed chronologically by subject and study days.

Exposure duration in hours will be calculated as (the stop date/time of the last dose – the start date/time of the first dose)/60.

9.2. Treatment Compliance

Any interruption or adjustment of the rate of an infusion will be noted in the eCRF. The reason for interruption or adjustment also will be noted in the eCRF and provided in data listings.

9.3. 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 eCRF, including onset date, end date, severity, seriousness, relationship with the study drug, action taken to manage the AE, and the outcome of the AE, including the date.

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

Treatment emergence will be determined by comparing the onset date with the actual date of dosing. In the case that the AE onset date are incomplete, treatment emergence will be imputed according to the algorithm in Section 6.3.1.

Listings of AEs will present the date, severity, and relationship as recorded in the eCRF and will not display the imputed data.

Adverse events will be classified by System Organ Class and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1.

All AEs will be listed by subject and chronologically by date and time of AE onset. This listing will include all data collected in the eCRF and the coded variables.

9.3.1. Summaries of Adverse Events

No table summaries will be provided. All the AEs, SAEs, AEs related to study drug, and AEs leading to study drug withdrawal will be presented in listings. Adverse events that start prior to the first application of study drug will be included in the listings.

9.4. Laboratory Evaluations

Clinical laboratory tests will be performed at prespecified time points per the Time and Events Schedule in Table 3. 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 at Screening and from the first dose of cefiderocol, during administration of cefiderocol until the last dose of cefiderocol.

Routine hematology and blood chemistry that will be assessed at local laboratory are presented in Table 5. 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 diagnosis, the result from the test done closest to the day of screening or on the day of screening should be recorded in the eCRF. If the local laboratory performs a microbiology test using the BAL sample, the result must be recorded in the source documents and the eCRF.

Table 6 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 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

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 eCRF.

Cockcroft-Gault formula:

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

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.

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

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

The creatinine clearance data, and microbiology data will be listed.

The pregnancy test results will be listed.

9.5. Vital Signs

Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be performed at prespecified time points per the Time and Events Schedule in Table 3.

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

Height and weight data will be listed.

9.6. Physical Examination

Physical examinations will be performed at prespecified time points per the Time and Events Schedule in Table 3. In addition to prespecified time points, symptom-driven physical examination relevant to the subject's current condition will be performed as clinically indicated and at the investigator's discretion from pre-dose until end of treatment.

Physical examination results (Normal, Abnormal-not clinically significant, and Abnormal-clinically significant) and associated medical history or AE will be listed by subject and time points.

9.7. Chest X-Ray

A chest X-ray will be performed at Screening or within 48 hours of Screening per Table 3 Time and Events Schedule 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 eCRF.

Chest X-ray and CT scan results (normal and abnormal) will be listed by subject and time points.

10. Interim Analyses

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 2). Additional details for determining whether to proceed to each next step will be based on the data obtained for each category.

11. Changes from Analysis Planned in Protocol

Due to the small number of subjects enrolled in the study, a decision was made by the Shionogi Biostatistics & Programming team with the consent of Syneos Health Biostatistics & Programming team, to mainly present study results in terms of data listings. An exception was made to generate a few tables and figures to support the PK endpoints.

12. Programming Considerations

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

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

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

12.1. General Considerations

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

12.2. Table, Listing, and Figure Format

12.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are

appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.

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

12.2.2. Headers

- All output should have the following header at the top left of each page:

  Shionogi Inc.; Protocol 1713R2117
  Draft/Final Run <date>

- All output should have Page n of N at the top or bottom right corner of each page. TLFs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TLF are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination A decimal system (x.y and x.y.z) are used to identify TLFs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

12.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.

- For numeric variables, include "unit" in column or row heading when appropriate.

12.2.5. Body of the Data Display

12.2.5.1. General Conventions

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

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

12.2.5.2. Table Conventions

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

Severity Rating	N
severe	0
moderate	8
mild	3

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

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean, standard deviations, and median for a set of values are printed out to 1 more significant digit than the original values. The minimum and maximum should report the same significant digits as the original values. See Table 4. For example, for systolic blood pressure:

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

Maximum XXX

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or system organ class with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and system organ class, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

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

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

12.2.5.3. Listing Conventions

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

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

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing

because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

13. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907) .

Syneos Health SOPs Developing Statistical Programs (3907) and Quality Deliveries (SDTM, ADaM, TLF) (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.